Update of the

CLINICAL PRACTICE GUIDELINE

FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS

IN SPAIN

Final, December 2011

Table of Contents

INDEX TO TABLES

I. Methodology

The Spanish Society of Rheumatology (Spanish acronym SER) named a panel of 18 experts to update GUIPCAR, made up predominantly of persons who had participated in writing the guideline in 2001. Most of the expert panel members are rheumatologists, although the group also included a primary care physician, a nurse, and two physical therapists. In addition, a group of reviewers carried out the update of the scientific evidence. The company *Técnicas Avanzadas de Investigación en Servicios de Salud* (TAISS) was responsible for coordinating the work and editing the updated version of GUIPCAR (GUIPCAR_2007). The present document is an update of the 2007 GUIPCAR guidelines carried out by the SER. The only funding provided was from Pfizer, to cover the expense of translating the document into English. Click **here** to see a list of authors and conflict of interest statements.

Four methodological phases of the project can be distinguished:

Preliminary phase: Structure of GUIPCAR_2011 and task assignment

In this phase, the structure for the contents of GUIPCAR_2011 was developed. A team of experts was assigned to write each chapter, and decisions were made about the areas on which the literature review and update would focus.

Review of the evidence

The searches carried out for the systematic reviews used in GUIPCAR 2007 were repeated and improved, covering the years between the last review and the present. After ruling out abstracts that did not fulfill the search criteria, 2 expert reviewers who had already participated in the systematic reviews of the previous edition of the guidelines undertook a critical reading of those articles that did fulfill the search criteria. The results of these updated reviews were transferred to the respective recommendations, with changes in the level of evidence in those where new information had become available, addition of new recommendations, and elimination of those that were obsolete.

Drafting the contents of GUIPCAR_2011

Each team drafted the contents of GUIPCAR_11. The panelists developed recommendations based on the scientific evidence and on their clinical experience. The entire contents were reviewed by the group of experts.

Editing GUIPCAR_2011

In the final phase the documents produced by the different expert groups were organized and edited into a single final document. A Rapid Guideline for RA management was written, and a summary of the principal recommendations was made, describing the level of scientific evidence for each and the strength of the recommendation.

Preliminary phase: Structure of GUIPCAR_2011 and task assignment

In March 2011 a meeting was held with the experts responsible for drafting GUIPCAR_2011 and the SER investigators. At this meeting it was decided that GUIPCAR_2011 would be organized in 8 chapters: I. Methodology; II. Background; III. Diagnosis; IV. Evaluation; V.

Pharmacological treatment; VI. Safety of pharmacological treatment; VII. Other treatments; and VIII. Management. In drafting GUIPCAR_2011 the longest chapters were separated into sections. The drafting of each chapter or section was assigned to a working team made up of various panelists (from 1 to 3), so that each panelist was part of at least two teams, except for the physical therapists, the primary care physician and the nurse, who were assigned a single chapter or section directly related with their specialty (Other treatments; Nursing diagnosis and consultation, respectively).

The length of the literature review was also decided at this meeting, and the experts were offered the possibility of formulating research questions for the reviewers to be answered by the corresponding literature review. Finally, a working calendar was established and responsibilities were assigned.

Each working team developed the outline for the contents of the section or chapter to which it had been assigned. TAISS coordinated the receipt of all the contents and their incorporation into a single document, which was circulated to the entire group of experts for approval.

Review of the evidence

I.1.1. Summary

The group of reviewers of the Spanish Society of Rheumatology performed the reviews updating the previous GUIPCAR systematic literature reviews.

Specifically, the search strategy was reproduced and improved, adding the drugs approved following the publication of the first version of the guide and following the same criteria for study selection. All was carried out by three reviewers. The data extraction was performed by two of them working independently. After the information was collected, the third reviewer introduced all the data in the Review Manager software program and produced the systematic review and meta-analysis, where appropriate.

The following systematic reviews have been developed:

SYSTEMATIC REVIEWS OF RA DIAGNOSIS AND EVALUATION

SR 1. Value of anti-CCP in RA diagnosis and prognosis

SR 2. Value of the sonogram or ultrasound as predictor of radiologic joint damage in recent-onset RA

SR 3. Value of MR as predictor of radiologic joint damage in recent-onset RA (<5 years)

SYSTEMATIC REVIEWS OF RA COMORBIDITY

SR 4. Efficacy and safety of statins in RA patients

SR 5. Incidence of heart failure in RA with or without anti-TNFs

SYSTEMATIC REVIEWS OF TREATMENT

- Comparison of drug efficacy

SR 6. Comparative efficacy of non-biological DMARDs in monotherapy and combination therapy

- Questions on specific aspects of drug treatment

  SR 7. Are anti-TNF agents safe when administered after severe infection or infected prosthesis?

  SR 8. What is the efficacy of combining drug treatments with disease-modifying anti-rheumatic drugs other than methotrexate?

  SR 9. Are there significant survival differences for the different DMARD treatments? If so, what grade of evidence supports these differences?

  SR 10. What is the efficacy of initial treatment following the COBRA guidelines (corticosteroids + DMARDs) versus step-up methotrexate?

  SR 11. What is the efficacy of initial combination treatment with anti-TNF and methotrexate versus step-up methotrexate?

  SR 12. What is the efficacy of initial combination treatment with non-biological DMARDs versus monotherapy?

  SR 13. How susceptible is the Spanish population to the adverse effects of sulfasalazine?

  SR 14. Do low-dose corticosteroids have any effect on the radiologic progression of rheumatoid arthritis?

  SR 15. Is it possible to suspend a biologic which has achieved a significant response and maintain this response with a classic DMARD? When there is symptomatic recurrence of RA previously treated with an anti-TNF, should treatment be instituted with the same drug or with a different anti-TNF?

  SR 16. Is a new biologic agent effective in rheumatoid arthritis patients who have not responded to usual doses of another biologic agent?

- Efficacy and safety of biologic medications

  SR 17: Efficacy and safety of infliximab, etanercept, adalimumab, anakinra, rituximab, tocilizumab, golimumab and abatacept

The reviewers took 6 months to complete all the reviews.

I.1.2. Review group of the Spanish Society of Rheumatology

The review of the evidence was carried out by the review group of the Spanish Society of Rheumatology. This group is composed of trained rheumatologists with experience in systematic literature reviews, whose main interest is the use and dissemination of the tools of so-called Evidence-Based Medicine within the community of Spanish rheumatologists.

This group has been enriched by the persons who attended the seven courses on evaluation of the evidence that have been held annually or semi-annually since 2003 in the Spanish Society of Rheumatology. A selection was made from the most capable students interested in conducting systematic literature reviews.

The group is currently made up of 24 rheumatologists who have worked on numerous systematic reviews (available at the SER website under "Grupos de Trabajo": http://www.ser.es/investigacion/Grupo_Trabajo/RBE.php).

They methodology used is based on that proposed by the Cochrane Collaboration.

I.1.3. Systematic reviews

I.1.3.a. Update of the drug reviews

A methodology similar to that of GUIPCAR was used for the reviews updating the GUIPCAR evidence, that is, those referring to drugs used in monotherapy.

- Contribution of the reviewers

The search strategy was designed by MA Abad, A Ortiz, E Loza and MP Rosario based on the original GUIPCAR strategy. MA Abad and A Ortiz selected the studies by title and abstract. E Loza made a subsequent selection, divided the articles by drug group, and obtained the primary references. Afterwaards, MA Abad and A Ortiz performed the secondary searches, data extraction, and introduced the data in Review Manager and wrote the review.

Subsequently, E Loza supervised the reviews and their conclusions.

- Criteria for study selection

Types of studies

Inclusion criteria:

- All randomized controlled trials (RCTs) comparing a biologic with placebo, with methotrexate, or their combination with a DMARD versus the biologic in monotherapy.
- All the RCTs on DMARDs that had not been included in GUIPCAR.

Types of participants

Patients over 16 years of age diagnosed with RA according to the 1987 ACR criteria, regardless of previous disease duration. By design, the patients normally have active disease, as evinced by at least two of the following parameters: number of painful joints, number of swollen joints, morning stiffness or elevated erythrocyte sedimentation rate or C-reactive protein.

Types of interventions

All efficacy studies of the following drugs were included:

- Subcutaneous (SC) etanercept, intravenous (IV) infliximab, SC adalimumab, SC anakinra, IV rituximab, IV tocilizumab, SC golimumab, SC abatacept, or their original molecules either in monotherapy or in combination with a DMARD, primarily oral or SC methotrexate. Placebo or active treatments such as oral or SC methotrexate or other DMARD were accepted as the control group.
- Methotrexate, leflunomide, cyclosporin, etc., and any other DMARD.

Types of outcome measurements

RCTs with the following outcomes were included:

1) Efficacy:
   a) Activity: ACR 20%, 50% and 70%; EULAR response, differences in DAS (28 or complete).
   b) Quality of life: differences in HAQ, % improvement in HAQ.
   c) Radiologic progression: differences in the Sharp index, differences in the modified van der Heijde index or in Larsen's index.
2) Safety: difference in percentage of adverse effects.

- Search strategy to identify studies

a) Electronic search

An improved search strategy used in the original GUIPCAR was performed, updated to 2011. Searches were made for randomized controlled clinical trials (RCCTs) in the following databases:

1) MEDLINE (July 2011)
   a) From 2006, with all drugs included.
   b) Up to 1999, with drugs not included in GUIPCAR (adalimumab, abatacept, rituximab and anakinra)
2) EMBASE (July 2011)
   a) From 2006, with all drugs included.
   b) Up to 1999, with drugs not included in GUIPCAR (adalimumab, abatacept, rituximab and anakinra)
3) Cochrane Library (July 2011).
4) *Índice Médico Español* (IME)
5) Cochrane Central and other Cochrane groups (July 2011).

Medline (July 2011)

SR 1. Diagnostic value of anti-ccp
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SR 1. Diagnostic value of anti-ccp
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SR 1. Diagnostic value of anti-ccp
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Medline (July 2011)

SR 1. Prognostic value of anti-ccp
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SR 1. Prognostic value of anti-ccp
"disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
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"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
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"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
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"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
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SR 1. Prognostic value of anti-ccp
Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"cyclic citrullinated peptide"[Supplementary Concept] OR "cyclic citrullinated peptide"[All Fields] OR "ccp peptide"[All Fields]
"antibodies"[MeSH Terms] OR "antibodies"[All Fields]
"cyclic citrullinated peptide"[Supplementary Concept] OR "cyclic citrullinated peptide"[All Fields]
"peptides, cyclic"[MeSH Terms] OR ("peptides"[All Fields] AND "cyclic"[All Fields]) OR "cyclic peptides"[All Fields] OR ("cyclic"[All Fields] AND "peptides"[All Fields])
"prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields]
"incidence"[MeSH Terms:noexp]
"mortality"[MeSH Terms]
"follow-up studies"[MeSH Terms:noexp]

Medline (July 2011)

SR 2. Value of the sonogram or ultrasound as predictor of radiologic joint damage in recent-onset RA
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
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"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
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"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
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"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
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"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
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"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
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"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
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"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
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"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
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"ultrasonography"[MeSH Terms] OR "ultrasonography"[All Fields] OR ("tomography"[All Fields] AND "ultrasonic"[All Fields]) OR "tomography, ultrasonic"[All Fields]
"ultrasonography"[MeSH Terms] OR "ultrasonography"[All Fields] OR ("ultrasonic"[All Fields] AND "tomography"[All Fields]) OR "ultrasonic tomography"[All Fields]
"ultrasonography"[MeSH Terms] OR "ultrasonography"[All Fields] OR ("diagnosis"[All Fields] AND "ultrasonic"[All Fields])
"ultrasonography"[MeSH Terms] OR "ultrasonography"[All Fields] OR ("diagnoses"[All Fields] AND "ultrasonic"[All Fields])
"ultrasonography"[MeSH Terms] OR "ultrasonography"[All Fields] OR ("ultrasonic"[All Fields] AND "diagnoses"[All Fields]) OR "ultrasonic diagnoses"[All Fields]
"ultrasonography"[Subheading] OR "ultrasonography"[All Fields] OR ("ultrasonic"[All Fields] AND "diagnosis"[All Fields]) OR "ultrasonic diagnosis"[All Fields] OR "ultrasonography"[MeSH Terms] OR ("ultrasonic"[All Fields] AND "diagnosis"[All Fields]) OR "ultrasonic diagnosis"[All Fields]
"prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields]
"incidence"[MeSH Terms:noexp]
"mortality"[MeSH Terms]
"follow-up studies"[MeSH Terms:noexp]
"sensitivity and specificity"[MeSH Terms]
"diagnosis"[MeSH Terms:noexp]
"diagnosis, differential"[MeSH Terms:noexp]
"diagnosis"[Subheading:noexp]

Medline (July 2011)

RS 3. Value of MR as predictor of radiologic joint damage in recent-onset RA (< 5 years)
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])

RS 3. Value of MR as predictor of radiologic joint damage in recent-onset RA (< 5 years)
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All

RS 3. Value of MR as predictor of radiologic joint damage in recent-onset RA (< 5 years)
Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"Bildgebung"[Journal] OR "imaging"[All Fields]
"magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR ("imaging"[All Fields] AND "magnetic"[All Fields] AND "resonance"[All Fields]) OR "imaging, magnetic resonance"[All Fields]
"magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "nmr"[All Fields]
"magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR ("tomography"[All Fields] AND "mr"[All Fields])
"magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR ("mr"[All Fields] AND "tomography"[All Fields]) OR "mr tomography"[All Fields]
"tomography, x-ray computed"[MeSH Terms] OR ("tomography"[All Fields] AND "x-ray"[All Fields] AND "computed"[All Fields]) OR "x-ray computed tomography"[All Fields] OR "tomography"[All Fields] OR "tomography"[MeSH Terms]
"magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR ("tomography"[All Fields] AND "proton"[All Fields] AND "spin"[All Fields])
"transfer (psychology)"[MeSH Terms] OR ("transfer"[All Fields] AND "(psychology)"[All Fields]) OR "transfer (psychology)"[All Fields] OR "transfer"[All Fields]
"magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "mri"[All Fields]
"radionuclide imaging"[MeSH Terms] OR ("radionuclide"[All Fields] AND "imaging"[All Fields]) OR "radionuclide imaging"[All Fields] OR "scan"[All Fields]
"J Mol Catal A Chem"[Journal] OR "chemical"[All Fields]
"vibration"[MeSH Terms] OR "vibration"[All Fields] OR "resonance"[All Fields]
"magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "fmri"[All Fields]
"prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields]
"incidence"[MeSH Terms:noexp]
"mortality"[MeSH Terms]
"follow-up studies"[MeSH Terms:noexp]
"sensitivity and specificity"[MeSH Terms]
"diagnosis"[MeSH Terms:noexp]
"diagnosis, differential"[MeSH Terms:noexp]
"diagnosis"[Subheading:noexp]

Medline (July 2011)

SR 4. Efficacy and safety of statins in RA patients
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All

SR 4. Efficacy and safety of statins in RA patients
Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All

SR 4. Efficacy and safety of statins in RA patients
Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
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"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"coenzymes"[MeSH Terms] OR "coenzymes"[All Fields] OR "coenzyme"[All Fields]
"coenzyme a"[MeSH Terms] OR "coenzyme a"[All Fields]
"3-hydroxy-3-methylglutaryl-coenzyme A"[Supplementary Concept] OR "3-hydroxy-3-methylglutaryl-coenzyme A"[All Fields] OR "hmg coa"[All Fields]
"hydroxymethylglutaryl-coa-reductases, nadp-dependent"[MeSH Terms] OR ("hydroxymethylglutaryl-coa-reductases"[All Fields] AND "nadp-dependent"[All Fields]) OR "nadp-dependent hydroxymethylglutaryl-coa-reductases"[All Fields] OR ("hmg"[All Fields] AND "coa"[All Fields] AND "reductase"[All Fields]) OR "hmg coa reductase"[All Fields] OR "hydroxymethylglutaryl coa reductases"[MeSH Terms] OR ("hydroxymethylglutaryl"[All Fields] AND "coa"[All Fields] AND "reductases"[All Fields]) OR "hydroxymethylglutaryl coa reductases"[All Fields] OR ("hmg"[All Fields] AND "coa"[All Fields] AND "reductase"[All Fields])
"3-hydroxy-3-methylglutaryl-coenzyme A"[Supplementary Concept] OR "3-hydroxy-3-methylglutaryl-coenzyme A"[All Fields] OR "hmg coa"[All Fields]
"hydroxymethylglutaryl-coa-reductases, nadp-dependent"[MeSH Terms] OR ("hydroxymethylglutaryl-coa-reductases"[All Fields] AND "nadp-dependent"[All Fields]) OR "nadp-dependent hydroxymethylglutaryl-coa-reductases"[All Fields] OR ("hmg"[All Fields] AND "coa"[All Fields] AND "reductase"[All Fields]) OR "hmg coa reductase"[All Fields] OR "hydroxymethylglutaryl coa reductases"[MeSH Terms] OR ("hydroxymethylglutaryl"[All Fields] AND "coa"[All Fields] AND "reductases"[All Fields]) OR "hydroxymethylglutaryl coa reductases"[All Fields] OR ("hmg"[All Fields] AND "coa"[All Fields] AND "reductase"[All Fields])
"3-hydroxy-3-methylglutaryl-coenzyme A"[Supplementary Concept] OR "3-hydroxy-3-methylglutaryl-coenzyme A"[All Fields] OR "hydroxymethylglutaryl coa"[All Fields]
"hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR ("hydroxymethylglutaryl"[All Fields] AND "coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl coa reductase inhibitors"[All Fields] OR "hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action]
"3-hydroxy-3-methylglutaryl-coenzyme A"[Supplementary Concept] OR "3-hydroxy-3-methylglutaryl-coenzyme A"[All Fields] OR "hydroxymethylglutaryl coa"[All Fields]
"hydroxymethylglutaryl coa reductases"[MeSH Terms] OR ("hydroxymethylglutaryl"[All Fields] AND "coa"[All Fields] AND "reductases"[All Fields]) OR "hydroxymethylglutaryl coa reductases"[All Fields] OR ("hydroxymethylglutaryl"[All Fields] AND "coa"[All Fields] AND "reductase"[All Fields]) OR "hydroxymethylglutaryl coa reductase"[All Fields]
"antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields]
"hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR ("inhibitors"[All Fields] AND "hydroxymethylglutaryl"[All Fields] AND "coa"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action]
"oxidoreductases"[MeSH Terms] OR "oxidoreductases"[All Fields] OR "reductase"[All Fields]
"hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR

SR 4. Efficacy and safety of statins in RA patients
"statins"[All Fields] OR "hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("outcome"[All Fields] AND "treatment"[All Fields]) OR "outcome, treatment"[All Fields]
"rehabilitation"[Subheading] OR "rehabilitation"[All Fields] OR "rehabilitation"[MeSH Terms]
"therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]

Medline (July 2011)

SR 5. Incidence of heart failure in RA with or without anti-TNFs
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("cardiac"[All Fields] AND "failure"[All Fields]) OR "cardiac failure"[All Fields]
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("myocardial"[All Fields] AND "failure"[All Fields]) OR "myocardial failure"[All Fields]
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("heart"[All Fields] AND "failure"[All Fields] AND "left"[All Fields] AND "sided"[All Fields])
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("heart"[All Fields] AND "failure"[All Fields] AND "left"[All Fields] AND "sided"[All Fields])
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("left"[All Fields] AND "sided"[All Fields] AND "heart"[All Fields] AND "failure"[All Fields]) OR "left sided heart failure"[All Fields]
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("left"[All Fields] AND "sided"[All Fields] AND "heart"[All Fields] AND "failure"[All Fields]) OR "left sided heart failure"[All Fields]
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("heart"[All Fields] AND "failure"[All Fields] AND "right"[All Fields] AND "sided"[All Fields])
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("heart"[All Fields] AND "failure"[All Fields] AND "right"[All Fields] AND "sided"[All Fields])
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("right"[All Fields] AND "sided"[All Fields] AND "heart"[All Fields] AND "failure"[All Fields]) OR "right sided heart failure"[All Fields]
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("right"[All Fields] AND "sided"[All Fields] AND "heart"[All Fields] AND "failure"[All Fields]) OR "right sided heart failure"[All Fields]
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("congestive"[All Fields] AND "heart"[All Fields] AND "failure"[All Fields]) OR "congestive heart failure"[All Fields]
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("heart"[All Fields] AND "failure"[All Fields] AND "congestive"[All Fields]) OR "heart failure, congestive"[All Fields]
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("heart"[All Fields] AND "decompensation"[All Fields]) OR "heart decompensation"[All Fields]
"heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("decompensation"[All Fields] AND "heart"[All Fields])
"publishing"[MeSH Terms] OR "publishing"[All Fields] OR "publication"[All Fields] OR "publications"[MeSH Terms] OR "publications"[All Fields]
"hispanic americans"[MeSH Terms] OR ("hispanic"[All Fields] AND "americans"[All Fields]) OR "hispanic americans"[All Fields] OR "spanish"[All Fields]
"ventricular function"[MeSH Terms] OR ("ventricular"[All Fields] AND "function"[All Fields]) OR "ventricular function"[All Fields] OR ("function"[All Fields] AND "ventricular"[All Fields]) OR "function, ventricular"[All Fields]
"ventricular function"[MeSH Terms] OR ("ventricular"[All Fields] AND "function"[All Fields]) OR "ventricular function"[All Fields] OR ("functions"[All Fields] AND "ventricular"[All Fields])
"ventricular function"[MeSH Terms] OR ("ventricular"[All Fields] AND "function"[All Fields]) OR "ventricular function"[All Fields] OR ("ventricular"[All Fields] AND "functions"[All Fields]) OR "ventricular functions"[All Fields]
"cohort studies"[MeSH Terms]
"incidence"[MeSH Terms:noexp]
"mortality"[MeSH Terms]
"follow-up studies"[MeSH Terms:noexp]
"predictive value of tests"[MeSH Terms]
"observer variation"[MeSH Terms]
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])

SR 5. Incidence of heart failure in RA with or without anti-TNFs
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All

SR 5. Incidence of heart failure in RA with or without anti-TNFs
Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]

Medline (July 2011)

SR 6. Comparative efficacy of non-biological DMARDs in monotherapy and combination therapy
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All

SR 6. Comparative efficacy of non-biological DMARDs in monotherapy and combination therapy
Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields]

SR 6. Comparative efficacy of non-biological DMARDs in monotherapy and combination therapy
OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"methotrexate"[MeSH Terms] OR "methotrexate"[All Fields]
"sulphasalazine"[All Fields] OR "sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulphasalazine"[All Fields] OR "sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "salazosulfapyridine"[All Fields]
"cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "cyclosporin"[All Fields]
"cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "cyclosporin a"[All Fields]
"cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "cyclosporin a"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields] OR "arava"[All Fields]
"penicillamine"[MeSH Terms] OR "penicillamine"[All Fields] OR "d penicillamine"[All Fields]
"penicillamine"[MeSH Terms] OR "penicillamine"[All Fields]
"antimalarials"[MeSH Terms] OR "antimalarials"[All Fields] OR "antimalarial"[All Fields] OR "antimalarials"[Pharmacological Action]
"chloroquine"[MeSH Terms] OR "chloroquine"[All Fields]
"hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields]
"antimalarials"[MeSH Terms] OR "antimalarials"[All Fields] OR ("antimalarial"[All Fields] AND "agent"[All Fields]) OR "antimalarial agent"[All Fields] OR "antimalarials"[Pharmacological Action]
"azathioprine"[MeSH Terms] OR "azathioprine"[All Fields]
"gold"[MeSH Terms] OR "gold"[All Fields]
"sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields] OR "salt"[All Fields]
"therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR "aurothiomalate"[All Fields]
"gold sodium thiosulfate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiosulfate"[All Fields]) OR "gold sodium thiosulfate"[All Fields] OR ("sodium"[All Fields] AND "aurothiosulfate"[All Fields]) OR "sodium aurothiosulfate"[All Fields]
"auranofin"[MeSH Terms] OR "auranofin"[All Fields]
"cyclophosphamide"[MeSH Terms] OR "cyclophosphamide"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "monoclonal antibody ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "mab ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "remicade"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "recombinant human dimeric tnf receptor type ii igg fusion protein"[All Fields]

SR 6. Comparative efficacy of non-biological DMARDs in monotherapy and combination therapy
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "enbrel"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields] OR "humira"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "belatacept"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "lea29y"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "bms 224818"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "ctla 4 ig"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "cytotoxic t lymphocyte associated antigen 4 immunoglobulin"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "ctla4 fc"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "ctla4 ig"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "orencia"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "bms 188667"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "bms 188667"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "cdp 870"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "cimzia"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "certolizumab pegol"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("urine"[All Fields] AND "derived"[All Fields] AND "il1"[All Fields] AND "inhibitor"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("il1"[All Fields] AND "inhibitor"[All Fields] AND "urine"[All Fields] AND "derived"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("urine"[All Fields] AND "derived"[All Fields] AND "il1"[All Fields] AND "inhibitor"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("il1"[All Fields] AND "febrile"[All Fields] AND "inhibitor"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("febrile"[All Fields] AND "inhibitor"[All Fields] AND "il1"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields]
"urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "urine il 1 inhibitor"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("il"[All Fields] AND "1ra"[All Fields]) OR "il 1ra"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "kineret"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("amgen"[All Fields] AND "brand"[All Fields] AND "anakinra"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("anakinra"[All Fields] AND "amgen"[All Fields] AND "brand"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "antril"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("synergen"[All Fields] AND "brand"[All Fields] AND "anakinra"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("anakinra"[All Fields] AND "synergen"[All Fields] AND "brand"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "anakinra"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "mabthera"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "rituxan"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "idec c2b8 antibody"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "idec c2b8"[All Fields]
"tocilizumab"[Supplementary Concept] OR "tocilizumab"[All Fields] OR "actemra"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("necrosis"[All Fields] AND "factors"[All Fields] AND "tumor"[All Fields])
"ligands"[MeSH Terms] OR "ligands"[All Fields] OR "ligand"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tnf"[All Fields] AND "receptor"[All Fields]) OR "tnf receptor"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("receptor"[All Fields] AND "ligands"[All Fields] AND "tnf"[All Fields])
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "superfamily"[All Fields] AND "ligands"[All Fields]) OR "tumor necrosis factor superfamily ligands"[All Fields]
"tumour necrosis factor alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND

SR 6. Comparative efficacy of non-biological DMARDs in monotherapy and combination therapy
"necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor-alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor-alpha"[All Fields]) OR "Tumor Necrosis Factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor"[All Fields] AND "alpha"[All Fields]) OR "Tumor Necrosis Factor alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields])
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SR 6. Comparative efficacy of non-biological DMARDs in monotherapy and combination therapy
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SR 6. Comparative efficacy of non-biological DMARDs in monotherapy and combination therapy
Fields] OR ("study"[All Fields] AND "double"[All Fields] AND "blind"[All Fields])
"clinical trial, phase i"[Publication Type] OR "clinical trials, phase i as topic"[MeSH Terms] OR "clinical trial phase i"[All Fields] OR "phase i clinical trial"[All Fields]
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"randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]
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SR 6. Comparative efficacy of non-biological DMARDs in monotherapy and combination therapy
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("experimental"[All Fields] AND "design"[All Fields]) OR "experimental design"[All Fields]
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Medline (July 2011)

SR 7. Are anti-TNF agents safe when administered after severe infection or infected prosthesis?
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("outcome"[All Fields] AND "treatment"[All Fields]) OR "outcome, treatment"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("rehabilitation"[All Fields] AND "outcome"[All Fields]) OR "rehabilitation outcome"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("outcome"[All Fields] AND "rehabilitation"[All Fields]) OR "outcome, rehabilitation"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("treatment"[All Fields] AND "effectiveness"[All Fields]) OR "treatment effectiveness"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("effectiveness"[All Fields] AND "treatment"[All Fields]) OR "effectiveness, treatment"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("treatment"[All Fields] AND "efficacy"[All Fields]) OR "treatment efficacy"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("efficacy"[All Fields] AND "treatment"[All Fields])
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("necrosis"[All Fields] AND "factors"[All Fields] AND "tumor"[All Fields])

SR 7. Are anti-TNF agents safe when administered after severe infection or infected prosthesis?
"ligands"[MeSH Terms] OR "ligands"[All Fields] OR "ligand"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tnf"[All Fields] AND "receptor"[All Fields]) OR "tnf receptor"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("receptor"[All Fields] AND "ligands"[All Fields] AND "tnf"[All Fields])
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "superfamily"[All Fields] AND "ligands"[All Fields]) OR "tumor necrosis factor superfamily ligands"[All Fields]
"tumour necrosis factor alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor-alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor-alpha"[All Fields]) OR "Tumor Necrosis Factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor"[All Fields] AND "alpha"[All Fields]) OR "Tumor Necrosis Factor alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields])
"cachectin tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("cachectin"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "cachectin tumor necrosis factor"[All Fields]
"cachectin tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("cachectin"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "cachectin tumor necrosis factor"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "tnfalpha"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields]) OR "tnf alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields])
"tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "cachectin"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptors"[All Fields] AND "cachectin"[All Fields])
"tumour necrosis factor receptors"[All Fields] OR "receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "receptors"[All Fields])
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptor"[All Fields] AND "tnf"[All Fields]) OR "receptor, tnf"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tnf"[All Fields] AND "receptors"[All Fields]) OR "tnf receptors"[All Fields]
"tumour necrosis factor receptor"[All Fields] OR "receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "receptor"[All Fields]) OR "tumor necrosis factor receptor"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("cachectin"[All Fields] AND "receptors"[All Fields]) OR "cachectin receptors"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptors"[All Fields] AND "tnf"[All Fields]) OR "receptors, tnf"[All Fields]
"antibodies, monoclonal"[MeSH Terms] OR ("antibodies"[All Fields] AND "monoclonal"[All Fields]) OR "monoclonal antibodies"[All Fields] OR ("monoclonal"[All Fields] AND "antibodies"[All Fields])
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "monoclonal antibody ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "mab ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "remicade"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]

SR 7. Are anti-TNF agents safe when administered after severe infection or infected prosthesis?
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "recombinant human dimeric tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "enbrel"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields] OR "humira"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields]
"immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "antibody"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields]
"necrosis"[MeSH Terms] OR "necrosis"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR "pyemia"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR "pyemias"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR "pyohemia"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR "pyaemia"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields]
"septicaemia"[All Fields] OR "sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR "septicemia"[All Fields] OR "Septicemia"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR "septicemias"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR ("poisoning"[All Fields] AND "blood"[All Fields]) OR "poisoning, blood"[All Fields]
"toxemia"[MeSH Terms] OR "toxemia"[All Fields] OR ("blood"[All Fields] AND "poisoning"[All Fields]) OR "blood poisoning"[All Fields] OR "sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR ("blood"[All Fields] AND "poisoning"[All Fields]) OR "blood poisoning"[All Fields] OR "bacteremia"[MeSH Terms] OR "bacteremia"[All Fields] OR ("blood"[All Fields] AND "poisoning"[All Fields])
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR ("blood"[All Fields] AND "poisonings"[All Fields]) OR "blood poisonings"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR ("poisonings"[All Fields] AND "blood"[All Fields])
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR ("severe"[All Fields] AND "sepsis"[All Fields]) OR "severe sepsis"[All Fields]
"sepsis"[MeSH Terms] OR "sepsis"[All Fields] OR ("sepsis"[All Fields] AND "severe"[All Fields]) OR "sepsis, severe"[All Fields]
"infection"[MeSH Terms] OR "infection"[All Fields] OR "infections"[All Fields]
"prosthesis-related infections"[MeSH Terms] OR ("prosthesis-related"[All Fields] AND "infections"[All Fields]) OR "prosthesis-related infections"[All Fields] OR ("prosthesis"[All Fields] AND "related"[All Fields] AND "infections"[All Fields]) OR "prosthesis related infections"[All Fields]
"prosthesis-related infections"[MeSH Terms] OR ("prosthesis-related"[All Fields] AND "infections"[All Fields]) OR "prosthesis-related infections"[All Fields] OR ("infections"[All Fields] AND "prosthesis"[All Fields] AND "related"[All Fields])
"prosthesis implantation"[MeSH Terms] OR ("prosthesis"[All Fields] AND "implantation"[All Fields]) OR "prosthesis implantation"[All Fields] OR "prosthesis"[All Fields] OR "prostheses and implants"[MeSH Terms] OR ("prostheses"[All Fields] AND "implants"[All Fields]) OR "prostheses and implants"[All Fields]
"prosthesis-related infections"[MeSH Terms] OR ("prosthesis-related"[All Fields] AND "infections"[All Fields]) OR "prosthesis-related infections"[All Fields] OR ("prosthesis"[All Fields] AND "related"[All Fields] AND "infection"[All Fields]) OR "prosthesis related infection"[All Fields]

Medline (July 2011)

SR. 8. What is the efficacy of combining drug treatments with disease-modifiying anti-rheumatic drugs other than metrotexate?
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All

Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])

"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("necrosis"[All Fields] AND "factors"[All Fields] AND "tumor"[All Fields])
"ligands"[MeSH Terms] OR "ligands"[All Fields] OR "ligand"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tnf"[All Fields] AND "receptor"[All Fields]) OR "tnf receptor"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("receptor"[All Fields] AND "ligands"[All Fields] AND "tnf"[All Fields])
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"tumour necrosis factor alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor-alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor-alpha"[All Fields]) OR "Tumor Necrosis Factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor"[All Fields] AND "alpha"[All Fields]) OR "Tumor Necrosis Factor alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields])
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"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "tnfalpha"[All Fields]
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"tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All

Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor"[All Fields]
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"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "cachectin"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptors"[All Fields] AND "cachectin"[All Fields])
"tumour necrosis factor receptors"[All Fields] OR "receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "receptors"[All Fields])
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"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptors"[All Fields] AND "tnf"[All Fields]) OR "receptors, tnf"[All Fields]
"antibodies, monoclonal"[MeSH Terms] OR ("antibodies"[All Fields] AND "monoclonal"[All Fields]) OR "monoclonal antibodies"[All Fields] OR ("monoclonal"[All Fields] AND "antibodies"[All Fields])
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "monoclonal antibody ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "mab ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "remicade"[All Fields]
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"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
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"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
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"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "recombinant human dimeric tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "enbrel"[All Fields]
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"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]
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"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields] OR "humira"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields]
"immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "antibody"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields]
"necrosis"[MeSH Terms] OR "necrosis"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields]
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"antirheumatic agents"[MeSH Terms] OR ("antirheumatic"[All Fields] AND "agents"[All Fields]) OR "antirheumatic agents"[All

Fields] OR ("antirheumatic"[All Fields] AND "drugs"[All Fields] AND "disease"[All Fields] AND "modifying"[All Fields]) OR "antirheumatic agents"[Pharmacological Action]
"disease"[MeSH Terms] OR "disease"[All Fields]
"antirheumatic agents"[MeSH Terms] OR ("antirheumatic"[All Fields] AND "agents"[All Fields]) OR "antirheumatic agents"[All Fields] OR ("drugs"[All Fields] AND "disease"[All Fields] AND "modifying"[All Fields] AND "antirheumatic"[All Fields]) OR "antirheumatic agents"[Pharmacological Action]
"pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "drugs"[All Fields]
"antirheumatic agents"[MeSH Terms] OR ("antirheumatic"[All Fields] AND "agents"[All Fields]) OR "antirheumatic agents"[All Fields] OR "dmard"[All Fields] OR "antirheumatic agents"[Pharmacological Action]
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"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "salicylazosulfapyridine"[All Fields]
"sulphasalazine"[All Fields] OR "sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "salazosulfapyridine"[All Fields]
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"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "azulfidine"[All Fields]
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"antimalarials"[MeSH Terms] OR "antimalarials"[All Fields] OR ("drugs"[All Fields] AND "antimalarial"[All Fields]) OR "antimalarials"[Pharmacological Action]
"antimalarials"[MeSH Terms] OR "antimalarials"[All Fields] OR ("anti"[All Fields] AND "malarials"[All Fields]) OR "anti malarials"[All Fields] OR "antimalarials"[Pharmacological Action]
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"antimalarials"[MeSH Terms] OR "antimalarials"[All Fields] OR ("antimalarial"[All Fields] AND "agents"[All Fields]) OR "antimalarial agents"[All Fields] OR "antimalarials"[Pharmacological Action]
"antimalarials"[MeSH Terms] OR "antimalarials"[All Fields] OR ("agents"[All Fields] AND "antimalarial"[All Fields]) OR "antimalarials"[Pharmacological Action]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields] OR "hwa 486"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields] OR "hwa 486"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields] OR "su101"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields] OR "arava"[All Fields]
"3-bromoacetoxyandrostan-17-one"[Supplementary Concept] OR "3-bromoacetoxyandrostan-17-one"[All Fields] OR "brand"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields]

"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("sodium"[All Fields] AND "thiomalate"[All Fields] AND "gold"[All Fields]) OR "sodium thiomalate, gold"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("sodium"[All Fields] AND "aurothiomalate"[All Fields]) OR "sodium aurothiomalate"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("aurothiomalate"[All Fields] AND "sodium"[All Fields])
"succinic acid"[MeSH Terms] OR ("succinic"[All Fields] AND "acid"[All Fields]) OR "succinic acid"[All Fields] OR ("butanedioic"[All Fields] AND "acid"[All Fields]) OR "butanedioic acid"[All Fields]
"asian continental ancestry group"[MeSH Terms] OR ("asian"[All Fields] AND "continental"[All Fields] AND "ancestry"[All Fields] AND "group"[All Fields]) OR "asian continental ancestry group"[All Fields] OR "mongoloid"[All Fields]
"sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields] OR "salt"[All Fields]
"sodium, dietary"[MeSH Terms] OR ("sodium"[All Fields] AND "dietary"[All Fields]) OR "dietary sodium"[All Fields] OR "sodium"[All Fields] OR "sodium"[MeSH Terms]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("sodium"[All Fields] AND "gold"[All Fields] AND "thiomalate"[All Fields]) OR "sodium gold thiomalate"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("gold"[All Fields] AND "thiomalate"[All Fields] AND "sodium"[All Fields])
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("gold"[All Fields] AND "disodium"[All Fields] AND "thiomalate"[All Fields] AND "monohydrate"[All Fields])
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("gold"[All Fields] AND "thiomalate"[All Fields]) OR "gold thiomalate"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("thiomalate"[All Fields] AND "gold"[All Fields]) OR "thiomalate, gold"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("gold"[All Fields] AND "thiomalic"[All Fields] AND "acid"[All Fields])
"theophylline"[MeSH Terms] OR "theophylline"[All Fields] OR "aerolate"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("taylor"[All Fields] AND "brand"[All Fields] AND "gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields])
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"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR "myocrysine"[All Fields]
"gold"[MeSH Terms] OR "gold"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("aventis"[All Fields] AND "brand"[All Fields] AND "gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields])
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("merck"[All Fields] AND "brand"[All Fields] AND "gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields])
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR "myocrisin"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR "tauredon"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("altana"[All Fields] AND "pharma"[All Fields] AND "brand"[All Fields] AND "gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields])
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR "aurothiomalate"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR ("rubio"[All Fields] AND "brand"[All Fields] AND "gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields])
"humans"[MeSH Terms]

Medline (July 2011)

RS 9. Are there significant survival differences for the different DMARD treatments? If so, what grade of evidence supports these differences?
"Antirheumatic Agents/therapeutic use"[MeSH:noexp] OR "Antirheumatic Agents"[Pharmacological Action] AND ("Arthritis, Rheumatoid/drug therapy"[MeSH:noexp] OR "Arthritis, Rheumatoid/therapy"[MeSH:noexp]) OR "inflammatory polyarthritis"[All Fields] AND "Gold/therapeutic use"[MeSH] OR "Gold Sodium Thiomalate/therapeutic use"[MeSH] OR "Gold Sodium Thiosulfate/therapeutic use"[MeSH] OR "Gold Compounds/therapeutic use"[MeSH] OR "Auranofin/therapeutic use"[MeSH] AND "Survival Analysis"[MeSH] OR "drug survival"[All Fields] AND (English[lang] OR Spanish[lang]) AND "humans"[MeSH Terms]
"Antirheumatic Agents/therapeutic use"[MeSH:noexp] OR "Antirheumatic Agents"[Pharmacological Action] AND ("Arthritis, Rheumatoid/drug therapy"[MeSH:noexp] OR "Arthritis, Rheumatoid/therapy"[MeSH:noexp]) OR "inflammatory polyarthritis"[All Fields] OR "chronic arthritis"[All Fields] AND ("Survival Analysis"[MeSH] OR "drug analysis"[All Fields]) AND

RS 9. Are there significant survival differences for the different DMARD treatments? If so, what grade of evidence supports these differences?
"Sulfasalazine/therapeutic use"[MeSH] AND (English[lang] OR Spanish[lang]) AND "humans"[MeSH Terms]
"Antirheumatic Agents/therapeutic use"[MeSH] OR "Antirheumatic Agents"[Pharmacological Action] OR "Cyclosporine/therapeutic use"[MeSH] AND ("Arthritis, Rheumatoid/drug therapy"[MeSH:noexp] OR "Arthritis, Rheumatoid/therapy"[MeSH:noexp]) AND "Survival Analysis"[MeSH] OR "drug survival"[All Fields] AND English[lang] AND "humans"[MeSH Terms] AND (English[lang] OR Spanish[lang]) AND "humans"[MeSH Terms]
"Antirheumatic Agents/therapeutic use"[MeSH:noexp] OR "Antirheumatic Agents"[Pharmacological Action] OR "Azathioprine/therapeutic use"[MeSH:noexp] AND ("Arthritis, Rheumatoid/drug therapy"[MeSH:noexp] OR "Arthritis, Rheumatoid/therapy"[MeSH:noexp]) AND "Survival Analysis"[MeSH] OR "drug survival"[All Fields] AND (English[lang] OR Spanish[lang]) AND "humans"[MeSH Terms]
"Antirheumatic Agents/therapeutic use"[MeSH:noexp] OR "Antirheumatic Agents"[Pharmacological Action] OR "Chlorambucil/therapeutic use"[MeSH:noexp] AND "Arthritis, Rheumatoid"[MeSH] AND "Survival Analysis"[MeSH] OR "drug survival"[All Fields] AND (English[lang] OR Spanish[lang]) AND "humans"[MeSH Terms]
"Antirheumatic Agents/therapeutic use"[MeSH] OR "Antirheumatic Agents"[Pharmacological Action] OR "leflunomide"[Substance Name] AND "Arthritis, Rheumatoid"[MeSH] OR "inflammatory polyarthritis"[All Fields] OR "chronic arthritis"[All Fields] AND "Survival Analysis"[MeSH] OR "drug survival"[All Fields] AND (English[lang] OR Spanish[lang]) AND "humans"[MeSH Terms]
"Antirheumatic Agents/therapeutic use"[MeSH:noexp] OR "Antirheumatic Agents"[Pharmacological Action] OR ("Antimalarials/therapeutic use"[MeSH] OR "Antimalarials/therapy"[MeSH]) OR ("Chloroquine/drug therapy"[MeSH] OR "Chloroquine/therapeutic use"[MeSH] OR "Chloroquine/therapy"[MeSH]) OR "Hydroxychloroquine/therapeutic use"[MeSH] AND "Arthritis, Rheumatoid"[MeSH:noexp] AND "Survival Analysis"[MeSH] OR "drug survival"[All Fields]
"Methotrexate"[MeSH] AND "Arthritis, Rheumatoid"[MeSH] OR "inflammatory polyarthritis"[All Fields] OR "chronic arthritis"[All Fields] AND "Survival Analysis"[MeSH] OR "drug survival"[All Fields] AND English[lang] AND "humans"[MeSH Terms] AND (English[lang] OR Spanish[lang])
(anti[All Fields] AND (tumor necrosis factor alpha[Text Word] OR tumour necrosis factor alpha[Text Word] OR "tumor necrosis factor-alpha"[MeSH Terms])) OR (anakinra) AND ("arthritis, rheumatoid"[MeSH Terms] OR rheumatoid arthritis[Text Word]) AND drug survival
"Antirheumatic Agents/therapeutic use"[MeSH:noexp] OR "Antirheumatic Agents"[Pharmacological Action] AND ("Arthritis, Rheumatoid/drug therapy"[MeSH:noexp] OR "Arthritis, Rheumatoid/therapy"[MeSH:noexp]) OR "inflammatory polyarthritis"[All Fields] AND "Gold/therapeutic use"[MeSH] OR "Gold Sodium Thiomalate/therapeutic use"[MeSH] OR "Gold Sodium Thiosulfate/therapeutic use"[MeSH] OR "Gold Compounds/therapeutic use"[MeSH] OR "Auranofin/therapeutic use"[MeSH] OR "Sulfasalazine/therapeutic use"[MeSH] OR "Cyclosporine/therapeutic use"[MeSH] OR "Azathioprine/therapeutic use"[MeSH] OR "Cyclophosphamide/therapeutic use"[MeSH:noexp] OR "Chlorambucil/therapeutic use"[MeSH:noexp] OR "Penicillamine/therapeutic use"[MeSH:noexp] OR "leflunomide"[Substance Name] OR ("Chloroquine/therapeutic use"[MeSH] OR "Chloroquine/therapy"[MeSH]) OR "Hydroxychloroquine/therapeutic use"[MeSH] AND "Survival Analysis"[MeSH] OR "drug survival"[All Fields] AND (English[lang] OR Spanish[lang]) AND "humans"[MeSH Terms] NOT (transplantion[All Fields] OR (("transplants"[TIAB] NOT Medline[SB]) OR "transplants"[MeSH Terms] OR ("transplantation"[TIAB] NOT Medline[SB]) OR "transplantation"[MeSH Terms] OR transplant[Text Word]) OR (("neoplasms"[TIAB] NOT Medline[SB]) OR "neoplasms"[MeSH Terms] OR cancer[Text Word]) OR ("malaria"[MeSH Terms] OR malaria[Text Word]))

Medline (July 2011)

SR 10. What is the efficacy of initial treatment following the COBRA guidelines (corticosteroids+DMARDs) versus step-up methotrexate?
(escalate[All Fields] OR escalating[All Fields] OR escalation[All Fields] OR increase[All Fields] OR increased[All Fields] OR increasing[All Fields] OR ("higher dose"[Title/Abstract])) AND
("methotrexate"[MeSH Terms] OR methotrexate[Text Word]) AND
("arthritis, rheumatoid"[MeSH Terms] OR rheumatoid arthritis[Text Word]) NOT (("psoriasis"[MeSH Terms] OR Psoriasis[Text Word]) OR (("adolescent"[TIAB] NOT Medline[SB]) OR "adolescent"[MeSH Terms] OR Juvenile[Text Word]))

Medline (July 2011)

SR 11. What is the efficacy of initial combination treatment with anti-TNF and methotrexate versus step-up methotrexate?
"methotrexate"[MeSH Terms]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("necrosis"[All Fields] AND "factors"[All Fields] AND "tumor"[All Fields])
"ligands"[MeSH Terms] OR "ligands"[All Fields] OR "ligand"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tnf"[All Fields] AND "receptor"[All Fields]) OR "tnf receptor"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("receptor"[All Fields] AND "ligands"[All Fields] AND "tnf"[All Fields])
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "superfamily"[All Fields] AND "ligands"[All Fields]) OR "tumor necrosis factor superfamily ligands"[All Fields]
"tumour necrosis factor alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor

SR 11. What is the efficacy of initial combination treatment with anti-TNF and methotrexate versus step-up methotrexate?
Necrosis Factor-alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor-alpha"[All Fields]) OR "Tumor Necrosis Factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor"[All Fields] AND "alpha"[All Fields]) OR "Tumor Necrosis Factor alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields])
"cachectin tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("cachectin"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "cachectin tumor necrosis factor"[All Fields]
"cachectin tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("cachectin"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "cachectin tumor necrosis factor"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "tnfalpha"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields]) OR "tnf alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields])
"tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "cachectin"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptors"[All Fields] AND "cachectin"[All Fields])
"tumour necrosis factor receptors"[All Fields] OR "receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "receptors"[All Fields])
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptor"[All Fields] AND "tnf"[All Fields]) OR "receptor, tnf"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tnf"[All Fields] AND "receptors"[All Fields]) OR "tnf receptors"[All Fields]
"tumour necrosis factor receptor"[All Fields] OR "receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "receptor"[All Fields]) OR "tumor necrosis factor receptor"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("cachectin"[All Fields] AND "receptors"[All Fields]) OR "cachectin receptors"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptors"[All Fields] AND "tnf"[All Fields]) OR "receptors, tnf"[All Fields]
"antibodies, monoclonal"[MeSH Terms] OR ("antibodies"[All Fields] AND "monoclonal"[All Fields]) OR "monoclonal antibodies"[All Fields] OR ("monoclonal"[All Fields] AND "antibodies"[All Fields])
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "monoclonal antibody ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "mab ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "remicade"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "recombinant human dimeric tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "enbrel"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields] OR "humira"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields]
"immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "antibody"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields]
"necrosis"[MeSH Terms] OR "necrosis"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields]
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])

SR 11. What is the efficacy of initial combination treatment with anti-TNF and methotrexate versus step-up methotrexate?
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])

SR 11. What is the efficacy of initial combination treatment with anti-TNF and methotrexate versus step-up methotrexate?
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]

Medline (July 2011)

SR 12. What is the efficacy of initial combination treatment with non-biological DMARDs versus monotherapy?
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All

SR 12. What is the efficacy of initial combination treatment with non-biological DMARDs versus monotherapy?
Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]

SR 12. What is the efficacy of initial combination treatment with non-biological DMARDs versus monotherapy?
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("combination"[All Fields] AND "chemotherapy"[All Fields]) OR "combination chemotherapy"[All Fields]
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("drug"[All Fields] AND "polytherapy"[All Fields]) OR "drug polytherapy"[All Fields]
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("drug"[All Fields] AND "polytherapies"[All Fields]) OR "drug polytherapies"[All Fields]
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("polytherapies"[All Fields] AND "drug"[All Fields])
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("polytherapy"[All Fields] AND "drug"[All Fields])
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("therapy"[All Fields] AND "combination"[All Fields] AND "drug"[All Fields])
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("chemotherapy"[All Fields] AND "combination"[All Fields]) OR "chemotherapy, combination"[All Fields]
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("chemotherapies"[All Fields] AND "combination"[All Fields])
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("combination"[All Fields] AND "chemotherapies"[All Fields]) OR "combination chemotherapies"[All Fields]
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("combination"[All Fields] AND "drug"[All Fields] AND "therapy"[All Fields])
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("combination"[All Fields] AND "drug"[All Fields] AND "therapies"[All Fields]) OR "combination drug therapies"[All Fields]
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("drug"[All Fields] AND "therapies"[All Fields] AND "combination"[All Fields])
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR ("therapies"[All Fields] AND "combination"[All Fields] AND "drug"[All Fields])
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR "polychemotherapy"[All Fields]

SR 12. What is the efficacy of initial combination treatment with non-biological DMARDs versus monotherapy?
"drug therapy, combination"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields] AND "combination"[All Fields]) OR "combination drug therapy"[All Fields] OR "polychemotherapies"[All Fields]

Medline (July 2011)

SR 13. How susceptible is the Spanish population to the adverse effects of sulfasalazine?
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR

SR 13. How susceptible is the Spanish population to the adverse effects of sulfasalazine?
("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "salicylazosulfapyridine"[All Fields]
"sulphasalazine"[All Fields] OR "sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "salazosulfapyridine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("colo"[All Fields] AND "pleon"[All Fields]) OR "colo pleon"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("colo"[All Fields] AND "pleon"[All Fields]) OR "colo pleon"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "pleon"[All Fields]

SR 13. How susceptible is the Spanish population to the adverse effects of sulfasalazine?
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("sanofi"[All Fields] AND "synthelabo"[All Fields] AND "brand"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("henning"[All Fields] AND "berlin"[All Fields] AND "brand"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("ratio"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("ratio"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("ratiopharm"[All Fields] AND "brand"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("alphapharm"[All Fields] AND "brand"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("sulfasalazin"[All Fields] AND "heyl"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("sulfasalazin"[All Fields] AND "heyl"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("heyl"[All Fields] AND "brand"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("sulfasalazine"[All Fields] AND "fna"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("fna"[All Fields] AND "brand"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "ucine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("ashbourne"[All Fields] AND "brand"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "azulfidine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "salazopyrin"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("pfizer"[All Fields] AND "brand"[All Fields] AND "sulfasalazine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("sulfasalazine"[All Fields] AND "pfizer"[All Fields] AND "brand"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("pyralin"[All Fields] AND "en"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("azulfidine"[All Fields] AND "en"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("en"[All Fields] AND "azulfidine"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("sulfasalazin"[All Fields] AND "medac"[All Fields])
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR ("medac"[All Fields] AND "brand"[All Fields] AND "sulfasalazine"[All Fields])
"adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields] OR ("side"[All Fields] AND "effects"[All Fields]) OR "side effects"[All Fields]
"adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields] OR ("undesirable"[All Fields] AND "effects"[All Fields]) OR "undesirable effects"[All Fields]
"adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields] OR ("injurious"[All Fields] AND "effects"[All Fields]) OR "injurious effects"[All Fields]
"safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("drug"[All Fields] AND "toxicities"[All Fields]) OR "drug toxicities"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("toxicity"[All Fields] AND "drug"[All Fields])
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("drug"[All Fields] AND "safety"[All Fields]) OR "drug safety"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("safety"[All Fields] AND "drug"[All Fields]) OR "safety, drug"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("adverse"[All Fields] AND "drug"[All Fields] AND "reaction"[All Fields]) OR "adverse drug reaction"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("adverse"[All Fields] AND "drug"[All Fields] AND "reactions"[All Fields]) OR "adverse drug reactions"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("drug"[All Fields] AND "reaction"[All Fields] AND "adverse"[All Fields]) OR "drug reaction, adverse"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("drug"[All Fields] AND "reactions"[All Fields] AND "adverse"[All Fields]) OR "drug reactions, adverse"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("reaction"[All Fields] AND "adverse"[All Fields] AND "drug"[All Fields]) OR "reaction, adverse drug"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("reactions"[All Fields] AND "adverse"[All Fields] AND "drug"[All Fields])
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("adverse"[All Fields] AND "drug"[All Fields] AND "event"[All Fields]) OR "adverse drug event"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("adverse"[All Fields] AND "drug"[All Fields] AND "events"[All Fields]) OR "adverse drug events"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("drug"[All Fields] AND "event"[All Fields] AND "adverse"[All Fields])
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("drug"[All Fields] AND "events"[All Fields] AND "adverse"[All Fields])
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("event"[All Fields] AND "adverse"[All Fields] AND "drug"[All Fields])
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("events"[All Fields] AND "adverse"[All Fields] AND "drug"[All Fields]) OR "events, adverse drug"[All Fields]
"toxicity"[Subheading] OR "toxicity"[All Fields] OR ("toxic"[All Fields] AND "potential"[All Fields]) OR "toxic potential"[All Fields]
"toxicity"[Subheading] OR "toxicity"[All Fields] OR ("margin"[All Fields] AND "safety"[All Fields]) OR "margin of safety"[All Fields]
"mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]
"poisoning"[Subheading] OR "poisoning"[All Fields] OR ("poisonous"[All Fields] AND "effects"[All Fields]) OR "poisonous

SR 13. How susceptible is the Spanish population to the adverse effects of sulfasalazine?
effects"[All Fields] OR "poisoning"[MeSH Terms] OR ("poisonous"[All Fields] AND "effects"[All Fields]) OR "poisonous effects"[All Fields]
"drug hypersensitivity"[MeSH Terms] OR ("drug"[All Fields] AND "hypersensitivity"[All Fields]) OR "drug hypersensitivity"[All Fields] OR ("drug"[All Fields] AND "hypersensitivities"[All Fields]) OR "drug hypersensitivities"[All Fields]
"drug hypersensitivity"[MeSH Terms] OR ("drug"[All Fields] AND "hypersensitivity"[All Fields]) OR "drug hypersensitivity"[All Fields] OR ("hypersensitivities"[All Fields] AND "drug"[All Fields])
"drug hypersensitivity"[MeSH Terms] OR ("drug"[All Fields] AND "hypersensitivity"[All Fields]) OR "drug hypersensitivity"[All Fields] OR ("drug"[All Fields] AND "allergy"[All Fields]) OR "drug allergy"[All Fields]
"drug hypersensitivity"[MeSH Terms] OR ("drug"[All Fields] AND "hypersensitivity"[All Fields]) OR "drug hypersensitivity"[All Fields] OR ("allergies"[All Fields] AND "drug"[All Fields])
"drug hypersensitivity"[MeSH Terms] OR ("drug"[All Fields] AND "hypersensitivity"[All Fields]) OR "drug hypersensitivity"[All Fields] OR ("drug"[All Fields] AND "allergies"[All Fields]) OR "drug allergies"[All Fields]
"drug hypersensitivity"[MeSH Terms] OR ("drug"[All Fields] AND "hypersensitivity"[All Fields]) OR "drug hypersensitivity"[All Fields] OR ("hypersensitivity"[All Fields] AND "drug"[All Fields])
"drug hypersensitivity"[MeSH Terms] OR ("drug"[All Fields] AND "hypersensitivity"[All Fields]) OR "drug hypersensitivity"[All Fields] OR ("allergy"[All Fields] AND "drug"[All Fields]) OR "allergy, drug"[All Fields]
"sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "sensitivity"[All Fields]
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR "test"[All Fields] OR "laboratory techniques and procedures"[MeSH Terms] OR ("laboratory"[All Fields] AND "techniques"[All Fields] AND "procedures"[All Fields]) OR "laboratory techniques and procedures"[All Fields]
"disease susceptibility"[MeSH Terms] OR ("disease"[All Fields] AND "susceptibility"[All Fields]) OR "disease susceptibility"[All Fields] OR "susceptibility"[All Fields]
"parasitic sensitivity tests"[MeSH Terms] OR ("parasitic"[All Fields] AND "sensitivity"[All Fields] AND "tests"[All Fields]) OR "parasitic sensitivity tests"[All Fields]
"drug interactions"[MeSH Terms] OR ("drug"[All Fields] AND "interactions"[All Fields]) OR "drug interactions"[All Fields] OR ("drug"[All Fields] AND "interaction"[All Fields]) OR "drug interaction"[All Fields]
"drug interactions"[MeSH Terms] OR ("drug"[All Fields] AND "interactions"[All Fields]) OR "drug interactions"[All Fields] OR ("interaction"[All Fields] AND "drug"[All Fields]) OR "interaction, drug"[All Fields]
"drug interactions"[MeSH Terms] OR ("drug"[All Fields] AND "interactions"[All Fields]) OR "drug interactions"[All Fields] OR ("interactions"[All Fields] AND "drug"[All Fields]) OR "interactions, drug"[All Fields]
"drug effects"[Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR ("pharmacologic"[All Fields] AND "effects"[All Fields]) OR "pharmacologic effects"[All Fields]
"drug effects"[Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR ("effect"[All Fields] AND "drugs"[All Fields]) OR "effect of drugs"[All Fields]
"adverse drug reaction reporting systems"[MeSH Terms] OR ("adverse"[All Fields] AND "drug"[All Fields] AND "reaction"[All Fields] AND "reporting"[All Fields] AND "systems"[All Fields]) OR "adverse drug reaction reporting systems"[All Fields] OR ("drug"[All Fields] AND "reaction"[All Fields] AND "reporting"[All Fields] AND "systems"[All Fields] AND "adverse"[All Fields])
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("adverse"[All Fields] AND "drug"[All Fields] AND "effect"[All Fields]) OR "adverse drug effect"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("drug"[All Fields] AND "adverse"[All Fields] AND "effect"[All Fields]) OR "drug adverse effect"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("drug"[All Fields] AND "adverse"[All Fields] AND "reaction"[All Fields]) OR "drug adverse reaction"[All Fields]
"drug toxicity"[MeSH Terms] OR ("drug"[All Fields] AND "toxicity"[All Fields]) OR "drug toxicity"[All Fields] OR ("drug"[All Fields] AND "side"[All Fields] AND "effect"[All Fields]) OR "drug side effect"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("outcome"[All Fields] AND "treatment"[All Fields]) OR "outcome, treatment"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("rehabilitation"[All Fields] AND "outcome"[All Fields]) OR "rehabilitation outcome"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("outcome"[All Fields] AND "rehabilitation"[All Fields]) OR "outcome, rehabilitation"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("treatment"[All Fields] AND "effectiveness"[All Fields]) OR "treatment effectiveness"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("effectiveness"[All Fields] AND "treatment"[All Fields]) OR "effectiveness, treatment"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("treatment"[All Fields] AND "efficacy"[All Fields]) OR "treatment efficacy"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("efficacy"[All Fields] AND "treatment"[All Fields])

Medline (July 2011)

RS 14. Do low-dose corticosteroids have any effect on the radiologic progression of rheumatoid arthritis?
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]

RS 14. Do low-dose corticosteroids have any effect on the radiologic progression of rheumatoid arthritis?
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR

RS 14. Do low-dose corticosteroids have any effect on the radiologic progression of rheumatoid arthritis?
("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
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"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR ("allocation"[All Fields] AND "random"[All Fields])
"random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomization"[All Fields]
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("method"[All Fields] AND "single"[All Fields] AND "blind"[All Fields])
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"methods"[Subheading] OR "methods"[All Fields] OR "methods"[MeSH Terms]
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"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All

RS 14. Do low-dose corticosteroids have any effect on the radiologic progression of rheumatoid arthritis?
Fields] OR ("single"[All Fields] AND "masked"[All Fields] AND "studies"[All Fields])
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("studies"[All Fields] AND "single"[All Fields] AND "masked"[All Fields])
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"double-blind method"[MeSH Terms] OR ("double-blind"[All Fields] AND "method"[All Fields]) OR "double-blind method"[All Fields] OR ("study"[All Fields] AND "double"[All Fields] AND "blind"[All Fields])
"clinical trial, phase i"[Publication Type] OR "clinical trials, phase i as topic"[MeSH Terms] OR "clinical trial phase i"[All Fields] OR "phase i clinical trial"[All Fields]
"clinical trial, phase ii"[Publication Type] OR "clinical trials, phase ii as topic"[MeSH Terms] OR "clinical trial phase ii"[All Fields] OR "phase ii clinical trial"[All Fields]
"clinical trial, phase iii"[Publication Type] OR "clinical trials, phase iii as topic"[MeSH Terms] OR "clinical trial phase iii"[All Fields] OR "phase iii clinical trial"[All Fields]
"clinical trial, phase iv"[Publication Type] OR "clinical trials, phase iv as topic"[MeSH Terms] OR "clinical trial phase iv"[All Fields] OR "phase iv clinical trial"[All Fields]
"controlled clinical trial"[Publication Type] OR "controlled clinical trials as topic"[MeSH Terms] OR "controlled clinical trial"[All Fields]
"multicenter study"[Publication Type] OR "multicenter studies as topic"[MeSH Terms] OR "multicenter study"[All Fields] OR "multicentre study"[All Fields]
"randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]
"visually impaired persons"[MeSH Terms] OR ("visually"[All Fields] AND "impaired"[All Fields] AND "persons"[All Fields]) OR "visually impaired persons"[All Fields] OR "blind"[All Fields] OR "blindness"[MeSH Terms] OR "blindness"[All Fields]
"masks"[MeSH Terms] OR "masks"[All Fields] OR "mask"[All Fields]
"placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields]
"placebos"[MeSH Terms] OR "placebos"[All Fields] OR ("sham"[All Fields] AND "treatment"[All Fields]) OR "sham treatment"[All Fields]
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("design"[All Fields] AND "research"[All Fields]) OR "design, research"[All Fields]
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("designs"[All Fields] AND "research"[All Fields])
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("research"[All Fields] AND "designs"[All Fields]) OR "research designs"[All Fields]

RS 14. Do low-dose corticosteroids have any effect on the radiologic progression of rheumatoid arthritis?
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("problem"[All Fields] AND "formulation"[All Fields]) OR "problem formulation"[All Fields]
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("formulation"[All Fields] AND "problem"[All Fields])
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"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("scoring"[All Fields] AND "methods"[All Fields]) OR "scoring methods"[All Fields]
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"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("error"[All Fields] AND "sources"[All Fields]) OR "error sources"[All Fields]
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"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR

RS 14. Do low-dose corticosteroids have any effect on the radiologic progression of rheumatoid arthritis?
("followup"[All Fields] AND "study"[All Fields]) OR "followup study"[All Fields]
"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR ("studies"[All Fields] AND "followup"[All Fields])
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"prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields]
"longitudinal studies"[MeSH Terms] OR ("longitudinal"[All Fields] AND "studies"[All Fields]) OR "longitudinal studies"[All Fields] OR "prospective"[All Fields]
"voluntary workers"[MeSH Terms] OR ("voluntary"[All Fields] AND "workers"[All Fields]) OR "voluntary workers"[All Fields] OR "volunteer"[All Fields]
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"cortisone"[MeSH Terms] OR "cortisone"[All Fields] OR "adreson"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "dehydrocortisone"[All Fields]
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"3-bromoacetoxyandrostan-17-one"[Supplementary Concept] OR "3-bromoacetoxyandrostan-17-one"[All Fields] OR "brand"[All Fields]
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"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "dacortin"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("merck"[All Fields] AND "brand"[All Fields] AND "prednisone"[All Fields])
"desoxycorticosterone"[MeSH Terms] OR "desoxycorticosterone"[All Fields] OR "decortin"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "deltasone"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "encortone"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "encorton"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("liquid"[All Fields] AND "pred"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "meticorten"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("solvay"[All Fields] AND "brand"[All Fields] AND "prednisone"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "panasol"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("predni"[All Fields] AND "tablinen"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("diba"[All Fields] AND "brand"[All Fields] AND "prednisone"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("ferring"[All Fields] AND "brand"[All Fields] AND "prednisone"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("prednison"[All Fields] AND "acsis"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("acis"[All Fields] AND "brand"[All Fields] AND "prednisone"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("prednison"[All Fields] AND "galen"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("galenpharma"[All Fields] AND "brand"[All Fields] AND "prednisone"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("prednison"[All Fields] AND "hexal"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR ("hexal"[All Fields] AND "brand"[All Fields] AND "prednisone"[All Fields])
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "pronisone"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "rectodelt"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "ultracorten"[All Fields]
"prednisone"[MeSH Terms] OR "prednisone"[All Fields] OR "sone"[All Fields]
"prednisolone"[MeSH Terms] OR "prednisolone"[All Fields] OR "predate"[All Fields]
"prednisolone"[MeSH Terms] OR "prednisolone"[All Fields] OR "predonine"[All Fields]
"prednisolone"[MeSH Terms] OR "prednisolone"[All Fields] OR "di adreson f"[All Fields]
"prednisolone"[MeSH Terms] OR "prednisolone"[All Fields] OR "di adreson f"[All Fields]
"prednisolone"[MeSH Terms] OR "prednisolone"[All Fields]
"adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR

RS 14. Do low-dose corticosteroids have any effect on the radiologic progression of rheumatoid arthritis?
"adrenal cortex hormones"[All Fields] OR ("hormones"[All Fields] AND "adrenal"[All Fields] AND "cortex"[All Fields]) OR "adrenal cortex hormones"[Pharmacological Action]
"adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroids"[All Fields] OR "adrenal cortex hormones"[Pharmacological Action]
"adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticoids"[All Fields] OR "adrenal cortex hormones"[Pharmacological Action]

Medline (July 2011)

SR 15. Is it possible to suspend a biologic which has archieved a significant response and maintain this response with a classic DMARD? When there is symptomatic recurrence of RA previously traeated with and anti-TNF, should treatment be instituted with the same drug or with a different anti-TNF?
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All

SR 15. Is it possible to suspend a biologic which has archieved a significant response and maintain this response with a classic DMARD? When there is symptomatic recurrence of RA previously traeated with and anti-TNF, should treatment be instituted with the same drug or with a different anti-TNF?
Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]

SR 15. Is it possible to suspend a biologic which has archieved a significant response and maintain this response with a classic DMARD? When there is symptomatic recurrence of RA previously traeated with and anti-TNF, should treatment be instituted with the same drug or with a different anti-TNF?
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"methotrexate"[MeSH Terms] OR "methotrexate"[All Fields]
"sulphasalazine"[All Fields] OR "sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulphasalazine"[All Fields] OR "sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "salazosulfapyridine"[All Fields]
"cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "cyclosporin"[All Fields]
"cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "cyclosporin a"[All Fields]
"cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "cyclosporin a"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields]
"leflunomide"[Supplementary Concept] OR "leflunomide"[All Fields] OR "arava"[All Fields]
"penicillamine"[MeSH Terms] OR "penicillamine"[All Fields] OR "d penicillamine"[All Fields]
"penicillamine"[MeSH Terms] OR "penicillamine"[All Fields]
"antimalarials"[MeSH Terms] OR "antimalarials"[All Fields] OR "antimalarial"[All Fields] OR "antimalarials"[Pharmacological Action]
"chloroquine"[MeSH Terms] OR "chloroquine"[All Fields]
"hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields]
"antimalarials"[MeSH Terms] OR "antimalarials"[All Fields] OR ("antimalarial"[All Fields] AND "agent"[All Fields]) OR "antimalarial agent"[All Fields] OR "antimalarials"[Pharmacological Action]
"azathioprine"[MeSH Terms] OR "azathioprine"[All Fields]
"gold"[MeSH Terms] OR "gold"[All Fields]
"sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields] OR "salt"[All Fields]
"therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]
"gold sodium thiomalate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiomalate"[All Fields]) OR "gold sodium thiomalate"[All Fields] OR "aurothiomalate"[All Fields]
"gold sodium thiosulfate"[MeSH Terms] OR ("gold"[All Fields] AND "sodium"[All Fields] AND "thiosulfate"[All Fields]) OR "gold sodium thiosulfate"[All Fields] OR ("sodium"[All Fields] AND "aurothiosulfate"[All Fields]) OR "sodium aurothiosulfate"[All Fields]
"auranofin"[MeSH Terms] OR "auranofin"[All Fields]
"cyclophosphamide"[MeSH Terms] OR "cyclophosphamide"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "monoclonal antibody ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "mab ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "remicade"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "recombinant human dimeric tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "enbrel"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields] OR "humira"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "belatacept"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "lea29y"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "bms 224818"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "ctla 4 ig"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "cytotoxic t lymphocyte associated antigen 4 immunoglobulin"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "ctla4 fc"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "ctla4 ig"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "orencia"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "bms 188667"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "bms 188667"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "cdp 870"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "cimzia"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "certolizumab pegol"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("urine"[All Fields] AND "derived"[All Fields] AND "il1"[All Fields] AND "inhibitor"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR

SR 15. Is it possible to suspend a biologic which has archieved a significant response and maintain this response with a classic DMARD? When there is symptomatic recurrence of RA previously traeated with and anti-TNF, should treatment be instituted with the same drug or with a different anti-TNF?
("il1"[All Fields] AND "inhibitor"[All Fields] AND "urine"[All Fields] AND "derived"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("urine"[All Fields] AND "derived"[All Fields] AND "il1"[All Fields] AND "inhibitor"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("il1"[All Fields] AND "febrile"[All Fields] AND "inhibitor"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("febrile"[All Fields] AND "inhibitor"[All Fields] AND "il1"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields]
"urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "urine il 1 inhibitor"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("il"[All Fields] AND "1ra"[All Fields]) OR "il 1ra"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "kineret"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("amgen"[All Fields] AND "brand"[All Fields] AND "anakinra"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("anakinra"[All Fields] AND "amgen"[All Fields] AND "brand"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "antril"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("synergen"[All Fields] AND "brand"[All Fields] AND "anakinra"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("anakinra"[All Fields] AND "synergen"[All Fields] AND "brand"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "anakinra"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "mabthera"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "rituxan"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "idec c2b8 antibody"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "idec c2b8"[All Fields]
"tocilizumab"[Supplementary Concept] OR "tocilizumab"[All Fields] OR "actemra"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("necrosis"[All Fields] AND "factors"[All Fields] AND "tumor"[All Fields])
"ligands"[MeSH Terms] OR "ligands"[All Fields] OR "ligand"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tnf"[All Fields] AND "receptor"[All Fields]) OR "tnf receptor"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("receptor"[All Fields] AND "ligands"[All Fields] AND "tnf"[All Fields])
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "superfamily"[All Fields] AND "ligands"[All Fields]) OR "tumor necrosis factor superfamily ligands"[All Fields]
"tumour necrosis factor alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor-alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor-alpha"[All Fields]) OR "Tumor Necrosis Factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor"[All Fields] AND "alpha"[All Fields]) OR "Tumor Necrosis Factor alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields])
"cachectin tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("cachectin"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "cachectin tumor necrosis factor"[All Fields]
"cachectin tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("cachectin"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "cachectin tumor necrosis factor"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "tnfalpha"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields]) OR "tnf alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields])
"tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "cachectin"[All Fields]

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"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptors"[All Fields] AND "cachectin"[All Fields])
"tumour necrosis factor receptors"[All Fields] OR "receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "receptors"[All Fields])
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptor"[All Fields] AND "tnf"[All Fields]) OR "receptor, tnf"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tnf"[All Fields] AND "receptors"[All Fields]) OR "tnf receptors"[All Fields]
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"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("cachectin"[All Fields] AND "receptors"[All Fields]) OR "cachectin receptors"[All Fields]
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"antibodies, monoclonal"[MeSH Terms] OR ("antibodies"[All Fields] AND "monoclonal"[All Fields]) OR "monoclonal antibodies"[All Fields] OR ("monoclonal"[All Fields] AND "antibodies"[All Fields])
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"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields]
"random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR ("allocation"[All Fields] AND "random"[All Fields])
"random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomization"[All Fields]
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("method"[All Fields] AND "single"[All Fields] AND "blind"[All Fields])
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"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("single"[All Fields] AND "blind"[All Fields] AND "methods"[All Fields])
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("single"[All Fields] AND "masked"[All Fields] AND "method"[All Fields])
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"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("single"[All Fields] AND "masked"[All Fields] AND "method"[All Fields])
"methods"[Subheading] OR "methods"[All Fields] OR "methods"[MeSH Terms]
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("single"[All Fields] AND "masked"[All Fields] AND "study"[All Fields]) OR "single masked study"[All Fields]

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"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("single"[All Fields] AND "masked"[All Fields] AND "study"[All Fields]) OR "single masked study"[All Fields]
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("single"[All Fields] AND "masked"[All Fields] AND "studies"[All Fields])
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("studies"[All Fields] AND "single"[All Fields] AND "masked"[All Fields])
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("study"[All Fields] AND "single"[All Fields] AND "masked"[All Fields])
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("single"[All Fields] AND "blind"[All Fields] AND "study"[All Fields]) OR "single blind study"[All Fields]
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("single"[All Fields] AND "blind"[All Fields] AND "study"[All Fields]) OR "single blind study"[All Fields]
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("single"[All Fields] AND "blind"[All Fields] AND "studies"[All Fields]) OR "single blind studies"[All Fields]
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("studies"[All Fields] AND "single"[All Fields] AND "blind"[All Fields])
"single-blind method"[MeSH Terms] OR ("single-blind"[All Fields] AND "method"[All Fields]) OR "single-blind method"[All Fields] OR ("study"[All Fields] AND "single"[All Fields] AND "blind"[All Fields]) OR "study, single blind"[All Fields]
"double-blind method"[MeSH Terms] OR ("double-blind"[All Fields] AND "method"[All Fields]) OR "double-blind method"[All Fields] OR ("double"[All Fields] AND "blind"[All Fields] AND "method"[All Fields]) OR "double blind method"[All Fields]
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"double-blind method"[MeSH Terms] OR ("double-blind"[All Fields] AND "method"[All Fields]) OR "double-blind method"[All Fields] OR ("double"[All Fields] AND "masked"[All Fields] AND "study"[All Fields]) OR "double masked study"[All Fields]
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"double-blind method"[MeSH Terms] OR ("double-blind"[All Fields] AND "method"[All Fields]) OR "double-blind method"[All Fields] OR ("study"[All Fields] AND "double"[All Fields] AND "blind"[All Fields])
"clinical trial, phase i"[Publication Type] OR "clinical trials, phase i as topic"[MeSH Terms] OR "clinical trial phase i"[All Fields] OR "phase i clinical trial"[All Fields]
"clinical trial, phase ii"[Publication Type] OR "clinical trials, phase ii as topic"[MeSH Terms] OR "clinical trial phase ii"[All Fields] OR "phase ii clinical trial"[All Fields]
"clinical trial, phase iii"[Publication Type] OR "clinical trials, phase iii as topic"[MeSH Terms] OR "clinical trial phase iii"[All Fields] OR "phase iii clinical trial"[All Fields]
"clinical trial, phase iv"[Publication Type] OR "clinical trials, phase iv as topic"[MeSH Terms] OR "clinical trial phase iv"[All Fields] OR "phase iv clinical trial"[All Fields]
"controlled clinical trial"[Publication Type] OR "controlled clinical trials as topic"[MeSH Terms] OR "controlled clinical trial"[All Fields]
"multicenter study"[Publication Type] OR "multicenter studies as topic"[MeSH Terms] OR "multicenter study"[All Fields] OR "multicentre study"[All Fields]
"randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]
"visually impaired persons"[MeSH Terms] OR ("visually"[All Fields] AND "impaired"[All Fields] AND "persons"[All Fields]) OR "visually impaired persons"[All Fields] OR "blind"[All Fields] OR "blindness"[MeSH Terms] OR "blindness"[All Fields]
"masks"[MeSH Terms] OR "masks"[All Fields] OR "mask"[All Fields]
"placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields]
"placebos"[MeSH Terms] OR "placebos"[All Fields] OR ("sham"[All Fields] AND "treatment"[All Fields]) OR "sham treatment"[All Fields]

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"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("design"[All Fields] AND "research"[All Fields]) OR "design, research"[All Fields]
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("designs"[All Fields] AND "research"[All Fields])
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("research"[All Fields] AND "designs"[All Fields]) OR "research designs"[All Fields]
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("problem"[All Fields] AND "formulation"[All Fields]) OR "problem formulation"[All Fields]
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"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("research"[All Fields] AND "proposal"[All Fields]) OR "research proposal"[All Fields]
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"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("proposals"[All Fields] AND "research"[All Fields])
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"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("scoring"[All Fields] AND "methods"[All Fields]) OR "scoring methods"[All Fields]
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"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("quality"[All Fields] AND "data"[All Fields]) OR "quality, data"[All Fields]
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"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("research"[All Fields] AND "methodology"[All Fields]) OR "research methodology"[All Fields]
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("methodology"[All Fields] AND "research"[All Fields]) OR "methodology, research"[All Fields]
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("data"[All Fields] AND "adjustment"[All Fields]) OR "data adjustment"[All Fields]
"research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR ("data"[All Fields] AND "adjustments"[All Fields]) OR "data adjustments"[All Fields]
"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR ("follow"[All Fields] AND "up"[All Fields] AND "studies"[All Fields]) OR "follow up studies"[All Fields]

SR 15. Is it possible to suspend a biologic which has archieved a significant response and maintain this response with a classic DMARD? When there is symptomatic recurrence of RA previously traeated with and anti-TNF, should treatment be instituted with the same drug or with a different anti-TNF?
"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR ("follow"[All Fields] AND "up"[All Fields] AND "study"[All Fields]) OR "follow up study"[All Fields]
"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR ("studies"[All Fields] AND "follow"[All Fields] AND "up"[All Fields])
"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR ("study"[All Fields] AND "follow"[All Fields] AND "up"[All Fields]) OR "study, follow up"[All Fields]
"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR ("followup"[All Fields] AND "studies"[All Fields]) OR "followup studies"[All Fields]
"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR ("followup"[All Fields] AND "study"[All Fields]) OR "followup study"[All Fields]
"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR ("studies"[All Fields] AND "followup"[All Fields])
"follow-up studies"[MeSH Terms] OR ("follow-up"[All Fields] AND "studies"[All Fields]) OR "follow-up studies"[All Fields] OR ("study"[All Fields] AND "followup"[All Fields])
"prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields]
"longitudinal studies"[MeSH Terms] OR ("longitudinal"[All Fields] AND "studies"[All Fields]) OR "longitudinal studies"[All Fields] OR "prospective"[All Fields]
"voluntary workers"[MeSH Terms] OR ("voluntary"[All Fields] AND "workers"[All Fields]) OR "voluntary workers"[All Fields] OR "volunteer"[All Fields]
"prospective studies"[MeSH Terms] OR ("prospective"[All Fields] AND "studies"[All Fields]) OR "prospective studies"[All Fields] OR ("prospective"[All Fields] AND "study"[All Fields]) OR "prospective study"[All Fields]
"prospective studies"[MeSH Terms] OR ("prospective"[All Fields] AND "studies"[All Fields]) OR "prospective studies"[All Fields] OR ("studies"[All Fields] AND "prospective"[All Fields]) OR "studies, prospective"[All Fields]
"prospective studies"[MeSH Terms] OR ("prospective"[All Fields] AND "studies"[All Fields]) OR "prospective studies"[All Fields] OR ("study"[All Fields] AND "prospective"[All Fields]) OR "study, prospective"[All Fields]

Medline (July 2011)

SR 16. Is a new biologic agent effective in rheumatoid arthritis patients who have not responded to usual doses of another biologic agent?
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All

SR 16. Is a new biologic agent effective in rheumatoid arthritis patients who have not responded to usual doses of another biologic agent?
Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodules"[All Fields]) OR "rheumatoid nodules"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitis"[All Fields] AND "rheumatoid"[All Fields])
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields] AND "syndrome"[All Fields]) OR "sjogren syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sjogrens"[All Fields] AND "syndrome"[All Fields]) OR "sjogrens syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sjogren's"[All Fields]) OR "syndrome, sjogren's"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("sicca"[All Fields] AND "syndrome"[All Fields]) OR "sicca syndrome"[All Fields]
"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All

SR 16. Is a new biologic agent effective in rheumatoid arthritis patients who have not responded to usual doses of another biologic agent?

Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "adult onset still's disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields]) OR "adult onset stills disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "monoclonal antibody ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "mab ca2"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "remicade"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"infliximab"[Supplementary Concept] OR "infliximab"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnr 001"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "recombinant human dimeric tnf receptor type ii igg fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "enbrel"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields]
"TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields] OR "humira"[All Fields]
"adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]
"golimumab"[Supplementary Concept] OR "golimumab"[All Fields] OR "simponi"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "belatacept"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "lea29y"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "bms 224818"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "ctla 4 ig"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "cytotoxic t lymphocyte associated antigen 4 immunoglobulin"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "ctla4 fc"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "ctla4 ig"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "orencia"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "bms 188667"[All Fields]
"abatacept"[Supplementary Concept] OR "abatacept"[All Fields] OR "bms 188667"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "cdp 870"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "cimzia"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "certolizumab pegol"[All Fields]
"CDP870"[Supplementary Concept] OR "CDP870"[All Fields] OR "certolizumab"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("urine"[All Fields] AND "derived"[All Fields] AND "il1"[All Fields] AND "inhibitor"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("il1"[All Fields] AND "inhibitor"[All Fields] AND "urine"[All Fields] AND "derived"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("urine"[All Fields] AND "derived"[All Fields] AND "il1"[All Fields] AND "inhibitor"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("il1"[All Fields] AND "febrile"[All Fields] AND "inhibitor"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("febrile"[All Fields] AND "inhibitor"[All Fields] AND "il1"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields]
"urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "urine il 1 inhibitor"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("il"[All

SR 16. Is a new biologic agent effective in rheumatoid arthritis patients who have not responded to usual doses of another biologic agent?
Fields] AND "1ra"[All Fields]) OR "il 1ra"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "kineret"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("amgen"[All Fields] AND "brand"[All Fields] AND "anakinra"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("anakinra"[All Fields] AND "amgen"[All Fields] AND "brand"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "antril"[All Fields]
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("synergen"[All Fields] AND "brand"[All Fields] AND "anakinra"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR ("anakinra"[All Fields] AND "synergen"[All Fields] AND "brand"[All Fields])
"interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "anakinra"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "mabthera"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "rituxan"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "idec c2b8 antibody"[All Fields]
"rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "idec c2b8"[All Fields]
"tocilizumab"[Supplementary Concept] OR "tocilizumab"[All Fields] OR "actemra"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("necrosis"[All Fields] AND "factors"[All Fields] AND "tumor"[All Fields])
"ligands"[MeSH Terms] OR "ligands"[All Fields] OR "ligand"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tnf"[All Fields] AND "receptor"[All Fields]) OR "tnf receptor"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("receptor"[All Fields] AND "ligands"[All Fields] AND "tnf"[All Fields])
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "superfamily"[All Fields] AND "ligands"[All Fields]) OR "tumor necrosis factor superfamily ligands"[All Fields]
"tumour necrosis factor alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor-alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor-alpha"[All Fields]) OR "Tumor Necrosis Factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields]) OR "tumor necrosis factor alpha"[All Fields] OR "Tumor Necrosis Factor alpha"[MeSH Terms] OR ("Tumor"[All Fields] AND "Necrosis"[All Fields] AND "Factor"[All Fields] AND "alpha"[All Fields]) OR "Tumor Necrosis Factor alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields])
"cachectin tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("cachectin"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "cachectin tumor necrosis factor"[All Fields]
"cachectin tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("cachectin"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "cachectin tumor necrosis factor"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "tnfalpha"[All Fields]
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields]) OR "tnf alpha"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields])
"tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR "cachectin"[All Fields]
"tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptors"[All Fields] AND "cachectin"[All Fields])
"tumour necrosis factor receptors"[All Fields] OR "receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "receptors"[All Fields])
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptor"[All Fields] AND "tnf"[All Fields]) OR "receptor, tnf"[All Fields]
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"tumour necrosis factor receptor"[All Fields] OR "receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR

SR 16. Is a new biologic agent effective in rheumatoid arthritis patients who have not responded to usual doses of another biologic agent?
("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "receptor"[All Fields]) OR "tumor necrosis factor receptor"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("cachectin"[All Fields] AND "receptors"[All Fields]) OR "cachectin receptors"[All Fields]
"receptors, tumor necrosis factor"[MeSH Terms] OR ("receptors"[All Fields] AND "tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor receptors"[All Fields] OR ("receptors"[All Fields] AND "tnf"[All Fields]) OR "receptors, tnf"[All Fields]
"antibodies, monoclonal"[MeSH Terms] OR ("antibodies"[All Fields] AND "monoclonal"[All Fields]) OR "monoclonal antibodies"[All Fields] OR ("monoclonal"[All Fields] AND "antibodies"[All Fields])
"biological therapy"[MeSH Terms] OR ("biological"[All Fields] AND "therapy"[All Fields]) OR "biological therapy"[All Fields] OR ("biologic"[All Fields] AND "therapy"[All Fields]) OR "biologic therapy"[All Fields]
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"biological therapy"[MeSH Terms] OR ("biological"[All Fields] AND "therapy"[All Fields]) OR "biological therapy"[All Fields] OR ("therapy"[All Fields] AND "biologic"[All Fields])
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"biological products"[MeSH Terms] OR ("biological"[All Fields] AND "products"[All Fields]) OR "biological products"[All Fields] OR ("products"[All Fields] AND "natural"[All Fields])
"tumor necrosis factors"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factors"[All Fields]) OR "tumor necrosis factors"[All Fields]
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"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("drug"[All Fields] AND "switching"[All Fields]) OR "drug switching"[All Fields]
"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("drug"[All Fields] AND "switchings"[All Fields])
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"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("switchings"[All Fields] AND "drug"[All Fields])
"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("therapeutic"[All Fields] AND "substitution"[All Fields]) OR "therapeutic substitution"[All Fields]
"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("substitution"[All Fields] AND "therapeutic"[All Fields])
"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("substitutions"[All Fields] AND "therapeutic"[All Fields])
"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("therapeutic"[All Fields] AND "substitutions"[All Fields]) OR "therapeutic substitutions"[All Fields]
"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("generic"[All Fields] AND "substitution"[All Fields]) OR "generic substitution"[All Fields]
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"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("substitution"[All Fields] AND "generic"[All Fields]) OR "substitution, generic"[All Fields]
"drug substitution"[MeSH Terms] OR ("drug"[All Fields] AND "substitution"[All Fields]) OR "drug substitution"[All Fields] OR ("substitutions"[All Fields] AND "generic"[All Fields])
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("outcome"[All Fields] AND "treatment"[All Fields]) OR "outcome, treatment"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("rehabilitation"[All Fields] AND "outcome"[All Fields]) OR "rehabilitation outcome"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("outcome"[All Fields] AND "rehabilitation"[All Fields]) OR "outcome, rehabilitation"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("treatment"[All Fields] AND "effectiveness"[All Fields]) OR "treatment effectiveness"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("effectiveness"[All Fields] AND "treatment"[All Fields]) OR "effectiveness, treatment"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields]

SR 16. Is a new biologic agent effective in rheumatoid arthritis patients who have not responded to usual doses of another biologic agent?
OR ("treatment"[All Fields] AND "efficacy"[All Fields]) OR "treatment efficacy"[All Fields]
"treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("efficacy"[All Fields] AND "treatment"[All Fields])
"drug resistance"[MeSH Terms] OR ("drug"[All Fields] AND "resistance"[All Fields]) OR "drug resistance"[All Fields] OR ("resistance"[All Fields] AND "drug"[All Fields]) OR "resistance, drug"[All Fields]
"treatment failure"[MeSH Terms] OR ("treatment"[All Fields] AND "failure"[All Fields]) OR "treatment failure"[All Fields] OR ("failure"[All Fields] AND "treatment"[All Fields]) OR "failure, treatment"[All Fields]
"treatment failure"[MeSH Terms] OR ("treatment"[All Fields] AND "failure"[All Fields]) OR "treatment failure"[All Fields] OR ("failures"[All Fields] AND "treatment"[All Fields])
"treatment failure"[MeSH Terms] OR ("treatment"[All Fields] AND "failure"[All Fields]) OR "treatment failure"[All Fields] OR ("treatment"[All Fields] AND "failures"[All Fields]) OR "treatment failures"[All Fields]

Medline (July 2011)

SR 17. Efficacy and safety of infliximab, etanercept, adalimumab, anakinra, rituximab, tocilizumab, golimumab and abatacept
"arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "rheumatoid"[All Fields] AND "arthritis"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "rheumatoid arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields]) OR "arthritis, juvenile idiopathic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritides"[All Fields] AND "juvenile"[All Fields] AND "idiopathic"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritides"[All Fields] AND "juvenile"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("idiopathic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "idiopathic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritides"[All Fields]) OR "juvenile idiopathic arthritides"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "chronic"[All Fields]) OR "arthritis, juvenile chronic"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("chronic"[All Fields] AND "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "chronic arthritis, juvenile"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "chronic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile chronic arthritis"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "still's"[All Fields] AND "disease"[All Fields]) OR "juvenile onset still's disease"[All Fields]
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])

"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "onset"[All Fields] AND "stills"[All Fields] AND "disease"[All Fields])
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "juvenile"[All Fields] AND "onset"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan"[All Fields] AND "syndromes"[All Fields])
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplan's"[All Fields] AND "syndrome"[All Fields]) OR "caplan's syndrome"[All Fields]
"caplan syndrome"[MeSH Terms] OR ("caplan"[All Fields] AND "syndrome"[All Fields]) OR "caplan syndrome"[All Fields] OR ("caplans"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty"[All Fields] AND "syndrome"[All Fields]) OR "felty syndrome"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "felty's"[All Fields])
"family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields]
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "felty"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("familial"[All Fields] AND "feltys"[All Fields] AND "syndrome"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("felty's"[All Fields] AND "syndrome"[All Fields] AND "familial"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "familial"[All Fields] AND "felty's"[All Fields])
"felty's syndrome"[MeSH Terms] OR ("felty's"[All Fields] AND "syndrome"[All Fields]) OR "felty's syndrome"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields] AND "splenomegaly"[All Fields] AND "neutropenia"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodule"[All Fields] AND "rheumatoid"[All Fields])
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("nodules"[All Fields] AND "rheumatoid"[All Fields])
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"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields] OR ("rheumatoid"[All Fields] AND "nodulosis"[All Fields]) OR "rheumatoid nodulosis"[All Fields]
"rheumatoid nodule"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "nodule"[All Fields]) OR "rheumatoid nodule"[All Fields]
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("rheumatoid"[All Fields] AND "vasculitides"[All Fields])
"rheumatoid vasculitis"[MeSH Terms] OR ("rheumatoid"[All Fields] AND "vasculitis"[All Fields]) OR "rheumatoid vasculitis"[All Fields] OR ("vasculitides"[All Fields] AND "rheumatoid"[All Fields])
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"sjogren's syndrome"[MeSH Terms] OR ("sjogren's"[All Fields] AND "syndrome"[All Fields]) OR "sjogren's syndrome"[All Fields] OR ("syndrome"[All Fields] AND "sicca"[All Fields])
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields]) OR "still's disease, adult onset"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("stills"[All Fields] AND "disease"[All Fields] AND "adult"[All Fields] AND "onset"[All Fields])
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Fields]) OR "adult onset still disease"[All Fields]
"still's disease, adult-onset"[MeSH Terms] OR ("still's"[All Fields] AND "disease"[All Fields] AND "adult-onset"[All Fields]) OR "adult-onset still's disease"[All Fields] OR ("adult"[All Fields] AND "onset"[All Fields] AND "still"[All Fields] AND "disease"[All Fields]) OR "adult onset still disease"[All Fields]
"methotrexate"[MeSH Terms] OR "methotrexate"[All Fields]
"sulphasalazine"[All Fields] OR "sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulphasalazine"[All Fields] OR "sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]
"sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "salazosulfapyridine"[All Fields]
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"cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "cyclosporin a"[All Fields]
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b) Manual search

Secondary searches were made using the reference lists of the selected articles.

- Review methods

Study selection

Two reviewers (AO and MA) carried out the initial study search and selection in two steps: selection by title and selection by abstract. Uncertainties during the selection process were discussed with a third reviewer (EL). This investigator subsequently selected the articles by type of intervention and obtained the complete text of the selected articles without an abstract, and of the studies selected by abstract.

Data extraction

AO and MA independently extracted the descriptive data, results and estimations of the studies meeting the selection criteria, using a standardized form. Disagreements were resolved by review of a third reviewer. They also carried out secondary searches for studies by reviewing the references of the selected articles.

Data analysis

The qualitative variables were extracted as absolute values, and were divided by the number of patients in the corresponding group (n/N), and the quantitative variables, as the mean and standard deviation in each group. If the article only contained confidence intervals for the mean, but not the standard deviation, the latter was calculate based on the former.

When the outcome measures and the trials were homogeneous, the possibility of performing meta-analysis was considered. The efficacy outcomes of the trials were combined using random effects models to calculate the difference in means (MD) for quantitative variables or the relative risks (RR) for qualitative variables, with their 95% confidence intervals (CI). Safety outcomes were combined using fixed effects models to calculate the RR with its 95% CI. Heterogeneity was studied using the chi-square statistic included in the RevMan program for review and meta-analysis (version 4.2.8), which was used for the review. In exploring heterogeneity, different sensitivity analyses were used whenever necessary: a) using only intention-to-treat analysis, and b) by financing of the CTs. Study quality and patient type were also used in exploring heterogeneity.

When meta-analysis was not possible because the trials could not be combined, the individual outcomes of each study are summarized in qualitative form.

- Results

The results of the reviews will be shown in different chpters.

I.1.3.b. Reviews of questions posed by the expert panel

In this edition it was decided to up-date to previous systematic literature reviews.

I.1.4. Application of the reviews

The reviews were sent to the panel of experts for their evaluation before the date on which they had to formulate their recommendations for their corresponding section. Thus, the experts could base their recommendations on the synthesis of the available evidence.

The reviews were used to rank the level of evidence for the GUIPCAR_2011 recommendations, in accordance with the Levels of Evidence of the Oxford Centre for Evidence-Based Medicine (after the March 2009 modification).

Drafting the contents of GUIPCAR_2011

With the support of the systematic literature review results, each team wrote the assigned chapter or section of GUIPCAR_2007 and formulated a series of provisional recommendations. The text produced was sent to research unit of the SER, which edited a first draft of GUIPCAR_2011 and circulated it to the group of experts.

The group of experts and SER investigators met in september 2011 to discuss the preliminary contents and recommendations. At this meeting some modifications to the text were proposed, and these were introduced by the corresponding team. The SER investigators again edited the manuscript which was resubmitted for the consideration of the group of experts to make the final review.

Each recommendation is highlighted in bold print on a green background. The level of evidence and the grade of recommendation are presented at the end of each recommendation, separated by a comma "," and enclosed in brackets "**[ ]**". Example:

The sooner RA treatment begins, the greater the probability of controlling the inflammatory process and reducing structural damage; thus, "recent-onset arthritis" should be considered a diagnostic priority. [1.a, A]

In this example "**1.a**" refers to the **level of evidence** and "**A**" to the **grade of recommendation** in accordance with the nomenclature of the Oxford Centre for Evidence-Based Medicine (see Table 1).

Some paragraphs in the text are shown in bold print without the green background, and without a level of evidence or grade of recommendation. These are informational paragraphs that summarize the information that follows, and are not in themselves expert panel recommendations.

Also found within the text are the main conclusions of the systematic reviews made to complement this guideline. These conclusions are shaded in gray, and are usually accompanied by the level of evidence that supports them, in accordance with the same nomenclature referred to previously. In these cases, there is no grade of recommendation since these are not recommendations of the expert panel.

Editing GUIPCAR_2011

The documents produced by the different teams of experts were combined into a single document, and given a uniform style. The most important information, from the practical point of view for the physician, was extracted and used to write the Rapid Guideline. Finally,

a list of the main recommendations was produced, with a description of the level of scientific evidence on which each is based, according to the Oxford classification for Evidence-Based Medicine, and the strength of the recommendation (see tables 1 to 3).

Table 1. Levels of Evidence. Oxford Centre for Evidence-Based Medicine (March 2011)

Grade of recommen-dation	Level of evidence	Efficacy and safety	Efficacy and safety between drugs in the same class	Prognosis	Diagnosis	Differential diagnosis, prevalence	Economic and decision analyses
A	1a	SR of RCTs (with homogeneity*)	SR (with homogeneity*) of "head-to-head" RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of level 1 diagnostic studies; CDR† of 1b multicenter studies	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of level 1 economic studies
	1b	Individual RCT (with narrow CI)	"Head-to-head" RCTs with clinically important outcomes	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good reference standards†††; CDR† validated in a single center	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; SR including multi-way sensitivity analyses
	1c	"All or none"§ RCT		"All or none" case series	Absolute SpIns and SnOuts††	"All or none" case series	Absolute better-value or worse-value analyses‡‡
B	2a	SR (with homogeneity*) of cohort studies	"Head-to-head" RCTs with validated surrogate outcomes ‡‡‡	SR (with homogeneity*) of either retrospective cohort studies or control groups in RCTs	SR (with homogeneity*) of level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of level >2 economic studies
	2b	Individual cohort study (or low quality RCT; e.g., <80% follow-up)	RCTs of different drugs vs. placebo in similar or different patients with clinically important or validated surrogate outcomes	Retrospective cohort study or follow-up of placebo group in RCT; Derivation of CRD† or validated on split sample§§§ only	Exploratory** cohort study with good††† reference standards; Derivation of CRD† or validated only on split-sample§§§ databases	Retrospective cohort study, or with poor follow-up	Analyses based on clinically sensible costs or alternatives; limited reviews(s) of the evidence, or single studies; and including multi-way sensitivity analyses
	2c	"Outcomes" Research; ecological studies		"Outcomes" research		Ecological studies	Audits or "outcomes research"
	3a	SR (with homogeneity*) of case-control studies	Subgroup analysis of RCTs of different drugs vs. placebo in similar or different patients with clinically important or validated surrogate outcomes		SR (with homogeneity*) of >=3b studies	SR (with homogeneity*) of >=3b studies	SR (with homogeneity*) of >=3b studies
	3b	Individual case-control study	RCTs of different drugs vs. Placebo in similar or different patients with unvalidated surrogate outcomes		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
C	4	Case series (and poor quality	Observational studies and administrative	Case series and poor quality prognostic	Case-control study, poor or non-	Case-series or superseded reference	Studies with no sensitivity analysis

Grade of recommen-dation	Level of evidence	Efficacy and safety	Efficacy and safety between drugs in the same class	Prognosis	Diagnosis	Differential diagnosis, prevalence	Economic and decision analyses
		cohort or case-control studies §§)	databases with clinically important outcomes	studies***	independent reference standard	standards	
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles", or on non-randomized studies with unvalidated surrogate outcomes	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles",	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles",	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles",	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles",

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes and Martin Dawes since November 1998.

Notes

Users should add a minus sign "-" to denote the level of evidence that fails to provide a conclusive answer because of:

1. EITHER a single result with a wide confidence interval
2. OR a systematic review with troublesome heterogeneity

In these cases the evidence is inconclusive, and therefore can only generate grade D recommendations.

Table 2. Explanatory notes for table 1

*	By homogeneity we mean lack of worrisome heterogeneity, either statistical or in design. There may be reviews with heterogeneity that is statistical but not clinically relevant.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
‡	See note number 1 above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by dividing the sample randomly into two parts, and doing the exploratory analysis in one part and the confirmation of results in the other.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and are applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but are still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. Exploratory studies collect information and analyze it to look for factors that are “significantly” associated.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favor of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (e.g. 1-6 months acute, 1-5 years chronic).

Table 3. Grades of recommendation

A	Based on the results of consistent level 1 studies
B	Based on the results of consistent level 2 or 3 studies **or** on extrapolations* from level 1 studies
C	Based on the results of level 4 studies **or** on extrapolations* from level 2 or 3 studies
D	Based on the results of level 5 studies **or** on troublingly inconsistent or inconclusive studies of any level

* ”Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.

II. BACKGROUND

RA is a chronic disease that has a great impact on the patient's quality of life and gives rise to important economic and social costs.

Importance of RA to the individual

From the early stages of the disease, rheumatoid arthritis has a significant effect on the daily activities of those afflicted, not only on their physical dimensions, such as work or recreational activities, but also on social, psychological and economic dimensions.

RA symptoms have an impact on the individual even before diagnosis, since RA is a disease of insidious onset. The patient may wait months before seeking advice from a physician, attributing the symptoms to mechanical causes or a process of deterioration. Once the diagnosis is established and the patient understands the significance of the disease, a period of adaptation begins, which also includes family and friends (Griffith, 2001). In most studies a significant improvement is seen in scores on the Health Assessment Questionnaire (HAQ) after the first year of the disease, possibly related with the improved clinical picture, but also due to processes of adaptation. In the same way, pain scale scores during the first year are higher than those for established disease, which suggests a psychological process of adaptation and pain tolerance that must be kept in mind (Griffith, 2001). The process of tolerance and adaptation to pain should not be interpreted as an improvement in the disease, therefore routine patient evaluation is of fundamental importance. In addition to chronic pain and altered physical and mental health, the most important long-term consequence of the disease is disability, which directly affects personal and social relations, work activity, and the economic situation of the individual and his/her family, and which is directly related with increased expenditure and the emergence of comorbidity (Sherrer, 1986).

Importance of RA to society

RA is a frequent disease with little variation in prevalence among countries, ranging between 0.5 and 1%.

RA is a frequent disease whose prevalence varies little among countries, ranging between 0.5 and 1% (Spector, 1990), with a prevalence of 0.5% in Spain (Carmona, 2002). It is estimated that 200,000 persons in Spain are afflicted with RA. Although no incidence data are available for Spain, in countries in our region of the world, like France, it is estimated that 8.8 new cases per 100,000 population occur per year (Guillemin, 1994). The social and economic burden of RA have been evaluated in some studies. In summary, the following aspects can be highlighted:

- Radiologic indications of joint destruction exist in 70% of patients 2 years after disease diagnosis (Scott, 2000a; Eberhardt, 1995).

- Between 15% and 20% of recently diagnosed patients require arthroplasty due to joint destruction within a period of 5 years (Eberhardt, 1995).

- 10 years after RA onset, over 50% of patients suffer severe disability; 15 years afterwards, only 40% can work (Blumberg, 2001.

- The prevalence of depression among RA patients is estimated to range between 14% and 43% (Pincus, 1993).

In Mediterranean countries the disease may have a more benign course than in the countries of northern Europe (Ronda, 1994; Drosos, 1992), with fewer extra-articular manifestations and erosions, although the data are not conclusive. It has also been suggested that the disease has become more benign in recent decades, but this is probably more a reflection of early diagnosis and more appropriate treatment than of a change in characteristics of the disease process (Welsing, 2005). Mortality associated with RA is higher than in the general population, is directly related with disease severity, and has changed little over time (Pincus, 2001; Gabriel, 2003).

In 2001, the costs due to RA in Spain exceeded 2,250 million euros, and the annual cost per patient was over 10,700 euros. In the same year, the direct costs attributable to RA were calculated at 1,575 million euros, representing 70% of total costs. The remaining 30% (675 million euros) was for indirect costs. The intangible costs are difficult to measure in monetary units, but it is worth noting that there is a very significant loss of health-related quality of life in RA patients (Lajas, 2003).

Thus, after analyzing these data it can be concluded that RA generates important costs to the National Health System and for society as a whole. It is estimated that the cost of treating one RA patient in Spain is, as is the case in the US, triple that of an individual of the same age and sex (Lajas, 2003). Moreover, it has been calculated that up to 5% of all permanent work disabilities in Spain are directly due to RA (Carmona, 2001).

III. DIAGNOSIS

Suspected RA

III.1.1. Importance of early diagnosis in RA

The sooner RA treatment begins, the higher the likelihood of controlling the inflammatory process and reducing structural damage; thus, "recent-onset arthritis" should be considered a diagnostic priority. [1.a, A]

It is vitally important to discriminate as soon as possible between RA and other forms of arthritis with different prognoses and approaches, therefore patients with "recent-onset arthritis" should be considered a diagnostic priority for both the primary care physician and the rheumatologist.

Early diagnosis is a cornerstone of disease control. However, it is not easy. (Quinn, 2001). Harrison et al. examined 486 primary care patients with recent-onset arthritis (duration 1-39 months), to whom they applied the 1987 ACR classification criteria, excluding the use of x-rays to establish the presence of radiologic changes. The diagnosis of RA was confirmed in only 50% of patients referred to a rheumatology service (Harrison, 1998).

The most important clinical characteristics of RA are chronicity and joint destruction, and both require time to manifest themselves. Several studies (Scott, 2000b; Boers, 2003), have shown that:

- Most patients have significant radiologic damage within the first 2 years of the disease, and this is the period when structural damage progresses most quickly.

- The sooner treatment begins, the greater the likelihood of controlling the inflammatory process and reducing structural damage ("therapeutic window of opportunity") (Raza, 2006).

III.1.2. Detection of RA in Primary Care

The longest a patient with suspected RA should wait for a rheumatology appointment is 2 weeks. [5, D]

According to a Spanish study (Hernández-García, 2000), the mean waiting time in RA from symptom onset to specialist care may be as long as 17 months, a time that is clearly excessive. The determinants of delayed detection are: 1) the patient's delay in seeking medical attention and 2) the physician's delay in referring the patient to specialist care.

The Spanish Society of Rheumatology has published standards for process times and quality of care in rheumatology. According to these standards, for a patient with inflammatory systemic disease, the maximum wait time between consultation with the primary care physician and access to a specialist in rheumatology should not exceed 2 weeks (SER, 2005).

III.1.2.a. Criteria for referral to from Primary Care to Rheumatology

All cases of arthritis lasting more than 4 weeks should be referred to specialty care, regardless of the suspected diagnosis. Patients with suspected septic arthritis should be referred immediately. [5, D]

There are various recommendations about criteria for referral from primary to specialty care, however, none of these have been validated or studied prospectively; those that exist have been formulated by consensus. Within the SERAP project (http://www.ser.es/), the SER, in conjunction with primary care physicians, has established three criteria for referral of recent-onset arthritis (Table 4). Referral is recommended when at least one of the three criteria has been present for at least 4 weeks. Preliminary analysis of this algorithm to detect RA patients has shown a sensitivity of 96.2%, a specificity of 94.9%, and positive and negative predictive values of 97.1% and 93.3%, respectively (Lisbona, 2006). Other studies (Emery, 2002) (Table 4), have also established specific criteria for RA referral. Although similar, the criteria for referral of recent-onset arthritis are less restrictive. It is currently agreed that all cases of recent-onset arthritis lasting more than 4 weeks should be referred to specialist care, regardless of the suspected diagnosis, except in the case of septic arthritis, which should be referred immediately, without waiting 4 weeks.

In practice it is often difficult to diagnose polyarthritis in the early stages since its onset is usually insidious and prolonged. Recent studies show that, before the emergence of clinical symptoms, there is a prolonged phase of subclinical or barely symptomatic inflammation that can be detected with special techniques such as Power Doppler scanning, the presence of antibodies, or slight elevations of acute phase reactants such as CRP. But these alterations can only be detected with highly sensitive techniques, such as ELISA, which are not usually available in most primary care centers (Kraan, 1998; Rantapaa-Dahlqvist, 2003; Nielen, 2004a; Nielen, 2006).

Table 4. Criteria for referral of recent-onset arthritis to Specialty Care

Criteria for arthritis referral from the SERAP project **Presence during > 4 weeks of:**
1. Swelling in **two** or more joints, as evidenced by the *squeeze test* (lateral compression of metacarpophalangeal or metatarsophalangeal joints)
2. Involvement of metacarpophalangeal or metatarsophalangeal joints
3. Morning stiffness lasting more than 30 minutes
Specific RA referral criteria according to Emery
1. Swelling in **three** or more joints
2. Pain on palpating metacarpophalangeal or metatarsophalangeal joints
3. Morning stiffness lasting more than 30 minutes

III.1.2.b. How to improve referral from primary care to rheumatology care

The diagnostic yield from primary care can be improved if patients are discussed previously with the specialty unit or reference rheumatologist and/or with joint development of protocols defining the criteria for referral. [5, D]

Patients with recent-onset RA should be treated as early as possible with DMARDs to control symptoms, delay disease progression and improve prognosis (Emery, 2002). This will require:

- Development of protocols that help to identify patients with recent-onset arthritis, in conjunction with primary care physicians.

- Definition of referral paths in accordance with protocols created in each area that lead to a reduction in existing delays and a more effective approach to cases of possible recent-onset RA.

For Klareskog, correct referral by the primary care physician depends on frequent contact between the two levels, the assurance of rapid assessment (1-2 weeks) of the patients referred, and of complementary visits (3-6 times a year) by the rheumatologist to the health centers in the hospital's area of reference (Klareskog, 2001). Cases are discussed during these visits, which improves the diagnostic skill of primary care physicians and familiarizes them with the therapeutic options, and allows the specialist to appreciate the difficulty of establishing a diagnosis, opening up possible paths of investigation for the development of screening instruments that can be used in primary care.

Access to the rheumatologist

Arthritis patients obtain access to the rheumatologist through recent-onset arthritis units (ROAUs), or by routine consultation with specialist care in rheumatology.

III.1.3. Recent-onset arthritis units

Recent-onset arthritis units are specialized units whose purpose is to receive, assess and "protocolize" care for patients with signs or symptoms suggestive of short-term inflammatory arthritis, in order to assure access to efficient diagnosis and treatment.

III.1.3.a. Requirements for its creation

The requirements for the creation of a ROAU are: a) existence of a health area with a sufficiently large population; b) collaboration between primary and specialty care (referral protocols) allowing the primary care physician to identify patients; c) presence of interested person/s in the reference hospital; and d) availability of adequate infrastructure.

III.1.3.b. Objectives of the ROAU

Each ROAU must **define the group of diseases** for which it aims to provide care. Any rheumatic disease may at some point in its evolution involve an episode of synovitis, which may sometimes be the first manifestation of RA, therefore patients with arthritis of different etiologies may be referred to these consultations. However, the evolution and prognosis of some of these cases of arthritis will often not require follow-up in the ROAU (as in the case of viral arthritis, arthritis from primary arthrosis or microcrystalline arthritis). Consequently,

patients diagnosed with one of these pathologies may be referred back to their primary care physician or to the general rheumatology consult.

The most important therapeutic objective of the ROAU is to find markers of severe disease that are present in the early stages, which can guide the treatment approach needed to achieve a more favorable prognosis. A time limit must be established for inclusion of patients in the unit. If the priority objective of the unit is treatment (study of prognostic factors and response to treatment), **the time limit to define early arthritis can be established at 1 year.**

For research purposes, the ROAU **should establish the time limit for evolution of arthritis as a maximum of 3 months.** This objective implies a highly responsive and well equipped health organization and infrastructure, to be able to receive patients with such a short time of evolution.

III.1.4. Organization of the consult in its interaction with primary care

Training measures and protocols should be agreed with primary care physicians, with good communication between the two levels (primary and specialty care); this makes it possible to evaluate the effectiveness of the protocols, be reminded of the importance of using them, and demonstrate their utility. [5, D]

In both the ROAU and ordinary specialty care rheumatology, the necessary organizational measures should be established to permit detection of incident cases of arthritis. For this purpose, training measures and protocols should be implemented in agreement with primary care, according to their availability in each area, as stated in the preceding section. Once these measures or protocols are established, it is important to have good communication with primary care to so as to evaluate their degree of effectiveness, be reminded of their validity, and demonstrate their usefulness (Klareskog, 2001).

Possible mechanisms to achieve good communication between primary and specialty care include:

- Conduct discussion sessions, present cases and the latest news on diagnosis and treatment, with the periodicity of these sessions to be agreed in accordance with realistic possibilities.

- Establish telephone, email or fax contact (in both directions) for cases that cannot be delayed or specific problems, thus avoiding unnecessary consultations.

- Write “interconsultation” reports for patients being followed up, with information to facilitate control on the part of the family physician until the next checkup: clinical evolution, correct compliance with treatment, detection of the emergence of complications of the disease *per se* and those of treatment itself (hepatic tolerance, renal function, hematological disorders).

- Carry out coordinated activities when the collaboration of other specialists is required, such as physical therapists, surgeons or mental health professionals.

Diagnosis of rheumatoid arthritis

More than a science, RA diagnosis is an art that combines symptoms, signs and biological and imaging tests. Accurate diagnosis is not difficult in established disease, even for untrained persons. There are RA classification criteria, such as the **1987 ACR classification criteria,** which have shown good sensitivity and specificity in the diagnosis of advanced cases of RA. However, although these criteria were accepted as a starting point for a definition of the disease, and in order to differentiate between patients with established RA and those with another rheumatic disease, they are not valid for identification of patients who could benefit from effective early intervention. Therefore, the 2010 ACR/EULAR criteria were developed (Aletaha 2010a; Aletaha 2010b).

The diagnostic value of **laboratory biological tests** is highly variable in early RA diagnosis. These tests include: synovial fluid analysis, acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), rheumatoid factor (RF) and the anti-cyclic citrullinated peptide antibodies (anti-CCP). Visser et al. have published criteria **to estimate the probabilities of evolution of early-onset RA** (Visser, 2002), based on some of these tests in addition to clinical signs and symptoms.

The discussion of whether or not to adopt new RA diagnostic criteria other than the 1987 ACR classification has been synthesized by Scott (Scott, 2002). In favor of the change are, on the one hand, the need to have criteria in the initial stages of RA since the ACR criteria are not very useful for this purpose, and, on the other, to be able to divide patients according to prognosis, which would make it possible to suggest different treatment strategies. Nevertheless, against the change of criteria is the fact that not all centers are able to perform the newest and most effective biological tests such as anti-CCP; furthermore, changing the diagnostic criteria would make it difficult to compare patients thus diagnosed with historical series that have used the classic criteria.

III.1.5. 1987 ACR classification criteria

In 1987, the ACR published a set of criteria based on their ability to distinguish between 262 patients with established rheumatoid arthritis (mean duration 7.7 ± 8.6 years) and 262 patients with other rheumatic diseases of similar duration (arthrosis, systemic lupus erythematosus, fibromyalgia and others) (Arnett, 1988), replacing the term “diagnostic” with “classification”.

These criteria were originally published in two forms, an algorithm and a list (Table 5). The classification with the algorithm is more attractive since it weighs each component differently and has the advantage that it can be used in epidemiological studies in which there are neither analytic nor radiographic results. However, the algorithm has been used only occasionally in clinical practice and has currently fallen into disuse.

III.1.5.a. Diagnostic utility of the 1987 ACR criteria for established RA

The 1987 ACR criteria have good sensitivity and specificity for the classification of previously established RA.

The 1987 ACR criteria in list form (Table 5), perform well in patients with established disease. RA is considered to be probable when 4 or more of the 7 criteria in the list are

present. This diagnostic classification has a sensitivity ranging between 75% and 95%, and a specificity of 73% – 95% (Arnett, 1988; Hakala, 1993; Levin, 1996) (

Table 6). The 1987 ACR classification criteria are currently widely used as the gold standard for RA diagnosis.

Table 5. ACR classification criteria for rheumatoid arthritis (1987)

1.- Morning stiffness	Morning joint stiffness lasting at least 1 hour.
2.- Arthritis of 3 or more joint areas	Simultaneous inflammation of at least 3 joint areas, as observed by a physician. The 14 joint areas are: proximal interphalanges, metacarpophalanges, wrists, elbows, knees, ankles and metatarsophalanges.
3.- Arthritis of hand joints	Inflammation of at least one hand area (carpal, metacarpophalangeal, proximal interphalangeal).
4.- Symmetrical arthritis	Simultaneous involvement of the same joint areas (as defined in criterion 2) on both sides of the body.
5.- Rheumatoid nodules	Subcutaneous nodules over bony prominences, extensor surfaces or in juxta-articular regions, observed by a physician.
6.- Serum rheumatoid factor	Demonstration of elevated amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of control subjects.
7.- Radiologic changes	Radiologic changes typical of rheumatoid arthritis on posteroanterior hand radiographs. Must include erosions or unequivocal juxta-articular osteoporosis in involved joints.

Table 6. Comparative performance of the 1987 ACR criteria in patients with established RA, according to recent studies

Author	Duration of RA	Sensitivity (%)	Specificity (%)
Arnett, 1987	7.7 years	91	89
Kobayashi, 1991	-	90	95
Tanimoto, 1991	-	88	93
Hakala et al, 1993	16 years	71	94
Levin et al, 1996	12 years	95	73

III.1.5.b. Diagnostic utility of the 1987 ACR criteria for recent-onset RA

The 1987 ACR criteria perform more poorly in disease of recent onset. In this stage the clinical criteria (1 to 4) are sensitive but not very specific for RA, while the remaining criteria are specific but not very sensitive.

In longitudinal studies of patients with recent-onset arthritis, it has been shown that the number of criteria met increases with length of follow-up and that not all the criteria perform equally (Saraux, 2001). In the initial stages of disease, the clinical criteria (from 1 to 4) have a good sensitivity (high probability that patients who have RA will manifest them), but poor specificity (high probability that patients with other types of arthritis different from RA will manifest them), whereas nodules and RF have good specificity (they do not usually appear in patients who have a type of arthritis different from RA), but low sensitivity (they do not usually appear in early stages of RA) (Saraux, 2001). Nor do radiologic changes appear in early stages of RA. Rheumatoid factor may be the most useful of all the criteria (Saraux, 2001).

The 1987 ACR criteria continue to be used for the diagnosis of patients with recent-onset disease; however, it should be kept in mind that these criteria were developed in a patient population selected according to presence or absence of disease, with the intention of "classifying", not "diagnosing" them. Consequently, their yield in the early stages of disease is limited because:

1. diagnosis was not the main purpose of developing the criteria,

2. most of the patients had long-term disease,

3. the predictive value of each criterion was not evaluated because the number of patients and control subjects was defined beforehand,

4. the controls had diseases that were sometimes clearly different from RA,

5. criteria 5, 7 and sometimes 6, appear at least a year after symptom onset, therefore they lack sensitivity in the early stages of the disease (Saraux, 2001).

Very few studies have investigated the diagnostic value of the 1987 ACR criteria in patient cohorts with recent-onset arthritis, and it is difficult to compare their results due to differences in the clinical characteristics of patients, in disease duration, and in the outcomes analyzed (Dugowson, 1990; Taylor, 1991; Kaarela, 1995; Harrison, 1998; Hulsemann, 1999; Saraux, 2001). Table 7 shows how the performance of the criteria improves with increasing time of disease evolution.

Table 7. Performance of the 1987 ACR criteria in different studies of patients with recent onset RA.

Author	Duration of RA	Sensitivity (%)	Specificity (%)
Dugowson, 1990	3.5 months	74	-
Taylor, 1991	< 3 months	93	63
Kaarela, 1995	< 6 months	84	86

Harrison, 1998	Median 5 months	57 - 68	43 - 67
Huselman, 1999	< 12 months	90	90
Saraux, 2001	< 12 months	91	75

III.1.5.c. 72010 ACR/EULAR classification criteria

The main reason for drafting new criteria was the lack of sensitivity of the previous criteria (1987) in early disease.

The objective was not to create diagnostic criteria or a referral tool for general physicians, but to develop new classification criteria to facilitate the study of patients in early stages of the disease.

The criteria were developed by studying the role of different clinical and analytical variables and the relative weight of each one as a predictor of the initiation of treatment with DMARDs in patients with early undifferentiated arthritis. The physician's decision to start treatment with DMARDs was used as an indicator that the patient was at risk of developing erosive and/or persistent arthritis. Data from 3115 patients with recent-onset arthritis were used. In a second phase, an expert panel provided real cases of patients with early undifferentiated arthritis and any degree of probability of developing RA. They identified important domains and categories in the determination of the probability of developing RA. The relative importance or weight of these variables was determined using a computer program. An individual index of the probability of developing RA (measured from 0 to 100) was calculated. In a third phase, the working party integrated the findings of the 2 previous phases, streamlined the system, and established the optimal cut-off point for confirming RA. Finally, the criteria were validated by applying them in 3 cohorts not used during the development of the criteria.

The new criteria classify a disease as RA if the patient presents synovitis in at least 1 joint in the absence of a diagnosis that accounts for it and a score of 6 (out of a total of 10) in 4 domains:

Table 8. 2010 EULAR/ACR Classification Criteria.

Number and site of joints involved	(0-5)
Serologic abnormalities	(0-3)
Increased acute phase reactants	(0-1)
Duration of symptoms	(0-1)

It is important to take the following into account:

- The starting point for application of these criteria is the presence of synovitis; they should not be applied in healthy patients or in patients with arthralgia.

- The criteria should only be applied in patients with synovitis of unknown origin; it is the responsibility of the attending physician to make this differential diagnosis.

- Synovitis does not have to be symmetrical.

- These criteria are dynamic. A patient who is not initially classified as having RA can be classified as such over time.

- These criteria do not enable a family physician to refer a patient to the rheumatologist.

- These criteria are based on current knowledge; therefore, they should be revised if new imaging, serologic, or genetic biomarkers appear.

- The cut-off point can probably vary depending on how the criteria are applied.

These criteria are for classification, not for diagnosis. They aim to provide a standardized method of identification of the subgroup with the highest probability of developing persistent erosive RA, so that they can be included in clinical trials or other studies that require uniform criteria. These patients will benefit from treatment with DMARDs. Nevertheless, a rheumatologist can diagnose a person with RA, even if they do not fulfill the criteria or have manifestations not included in the criteria.

The new criteria must be tested in various clinical situations.

III.1.6. Diagnostic utility of biological tests in recent-onset RA

Of the currently available biological tests, RF and anti-CCP antibodies have shown the greatest diagnostic and prognostic utility for recent-onset RA.

III.1.6.a. Synovial fluid

Inflammatory synovial fluid confirms the diagnosis of arthritis, but is not highly specific for RA.

Synovial fluid is of very limited value in RA diagnosis and is not included in any modality of diagnostic criteria. On occasion its analysis may be relevant, since the presence of inflammatory synovial fluid confirms the diagnosis of arthritis. Cellularity and other parameters make it possible to classify synovial fluid into 5 categories: normal, non-inflammatory, inflammatory, purulent and hemorrhagic (

Table), **but a specific diagnosis can never be made, except in the case of microcrystalline and infectious arthritis.**

Table 9. Classification of synovial fluid according to composition

	Normal	Non-inflammatory	Inflammatory	Septic	Hemorrhagic
Color	Clear	Yellow	Iridescent yellow	Yellow or green	Red
Leucocytes/mm3	<200	200-2,000	2,000-50,000	>50.000	200-2,000
Proteins (g/dl)	1-2	1-3	3-5	3-5	4-6

Glucose (mg/dl)	Same as blood	Same as blood	25% less than blood	>25% less than blood	Same as blood

III.1.6.b. Acute phase reactants

The acute phase reactants (ESR and CRP) reflect the presence and intensity of an inflammatory process, but are not specific for RA.

The acute phase reactants appear or vary in concentration by more than 25% in the presence of an inflammatory process, independently of the cause, and are not useful in diagnosing RA. The situations which produce the greatest variation in the acute phase reactants are infections, surgery, traumas, burns, tissue infarcts, inflammations of immune origin and neoplasms. The two acute phase reactants most often used are erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (Paulus, 1999; van Leeuwen, 1997).

III.1.6.c. Rheumatoid factor (RF)

The presence of RF in a patient with polyarthritis makes the diagnosis of RA very probable, but its absence does not rule out RA (its sensitivity ranges between 40% and 80% depending on the setting in which it is determined). RF has prognostic value since it is associated with more serious disease, more extensive joint involvement, more destruction and greater disability. It may appear years before the onset of arthritis symptoms.

RF is an antibody against the Fc portion of IgG. IgM is the most common isotype, although there may also be others, mainly IgG and IgA isotypes. It is currently determined generally by nephelometry, although ELISA techniques are needed for some isotypes.

IgM RF is characteristic of RA and is detected in 40-80% of cases, depending on whether the RA has been diagnosed in the community or in a hospital setting. It presence in a patient with polyarthritis makes the diagnosis of RA very probable, but its absence does not rule it out. RF may appear years before arthritis symptoms are seen or, less frequently, after symptom onset, and may disappear in response to treatment.

RF appears in 50% of cases of palindromic rheumatism (recurring episodes of monoarticular or oligoarticular inflammation occurring at intervals ranging from weeks to months). The presence of RF increases the probability of evolving to RA (Zendman, 2006). In these cases, inflammatory episodes become more and more frequent and extensive as RA evolves.

RF may also appear in older healthy persons, but at low titers, and in patients with other diseases such as lupus, Sjögren's syndrome, primary biliary cirrhosis, chronic infections and neoplasms.

The diagnostic utility of RF for RA varies depending on whether the test is made in persons with RA-compatible symptoms or not. In hospital patients with arthritis, the positive and negative predictive values are 70-80% and over 95%, respectively (Wolfe, 1998a; Wolfe, 1991a). Besides its diagnostic value, RF has prognostic value since it is associated with more serious disease, with more extensive joint involvement, greater destruction and more disability (Scott, 2000b).

III.1.6.d. Anti-cyclic citrullinated peptide antibody (anti-CCP)

The sensitivity of anti-CCP antibodies ranges from 12% to 93% and their specificity from 63% to 100%). They may appear years before the disease and are related with the prognosis for its progression.

Anti-CCP determination should be requested when evaluating a patient with recent-onset arthritis. [1b, A]

Citrullination is a post-translational modification of arginine produced by the peptidylarginine deiminase enzyme (van Venrooij, 2004). For decades, anti-CCP antibodies have been detected in the serum of RA patients in different forms, such as anti-perinuclear factor or anti-keratin antibodies. Citrullinated synthetic peptides are currently used as an ELISA substrate, which has considerably improved the sensitivity of the technique and allows its quantification.

The sensitivity of anti-CCP antibodies ranges from 12% to 93% and their specificity from 63% to 100%. Their specificity is greater than that of RF (96% vs 86%), and their sensitivity is similar; they are present in only 1-3% of healthy persons (Zendman, 2006), which leads some authors to consider them more useful than RF (Visser, 2005). The fact that around 40% of RA patients with negative RF have positive anti-CCP increases its diagnostic value (Zendman, 2006; Quinn, 2006). The same as RF, anti-CCP antibodies may be present for several years before the disease appears, and their presence is related with severity. They also appear in 50% of cases of palindromic rheumatism and, like RF, are a prognostic factor for RA progression.

A systematic review (SR 1) has been made to study the "Value of anti-CCP in RA diagnosis and prognosis". The review included 52 articles that are of diagnostic and/or prognostic utility.

The conclusions of this review are as follows:

- ELISA anti-CCPs are useful for diagnosis because their probability quotients are very high **[1a].**
- Combining anti-CCP with any RF isotype is more valuable than RF alone in undifferentiated early oligoarthritis and polyarthritis **[1b].**
- The use of anti-CCP antibody as a marker is open to debate. As a marker of activity and remission, its utility is moderate **[2a and 1b respectively],** and further studies are necessary to establish its validity in this respect. As a prognostic marker, in terms of radiologic progression, its utility is also moderate **[1b]** and, although most studies associate this marker with greater radiologic progression, the existence of contradictory results means that further studies should be performed to confirm the findings.

III.1.7. Proposals of new diagnostic criteria for recent-onset arthritis

The 1987 ACR criteria perform better at defining disease chronicity than at distinguishing between patients who will have a destructive and incapacitating course of disease from those who will not. Visser et al have published criteria to estimate the probability that

patients with recent-onset arthritis will develop self-limiting, persistent non-erosive or persistent destructive disease.

Another way to approach the diagnosis of recent-onset arthritis is based on the probability of reaching different outcomes: resolution, chronic non-erosive or chronic erosive. From an operational point of view, this approach to prognostic classification of RA is more practical for the patient and physician, but it may cause difficulties when comparing outcomes with studies made using different criteria.

No one currently doubts the critical importance of diagnosing recent-onset RA to initiate early treatment and improve prognosis. However, there are important gaps in our knowledge of the disease, for example, with regard to the most appropriate treatment at each stage of the natural history of the disease or the prognostic markers that can predict more serious disease (Kim, 2000).

The 1987 ACR criteria perform better at defining disease chronicity than at distinguishing between patients who will have a destructive and incapacitating course of disease and those who will not (Quinn, 2001). Instead of looking for criteria that will discriminate among patients who will meet the criteria in the future, it seems more useful to seek a combination of clinical and biological variables that will make it possible to distinguish, from the time of symptom onset, autolimiting or persistent non-destructive forms of disease from those that are persistent and erosive (Huizinga, 2002).

It is unethical to observe the natural history of disease over long periods of time without offering treatment, while waiting for different outcomes to occur. Therapeutic interventions impede our knowledge of the natural history of disease since treatment changes clinical and test measurements. Nevertheless, it is accepted that most patients develop erosions before 2 years of disease evolution, although this has not been found in all studies (Bukhari, 2001).

Visser et al (Visser, 2002) have published criteria to estimate the probability that patients with recent-onset arthritis will develop self-limiting, persistent non-erosive or persistent-destructive disease. These criteria are based on 7 variables: 1) duration of symptoms at the first visit; 2) morning stiffness of at least 1 hour; 3) arthritis in 3 or more joints; 4) pain on lateral compression of the metatarsophalangeal joints; 5) presence of RF; 6) presence of anti-CCP; and 7) initial erosions on hands or feet. The weight of each of these criteria varies according to clinical outcome (

Table 10). The equation obtained makes it possible to estimate the probability of experiencing the outcome at the first visit (Table 19).

Table 10. Value of each criterion in predicting different outcomes, according to Visser et al.

Criterion	Persistent vs. self-limiting	Erosive vs. non-erosive in persistent disease
Duration of symptoms:		
≥ 6 weeks and < 6 months	2	0

≥ 6 months	3	0
Morning stiffness ≥ 1 hour	1	1
Arthritis in ≥ 3 joint areas	1	1
Pain on compression of MTP	1	2
Positive rheumatoid factor	2	2
Anti-CCP antibodies	3	3
Rx: Erosions on hands or feet	2	Infinite

MTP = metatarsophalangeal joint; anti-CCP = anti-cyclic citrullinated peptide

Table 19. Value of the sum of all criteria for predicting different outcomes, according to Visser et al.

Persistent vs. self-limiting arthritis		Erosive vs. non-erosive arthritis in persistent disease	
Total value	**Probability of persistence**	**Total value**	**Probability of erosions**
0	0.18	0	0.10
1	0.15	1	0.16
2	0.23	2	0.25
3	0.34	3	0.38
4	0.46	4	0.52
5	0.59	5	0.66
6	0.71	6	0.78
7	0.80	7	0.86
8	0.87	8	0.92
9	0.92	9	0.95
10	0.95	∞	1
11	0.97		
12	0.98		
13	0.99		

The most important points of these criteria are:

1. They extend the duration of arthritis symptoms beyond 6 weeks, like the ACR criteria, and they agree with another study showing that persistence of symptoms for more than 12 weeks reduces the probability that self-limiting arthritis will be included in the group of persistent arthritis (Green, 1999).

2. Similar to the ACR, they include morning stiffness and arthritis of 3 or more joint areas.

3. They replace symmetrical involvement and arthritis of the hands with pain on lateral compression of the metatarsophalangeal joints (subrogate marker of arthritis), which is not incompatible with the observation that erosions very often begin on the feet before the hands (Scott, 1997).

4. With regard to the laboratory criteria, they maintain the importance of RF, but add the presence of anti-CCP as an independent marker. The value of these antibodies in the early diagnosis of RA has been described in other publications (Bas, 2002).

5. The maintain radiologic erosions on the hands, and include the feet.

IV. EVALUATION

Specific RA evaluation

IV.1.1. Appropriate data for first evaluation of RA patient

The first evaluation of an RA patient should include: clinical history, physical examination, blood test and urinalysis. [5, D]

These basic exams facilitate RA follow-up and early detection of disease complications and side effects of treatment. Other complementary exams may be requested at the discretion of the physician, who should consider for each case the medical history, age, associated treatments, possibility of preventive interventions (e.g., cholesterol or glycemia) and associated comorbidity.

IV.1.1.a. Clinical history

The clinical history should include: family and personal history, sociodemographic data, previous history of current disease and treatments (previous and concomitant). [5, D]

As in other clinical conditions, the first evaluation should include a clinical history. This should include a **family and personal history** (of diseases, surgical procedures, allergies), with special emphasis on those conditions that required medical treatment, hospital admission or were life-threatening. Other data to be collected are lifestyles relating to exercise, nutrition, smoking and alcohol. Gynecological history and date of last menstruation should also be recorded.

The **sociodemographic data** should include sex, age, educational level, main work activity and employment status, given the importance of these factors for RA prognosis.

Also to be considered are **previous history of the disease** and disease duration, clinical manifestations and treatments received. Some patients will have RA of short evolution and will have received hardly any medical treatment, whereas others may visit the physician after a more or less prolonged period of arthritis, with a clinical and treatment history that must be taken into account. In these cases the clinical characteristics of the disease should be determined by questioning the patient and reviewing reports and other documents provided by the patient, such as radiographs and laboratory tests. It is particularly important to know about any kind of **previous and concomitant treatments**, especially with analgesics, NSAIDs, corticosteroids, DMARDs and biologic medications. A detailed history should be taken of DMARDs received to date, attempting to determine the dosage, duration, reasons for suspending treatment and side effects. The same information should be obtained for corticosteroids. With regard to NSAIDs, the patient should be questioned as to tolerance and observed side effects, especially in relation to the digestive system.

IV.1.1.b. Physical examination

The physical examination, in addition to the routine exam of organs and systems, should include a detailed evaluation of the musculoskeletal system. [5, D]

The **physical examination,** in addition to the routine examination of organs and systems necessary in any patient, should include a detailed evaluation of the musculoskeletal system, with special reference to the presence of pain, swelling, mobility, deformities, subcutaneous nodules, skin alterations, and, in general, any other signs and symptoms related with arthritis.

IV.1.1.c. Blood test and urinalysis

The blood test should include: complete blood count, ESR, CRP, RF, anti-CCP, liver biochemistry and serology, and renal function. For urine, a basic urinalysis is sufficient. [5, D]

The **laboratory tests** consist of a complete blood count, acute phase reactants (ESR, CRP), RF, anti-CCP antibodies, liver biochemistry (GOT, GPT, GGT, alkaline phosphate, albumin), kidney function (creatinine), calcium and basic urinalysis. Evaluation of the presence of hepatitis B and C is also recommended (considering the hepatotoxicity of some drugs used in treatment).

IV.1.2. Data common to the initial evaluation and follow-up of RA

Both the initial and follow-up RA evaluations should be based on the systematic assessment of a minimum set of parameters which allow evaluation of the degree of inflammatory activity, functional disability and residual structural damage. The use of specific forms to facilitate systematic data collection is recommended. [5, D]

At the first conference of OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials), held in Maastricht en 1992, North Americans (Felson, 1993a; Felson 1993b) and Europeans (Scott, 1992) reached an historic agreement on resolutions regarding the minimum set of parameters to be used in evaluating RA patients included in clinical trials (OMERACT, 1993). These recommendations were subsequently ratified by the ACR (Felson, 1993a), the World Health Organization (WHO), the European Leagues Against Rheumatism (EULAR), and the International Leagues Against Rheumatism (ILAR) (Boers, 1994). The parameters were chosen by consensus after examining the reliability, validity, and sensitivity of those most frequently used in the clinical evaluation of RA, with the aim of obtaining a set of parameters that would allow evaluation of all relevant aspects of the disease, without redundancy. This core set of parameters, which was originally selected for use in clinical trials, has been shown to be useful in daily clinical practice.

Table 102. Minimum set of parameters for RA evaluation recommended by OMERACT 1993 (Outcome Measures in Rheumatoid Arthritis Clinical Trials)

1) Number of painful joints
2) Number of swollen joints
3) Pain
4) Global disease assessment by the patient
5) Global disease assessment by the physician
6) Acute phase reactants
7) Physical functional capacity
8) Radiologic damage (RA of more than 1 year's evolution)*

*The evaluation of radiographic damage is recommended for studies lasting 1 year or more, although the results of more recent studies have shown that radiographic changes in the hands and feet can be observed in periods of as little as 6 months (Sharp, 2000).

There are clear advantages to using these parameters to monitor patients (Pincus, 1996; Wolfe, 1999a). However, studies show that rheumatologists' follow-up of RA patients is not done in a systematic way, and their use of different parameters for disease evaluation varies greatly (Bellamy, 1998; Bellamy, 1999) (Pincus, 2006a). The data for Spain are no more encouraging (Villaverde, 2003).

Nevertheless, rheumatologists are currently more aware of the benefits of making a **systematic clinical evaluation**. The limited use made of the minimum set of parameters and the variability shown in their application could be related with the effort needed to implement them in daily clinical practice in a high-pressure health care setting. They are probably applied more in some subgroups of patients with early arthritis, with shorter time of evolution and in treatment with biologics.

The use of specific forms (appendix 1) is highly recommended as this facilitates the use and follow-up of the parameters included in the minimum data set.

IV.1.2.a. Parameters to measure the degree of inflammatory activity

Evaluation of inflammatory activity is recommended by counting the number of painful and swollen joints, assessment of pain, global disease assessment (by patient and by physician), measurement of acute phase reactants and synthesis of this information using combined activity indices (DAS, SDAI). [5, D]

- Joint counts

The evaluation of the number of painful joint and the number of swollen joints should be performed using validated methods based on counting at least 28 joints. [5, D]

Although complete counts, based on the examination of 68 joints for tenderness and 66 for swelling (excluding the hip), offer more information, it takes twice as long as the simplified 28-joint count used in the calculation of combined indices (DAS28, SDAI). An intermediate situation is a good compromise: the use of 44-joint counts, which was used in the original version of the DAS.

The ACR originally recommended the use of complete 68-joint counts, although it later accepted the use of 28-joint counts in clinical trials. However, the same committee emphasized that indices based on 28 joints exclude those of the feet and ankles, which are affected in over 50% of patients, therefore they provide less information at the individual level (OMERACT, 1994). The use of a reduced index does not mean that these joints should not be examined, but in clinical practice the use of 28-joint indices is recommended. Appendix 2 summarizes the main validated methods for the evaluation of the number of tender joints and the number of swollen joints.

This panel recommends joint counts based on simple quantification of the presence or absence of tenderness (number of tender joints) and swelling (number of swollen joints) in the joints evaluated. The apparent advantages of a semi-quantifying the degree of tenderness and selling in each joint using a 4-level ordinal scale (0-3) are offset by the greater variability in measurements.

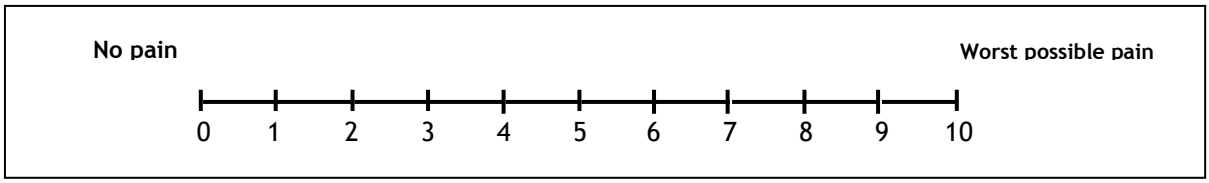
The use of a joint diagram where, in addition to noting the tender and swollen joints, other observations of clinical interest can be made, is highly recommended (appendix 2).

- Evaluation of pain

Pain should be assessed by the patient him/herself. It is recommended that pain be measured using a horizontal visual analog scale, 10 cm in length, divided by vertical marks into ten equal 1-cm segments. The measurements should be accompanied by numeric descriptors from 0 to 10, with indicators at each end showing no pain (0) and worst pain (10). (Figure 1). [5, D]

The ACR/OMERACT recommendations advise the use of a visual analog scale (VAS) or a Likert-type scale to measure pain, although existing studies show a clear preference for the VAS. Most patients are able to fill out this scale. It is first necessary to devote some time to explaining the scale and giving a specific example; patients then answer quickly and with confidence. Some modifications, such as the use of numeric descriptors, may improve reliability in persons with low educational level [Ferraz, 1990]. The VAS for pain shows good correlation with the Likert scale, and both are sensitive to clinically important changes, with the VAS showing certain advantages (Langley, 1984a; Anderson, 1993; Buchbinder, 1995).

Figure 1. Visual analog scale



- Global assessment of disease

A global assessment of disease should be made, from the point of view of both the physician and the patient. For this measurement, the use of a 10 cm horizontal visual analog scale is recommended, with vertical marks dividing it into 10 equal 1 cm segments. The measurements should be accompanied by numeric descriptors from 0 to 10, with "very good" (0) at one end and "very poor" (10) at the other. (Figures 2 and 3). [5, D]

Global assessments of disease by both the physician and the patient are useful because their evaluations may be quite different. The global assessment is very sensitive to clinical changes (Buchbinder, 1995; Anderson 1989). Moreover, the physician's global assessment of disease is the only way to quantify his/her opinion throughout the disease process.

Figure 2. Scale for patient's global assessment of disease (PaGA)

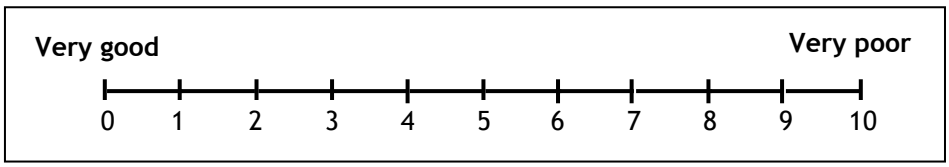
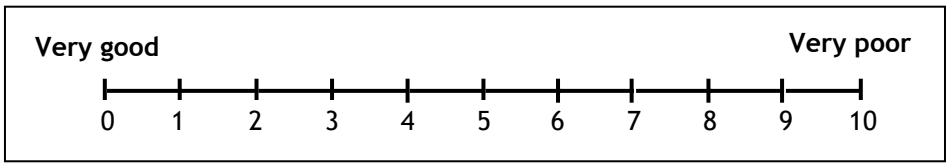


Figure 3. Scale for physician's global assessment of disease (PhGA)



- Acute phase reactants

Laboratory tests should include two acute phase reactants (APRs): erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The behavior of these two APRs is closely related with the inflammatory activity of the disease. [5, D]

Measurement of APRs is very helpful in monitoring inflammatory processes in general, and of joint inflammation in particular. Their levels are associated with the intensity of underlying inflammation. There are several acute phase reactants but, in practice, the ESR and CRP are the most widely used. Both were included in the ACR recommendations and have been shown to be about equally useful in assessing inflammatory activity [Paulus, 1999]. The advantage of the ESR is that it is inexpensive and available in any laboratory, and its disadvantage is its low specificity, since its levels can be modified by factors independent of joint inflammation. The advantage of CRP is that its levels are virtually non-existent in the absence of inflammation, and its synthesis is closely related with inflammatory activity, with a very short half life. The techniques for measuring CRP are currently available in most laboratories. Persistent elevation of acute phase reactants with respect to normal reference values, especially for CRP, has been associated with poorer disease outcome. (Dawes, 1986; van Leeuwen 1993; van Leeuwen, 1997).

- Composite indices of disease (DAS, SDAI)

The use of composite indices summarizing information on various parameters in a single indicator is a useful and valid procedure in assessing disease activity. This guideline recommend the use of the Disease Activity Score (DAS/DAS28) and/or the SDAI (Simplified Disease Activity Index). [5, D]

Different composite indices have been published, and their validity has been reviewed in the framework of the OMERACT conference [OMERACT, 1993]. Some good examples are the Pooled Index, the index of Mallya and Mace, the Stoke index, the Scott index, and the DAS. These indices differ in the number of parameters included as well as the methods used for their calculation. Their advantages in comparison to conventional assessment using single parameters are that they avoid duplicate measurements and are more sensitive to change. Their disadvantages are a certain degree of complexity in the calculations, difficulty of interpretation, and some problems related with how they are constructed.

The DAS deserves particular mention [Van der Heijde, 1990; van der Heijde, 1992a]. This index includes the following parameters: the Ritchie index (RI), number of swollen joints out of 44 joints (NSJ44), erythrocyte sedimentation rate (ESR), and the patient's global assessment (PaGA) of health on a visual analog scale (0 cm "very good" - 10 cm "very poor"). The patient's global assessment of disease can be used instead of the global assessment of health, using the same scale. The DAS is calculated using the following formula:

$$\mathrm{DAS} = 0.54(\sqrt{\mathrm{RI}}) + 0.065(\mathrm{NSJ44}) + 0.33(\ln \mathrm{ESR}) + 0.0072(\mathrm{PaGA})$$

There is a modified DAS based on the number of painful joints (NPJ28) and swollen joints (NSJ28) out of 28 joints, which is much more useful in clinical practice and is recommended by EULAR [Prevoo, 1995]:

$$DAS28 = 0.56(\sqrt{NPJ28}) + 0.28(\sqrt{NSJ28}) + 0.70(\ln ESR) + 0.014(PaGA)$$

The scores for the DAS and the DAS28 range from 0 to 10. The DAS is of particular interest because it is the basis for the EULAR improvement criteria (Van Gestel, 1996).

The DAS and DAS28 scores cannot be compared directly, but a formula exists to transform one to the other (van Gestelt, 1998). There are modifications to the DAS, using CRP instead of ESR (Aletaha, 2006), which have been developed for use in clinical trials in which CRP is measured in central laboratories. This index was developed as a mathematical approximation of the DAS and was not derived from patients, nor has it been validated, therefore its use and interpretation is controversial and it is not recommended in clinical practice.

Another, similar index has recently been proposed: the SDAI (Simplified Disease Activity Index) (Smollen, 2003), which is derived from an index developed to assess the activity of reactive arthritis (Eberl, 2000). The advantage of this index is that its measurement does not require a complex mathematical formula; rather, it is calculated by a simple arithmetic sum of the number of swollen and painful joints, using reduced 28-joint indices, assessment of disease activity by the patient and by the physician (measured from 0 to 10) and CRP concentration in mg/L. The inclusion of CRP instead of ESR is based on the fact that the former is a more precise measure of inflammation than the latter, it has more consistently been related with structural damage, and it is less influenced by other variables such as anemia or rheumatoid factor (Aletaha, 2005a). As with the DAS, there are modifications of the SDAI, in particular, one that does not include CRP: the Clinical Disease Activity Index (CDAI) (Aletaha, 2005b), which was developed for use in cases in which acute phase reactants are not immediately available or are given as semi-quantitative values.

$$SDAI = NPJ28 + NSJ28 + PaGA + PhGA + CRP\ (mg/dl)$$

To facilitate interpretation, limits need to be established so that patients with different levels of activity can be identified. Categorization into classes according to activity is important to propose, initiate, or change a treatment (in case of high or moderate activity) or to define treatment objectives (low activity or remission). It has recently been demonstrated that RA outcome improves with regular measurement of activity and adjustment of treatment to achieve low levels of activity or remission (Grigor, 2004). Moreover, the emergence of new drugs and the use of intensive treatment strategies has considerably changed the potential for achieving very low levels of activity or even remission (Quinn, 2003).

IV.1.2.b. Classification of level of inflammatory activity

Inflammatory activity can vary depending on the patient, the moment of disease evolution or the response to treatment. Classically, we can distinguish four types of inflammatory activity: remission, low, moderate or high activity. Different criteria have been developed to permit classification in one of these phases, among them, the ACR clinical remission criteria, and criteria for clinical remission and inflammatory activity based on indices.

- ACR criteria for clinical remission

The ACR considers clinical remission to exist when at least 5 of the 6 criteria are met for a period of at least 2 months. The clinical utility of this definition is low because it uses 2 criteria not routinely used in patient evaluation.

The ACR establishes 6 criteria for the evaluation of clinical remission of RA (Table). The presence of at least 5 of these criteria for 2 months or longer is enough to identify a patient as being in complete remission, with a sensitivity of 72-80% and a specificity of 96-100% (Wolfe, 1985; Pinals, 1981). The predictive values of these criteria can vary in different populations (Alarcón, 1987). Their main disadvantages are the lack of specific measures, their dichotomic value (small modifications in clinical disease activity can change the classification), and that 2 of the criteria (fatigue and morning stiffness) are not part of the parameters recommended to evaluate patients with RA (Tugwell, 1993; van Riel, 1992; Boers, 1994; Felson, 1993b; Wolfe, 1999b).

Table 13. ACR criteria* for clinical remission of RA

1. Morning stiffness absent or not exceeding 15 minutes
2. No fatigue
3. No joint pain in medical history
4. No joint tenderness
5. No soft tissue swelling in joints or tendon sheaths
6. Normal erythrocyte sedimentation rate

*** ACR considers clinical remission to occur when at least 5 of the 6 criteria are met.**

- Criteria for clinical remission based on indices

These criteria are of more clinical interest since they use the same tools as employed to measure RA activity (DAS and SDAI). Different cut-off points considered as clinical remission have been established. The current tendency is to consider a patient in clinical remission when DAS28<2.4 or SDAI<3.3.

The ACR criteria for remission are of very little clinical use. Logically, remission should be defined using the same tools as employed to measure disease activity, in this case, the DAS and SDAI. In 1996 the DAS cut-off point for remission was proposed as DAS <1.6 (Prevoo, 1996), using a modification of the ACR criteria as the gold standard. Some years later the value for the DAS28 was extrapolated using a relational formula, therefore this value does not derive from real patients (van Riel, 2000). Although it is the most commonly used in many clinical trials, this cut-off point (DAS28 <2.6) has been criticized from both the theoretical and clinical point of view. The DAS cut-off point was established using a modification of the ACR criteria, which are accepted as obsolete. The DAS28 cut-off point does not derive from real patients; rather, it is a mathematical extrapolation of the original DAS. A patient could be considered to be in remission according to the DAS while having both swollen and painful joints, so long as the ESR and patient assessment are not very high (this sometimes occurs). Finally, radiologic progression has been described in patients in persistent remission (Molenaar, 2004), which means that this criterion is unable to detect low levels of activity

that may not be recognized clinically. Using different patient cohorts and always with the modified ACR remission criteria as the gold standard, cut-off points have been described that are slightly higher (DAS28 <2.81) (Balsa, 2004), similar (DAS28 <2.6) (Fransen, 2004a) or lower (DAS28 <2.32) (Makinen, 2005). In the opinion of 35 rheumatologists, the DAS28 cut-off point for an ideal patient has been established at 2.4 (Aletaha, 2005c), which reflects the changed attitudes and perceptions about RA that have been occurring in recent years, and is the value that should probably be used. Finally, from a conceptual point of view, there has been criticism of the use of reduced indices to evaluate remission that exclude hips, ankles or feet, since patients can be classified as in remission even though these joints are affected (Landewe, 2006; van der, 2005). However, although this is theoretically true, this index is more useful clinically, therefore it is more commonly employed; the error can be partially corrected as has been proposed, that is, by reducing the cut-off point to 2.6 (Makinen, 2005).

The original cut-off point for the SDAI was established at <5 (Smolen, 2003). However, after a subsequent validation exercise by another group of rheumatologists on fictitious patients, and considering that structural damage and reduced functional capacity progress in the presence of moderate activity, the SDAI cut-off for remission was reduced to 3.3 (Aletaha, 2005b).

- Classification of inflammatory activity based on indices

In addition to remission, which is important but difficult to achieve, other categories of activity are distinguished, which have classically been defined as **low**, **moderate and high**. The cut-off points separating the preceding categories were defined using the original cohort from which the DAS was derived, in which patients were separated into categories of high or low disease activity in accordance with the rheumatologist's decision to begin treatment or not. To reduce the overlap between the two distributions, the 25^{th} percentile was chosen as the lower limit for high disease activity, and the 75^{th} percentile for low activity, with moderate activity categorized as the interval between the other two (van Gestel, 1996). The cut-off points separating the three categories were DAS <2.4 for low activity and DAS >3.7 for high activity, with moderate activity between the two. The same as for remission, the DAS values were used to extrapolate the values for the DAS28: DAS28 <3.2 for low activity and DAS28 $\geq$5.1 for high activity (van Riel, 2000). The cut-off points for the SDAI were defined in the original publication taking as the reference the values for the DAS28, and were SDAI <11 for low activity and SDAI >40 for high activity. A new modification of the DAS28 and SDAI values has recently been proposed, as shown in Table 11, based on consensus and the expert judgment of experienced rheumatologists (Aletaha, 2005c).

Table 11. Cut-off points for activity categories according to DAS, DAS28 and SDAI

	Category	Original definition	New proposed definition
DAS	Remission	<1.6	
	Low activity	<2.4	
	Moderate activity	2.4 < DAS <3.7	
	High activity	≥3.7	
DAS28	Remission	<2.6	<2.4
	Low activity	<3.2	<3.6
	Moderate activity	3.2 < DAS28 <5.1	3.6 < DAS28 <5.5
	High activity	≥5.1	≥5.5
SDAI	Remission	<5	<3.3
	Low activity	<20	<11
	Moderate activity	20 < SDAI < 40	11 < SDAI < 26
	High activity	≥40	≥26

IV.1.2.c. Evaluation of disability

- Physical disability

Self-perceived functional disability attributed to the disease should be evaluated with specific, previously validated questionnaires. This guideline recommends the use of the HAQ as a tool for the standard evaluation of disability, due to its wide diffusion, acceptance and proven metric characteristics. [5, D]

There are several ways to estimate functional capacity based on joint mobility or on an observer's evaluation of the ability to carry out certain tasks. The most widely used current methods are questionnaires specifically for rheumatic diseases, such as the HAQ, the Modified Health Assessment Questionnaire (MHAQ) (a reduced version of the HAQ) or the Arthritis Impact Measurement Scales (AIMS). These questionnaires are based on the patient's own opinion about his/her disease and are standardized instruments, with proven reliability and validity, which evaluate those health dimensions most affected by RA, one of the most important of which is disability, especially with regard to physical function and pain.

The HAQ is a 20-item self-administered questionnaire that evaluates self-perceived physical disability to carry out several basic activities of daily living, which are grouped into eight areas: dressing and grooming, arising, eating, walking, personal hygiene, reaching, gripping and other activities (Fries, 1980). A version of this questionnaire has been validated for Spain (Esteve-Vives, 1993). The MHAQ is a reduced version of the HAQ, with only eight items; its main advantage is its simplicity, making it possible to use it for routine patient follow-up (Pincus, 1983). The Spanish version of the MHAQ can be self-administered in most patients with RA (Esteve-Vives, 1994).

This guideline recommends the use of the HAQ as a standard tool for the evaluation of disability due to its wide diffusion, acceptance and proven metric characteristics.

In recent years new modifications of the HAQ have been developed, such as the MHAQ (Pincus, 2006b) and the HAQ-II (Wolfe, 2004a), in the interests of improving the characteristics of the HAQ itself. Other investigators have preferred to approach the subject by incorporating new RA-specific questionnaires, such as the RAQoL (Whalley, 1997; Tijhuis, 2001) or the ROAD (Recent Onset Arthritis Disability Index (Salaffi, 2005).

Health professionals who are interested in evaluating broader aspects of health-related quality of life can also use the so-called generic questionnaires, such as the Short-Form 36 (SF-36) (Ware, 1992), the Nottingham Health Profile (NHP) (Hunt, 1981), or the Sickness Impact Profile (SIP) (Deyo, 1982) or the EuroQoL-5D (Sokoll, 2001). These questionnaires provide an estimate of self-perceived physical, psychological and social health status based on questions about activities, feelings and emotions that cover a large number of situations in daily life. The generic questionnaires provide complementary information and make it possible to compare health status with other diseases.

- Ability to work

RA very frequently causes loss of the ability to work. The panel recommends that this aspect be jointly assessed with the patient to implement strategies that make it possible to continue working as long as possible without prejudice to the patient. [5, D]

One-third of patients lose their jobs during the first year of the disease (Jantti, 1999), which is closely related to the disease's inflammatory activity (Wolfe, 1998b; Reisine, 1998). The reduced income associated with loss of employment affects all members of the family unit (Wolfe, 1998b).

It is advisable to develop strategies to help patients keep their jobs for as long as possible (Gignac, 2004; Gignac, 2006).

- Psychological and social aspects

Some psychological aspects such as mood (depression, anxiety) or social support are very important for patients and can affect compliance with treatment and treatment response. The panel recommends keeping these aspects in mind when assessing the need for additional interventions. [5, D]

Symptoms of depression or anxiety are frequently manifested, especially at the beginning of the disease, and these should not be underestimated (Suurmeijer 2001). Higher mortality has been observed in patients with depression (Ang, 2005).

Patients who receive substantial social support from families and friends, especially from their partners, have a better prognosis and less disability (Fitzpatrick, 1991, Kraaimaat, 1995). Some clinical manifestations, such as pain or fatigue, are more frequent in persons who do not have social support (Riemsma, 1998; Neugebauer, 2004)

IV.1.2.d. Evaluation of structural damage

- Radiologic indices

Radiographs of the hands, feet and chest are recommended in the initial evaluation; hand and foot radiographs should be repeated annually during the first three years of disease evolution and subsequently as deemed necessary. [5, D]

One of the radiographic findings that should be evaluated is the presence of bone erosions, which are more frequent in the early stages of the disease. About 70% of patients present erosions in the hands or feet by the end of the second or third year (van der Heijde, 1995; Hulsmans, 2000). Their presence and speed of onset are associated with poorer outcome. Radiologic changes are clearly related with persistent inflammatory activity, which is greater in the early stages, and moderately related with physical disability, which increases over time (Scott, 2000b; Drossaers-Bakker, 1999).

As already noted, it has been demonstrated that radiographic changes can be detected in patients in periods as short as 6 months (Sharp, 2000).

Numerous methods have been described to quantify radiologic joint alterations. Almost all of them are based on the reading of hand radiographs, although some authors have emphasized the importance of including a systematic evaluation of the feet (van der Heijde, 1992b). Most of these methods are based on the method of Larsen (Larsen, 1977; Larsen, 1995; Edmonds, 1999) or of Sharp (Sharp, 1971; van der Heijde, 1992b; Sharp, 1985; Sharp, 1995; Kaye, 1987). None of them is clearly preferred (Pincus, 1995), although van der Heijde's method (van der Heijde, 1992b), which includes hands and feet, seems to offer some advantages. They all give good results, but have the disadvantage of requiring a great deal of time to apply, thus they appear to be reserved for research purposes (Boini, 2001; Bruynesteyn, 2002; Guillemin, 2005).

This guideline recommends a simple qualitative evaluation that permits identification of the presence of new erosions or their progression. Radiographs of both hands and feet are justified by the asymmetric appearance of erosions (right or left) and by the observation that in the first 2-3 years of disease erosions can appear only on the feet, without clinical symptoms, in up to 23-36% of patients (Brook, 1977; Paimela, 1992; van der Heijde, 1999).

With regard to the chest radiograph, a baseline radiograph is recommended, both to determine the initial stage and to identify the appearance of possible problems during the course of disease and treatment.

Table 12 shows a summary of the instruments usually employed to measure RA evaluation parameters, as well as those recommended in this guideline.

Table 12. Summary of instruments for the measurement of evaluation parameters in rheumatoid arthritis

PARAMETER	Valid options	RECOMMENDATION
Inflammation and joint pain	✓ ACR count ✓ Ritchie index ✓ 44-joint index ✓ 28-joint index	28-joint index
Global assessment of pain	✓ Patient's global assessment of pain (VAS) ✓ Likert scale	Patient's global assessment of pain (VAS)
Patient global assessment of disease activity	✓ VAS ✓ Likert scales of severity and/or activity	Patient's global assessment of disease activity (VAS).
Physician global assessment of disease activity	✓ VAS ✓ Likert scales of severity and/or activity	Physician's global assessment of disease activity (VAS).
Functional capacity	✓ HAQ ✓ MHAQ ✓ AIMS	HAQ
Laboratory tests	✓ ESR ✓ CRP	ESR and CRP
Radiographic damage	✓ Presence or absence of erosions ✓ Sharp index ✓ Larsen index	Presence or absence of erosions evaluated qualitatively by radiography

- Ultrasonography

Ultrasound imaging permits early evaluation of synovitis and the detection of erosions, therefore this technique is recommended in the diagnosis and follow-up of RA. [2.b]

Ultrasound is recommended when the physical examination raises doubts about the existence of signs of inflammatory joints, or when ultrasound detection of synovitis, effusion, or erosions will modify management of the patient's treatment. [5, D]

High-resolution ultrasound is more sensitive than physical examination and can distinguish between effusion and synovitis (Wakefield 2004). P*ower Doppler* is a technique that can

locate increased synovial vascularization related with inflammatory activity. (Walther, 2001; Szkudlarek, 2001; Hau , 2002).

Ultrasound is useful in the diagnosis of early arthritis when the physical examination raises doubts about the existence of inflammatory signs in a joint, although ultrasound findings are not specific for RA, but only for synovitis regardless of its origin (Systematic review: "Value of ultrasound in recent-onset RA"). It also makes it possible to evaluate the extension of arthritis, in which case ultrasound examination of the hand, wrist and metatarsophalangeal joints should be considered, as inflammation can be detected even in asymptomatic joints (Naredo, 2005a; Naredo, 2005b).

The higher sensitivity with respect to physical examination makes it especially valuable when there is a need to quantify the intensity and extension of synovitis, which is very useful in early RA, but also in established RA when the extension of sequelae and synovial proliferation raise reasonable doubts about the degree of underlying inflammation; and, in general, in any situation in which ultrasound facilitates treatment decisions.

Ultrasound shows bone erosions more easily than conventional radiography, since it can reach a larger number of joint planes, allowing a more extensive examination. There are solid data showing that ultrasound can detect erosions earlier than conventional radiography, although it is less sensitive than magnetic resonance.

The advantages of ultrasound are its safety, low cost and wide availability, and that it can be repeated. Training rheumatologists in ultrasound is very beneficial for the clinical evaluation of the patient with arthritis. The greatest disadvantages are that the technique is highly dependent on the operator and the time needed to apply it.

A systematic review (SR 2) was undertaken to respond to the question: "Validity of the sonogram or ultrasound as predictor of radiographic joint damage in recent-onset RA (<5years)". S-one studies were identified. The conclusions of this review were:

- Ultrasound is a reliable technique with good intraobserver and interobserver agreement when performed by rheumatologists who are experts in its application **[1.b]**
- Ultrasound could be useful in the diagnosis of RA **[2.a]**
- Ultrasound enables a differential diagnosis to be made **[2.b]**
- Ultrasound enables progression of erosive disease to be evaluated in early RA **[2.a]**
- Ultrasound evidence is lacking with regard to:
  - Its value in the prognosis and monitoring of early-onset RA, especially in the long term.
  - Differences between types of equipment.
  - Studies of reliability (intra- and inter-observer reliability, determination of least detectable difference).
  - Clinical research studies of diagnostic value in early RA (long-term studies).
  - Studies of monitoring and prognosis in early RA (long-term studies).
  - Usefulness of Doppler for patient follow-up.

- Magnetic resonance imaging (MRI)

MR is a reliable technique for the evaluation of RA. It has good intraobserver and interobserver agreement and good sensitivity to change [2a].

MR can prove useful in the diagnosis of RA in some cases; however, to date, routine application has not been justified [1b].

MR can predict the onset of future erosions [1b]

MRI identifies synovitis, tenosynovitis, bone erosions and bone edema, thus it is recommended in the diagnosis of RA. [2b]

MRI is recommended for the detection of synovitis, effusion and erosions when this information is considered to be clinically relevant. [5, D]

MRI has been shown to be more sensitive than physical examination and conventional radiography for the detection of inflammatory and destructive joint changes in early AR (Systematic review: "Value of magnetic resonance in recent-onset RA"). Magnetic resonance has also shown greater sensitivity than physical examination in the detection of arthritis. The appearance of joint bone edema is related with inflammation and with the subsequent appearance of erosions (McQueen, 2001; Scheel, 2006).

MRI shows an early increase in signal intensity, after the injection of gadolinium, in the inflamed synovial membrane and allows measurement of its volume (Systematic review: "Value of magnetic resonance in recent-onset RA"). There is good agreement between MRI findings and histopathological observations.

The role of MRI in RA diagnosis is uncertain, thus the panel recognizes that not enough information exists to recommend its use for this purpose. In any case, its findings are limited to the non-specific diagnosis of synovitis with bone edema and/or erosions, and should be interpreted together with the rest of the available information before forming a clinical opinion. Its high cost and lower accessibility make it a technique reserved for special situations for which no other diagnostic alternatives are available. However, the data about its value in predicting the subsequent appearance of radiographic erosions are much more solid, especially in the case of juxta-articular bone edema. (SR 3)

Ultrasound is more accessible than MRI but is highly dependent on the examiner, with low inter-observer agreement, although both examinations can detect erosions sooner than conventional radiography (Systematic review: "Value of magnetic resonance in recent-onset RA"). This systematic review (SR 3) was conducted to respond to the question "Value of MRI as a predictor of radiologic joint damage in recent-onset RA (<5 years)". It included 75 studies and had the following conclusions:

- MR is a reliable technique in the evaluation of RA, with good intraobserver and interobserver agreement and very good sensitivity to change, according to the RAMRIS system proposed by OMERACT **[2.a]**
- MR can identify synovitis, tenosynovitis, bone erosions, and bone edema; therefore, it can prove useful in the diagnosis of RA in some cases, especially doubtful cases. However, to date, routine application has not been justified **[1.b].**

- In patients with early RA of 6 months evolution, MRI permits early visualization of a moderate to high percentage of bone erosions, as compared with radiography, therefore it is a technique recommended in RA prognosis **[2.b].**
- Early detection of bone edema can predict future erosions in certain groups of patients with RA **[1.b].**
- MR can prove useful in the diagnosis of RA in patients with undifferentiated arthritis **[1.b]**
- MR can prove useful in the differential diagnosis of early RA and other types of polyarthritis **[2.b]**
- The early detection of bone edema predicts future erosions **[1.b].**
- There is no evidence about the following aspects of MRI:
  - Use in the differential diagnosis of recent-onset RA and other non-differentiated polyarthritis (longitudinal studies).
  - Standardization and reliability of the technique.
  - Better scoring system (what lesions, what areas and what joints should be considered).
  - Intra- and inter-observer agreement, and their comparison with other complementary examinations over the long term.
  - Monitoring of minimum change and treatment effect.

IV.1.2.e. Evaluation of prognosis

The initial and subsequent evaluation of RA patients should include a continuing estimate of disease prognosis. The evaluation of prognosis should take into account sociodemographic factors, genetic markers, disease-dependent factors, treatment-dependent factors, and psychological and social factors. [5, D]

RA prognosis varies among patients. The current treatment objective is to achieve the least possible inflammatory activity and maintain it as long as possible. Earlier and more intensive treatments improve RA prognosis, understood in terms of functional capacity, structural damage and/or mortality. The clinician must try to find a way to balance the risk of serious disease with the risks derived from more intensive treatment strategies. Assessment of the factors for poor prognosis in each patient will aid decision making. Given that most radiologic changes and, to a smaller degree, loss of functional capacity, occur in the first 2-3 years of disease evolution, the sooner a prognosis is established, the sooner the clinician will have information to make an informed decision on the most appropriate treatment strategy.

The factors predictive of serious disease can be classified as sociodemographic, disease-dependent, treatment-dependent and psycho-social. No single parameter by itself will permit estimation of RA prognosis, therefore a combination of parameters should be used. Moreover, it is difficult to separate the individual effect of a particular risk factor from its interrelation with other factors associated with poor outcome. It is important to remember that the worst prognostic factor is persistent joint inflammation.

The following factors are considered to be predictive of functional disability, radiologic erosions and/or mortality, and therefore of poor prognosis:

- Sociodemographic factors

- **Female gender**. Being a woman is associated with presentation of functional disability 4 years after disease onset (odds ratio=3.0) (Pease, 1999). Not all cohort studies have reproduced this finding. Female gender is probably associated with other factors predicting outcome.

- **Age at disease onset.** This is a controversial prognostic factor. In elderly patients, different groups have shown poorer, better or similar outcomes.

- **Low educational level.** This is associated with increased mortality. Less than secondary level education is associated with more than 50% reduction in functional status or with mortality at 9 years (OR=7.5) (Pincus, 1985). In Mexican patients with RA, fewer than 6 years of formal education is associated with severe forms of the disease (OR=3.5) (Glave-Testino, 1994).

- Genetic markers

- No well defined genetic markers are currently available, although it is suspected that there is a genetic susceptibility to RA that could distinguish between positive and negative anti-CCP antibody disease (Van der Helm, 2006; Deighton, 2006). Some authors have recently proposed the hypothesis that RA is not a single entity, but rather a syndrome consisting of at least two diseases with different etiology (Pedersen, 2006a).

- Disease-dependent factors

- **Positive RF.** Positive RF from 1/80 or ≥ 60 UI by nephelometry is associated with the development of erosions (OR: 4.2–12) (van der Heijde, 1992b). The persistence of elevated RF is associated with erosions at 6 years follow-up. At 3 years from symptom onset, the presence of positive RF IgA is associated with more erosions, poorer HAQ Score, and larger number of painful and swollen joints.

- **Presence of anti-CCP.** The presence of anti-CCP is considered to be a predictive factor for persistent arthritis and the appearance of erosions (Systematic review: "Value of Anti-CCP antibodies in RA diagnosis and prognosis"). The risk is higher when it is associated with positive RF.

- **Large number of swollen joints.** A large number of swollen joints (>20 at disease onset) is predictive of future activity, and even of mortality (Van Zeben, 1992). Cumulative inflammation of joints is associated with increased radiologic damage at 1 year (OR=2) (Pincus, 1985).

- **Elevated acute phase reactants.** CRP of twice the normal value at the patient's initial evaluation is associated with the development of erosions in 4 years (OR=1.8) (Glave-Testino, 1994). Continuous ESR higher than 60 mm in the first hour is associated with the presence of disability at 18 years (OR=4,9) (Furst, 1994a).

- **High HAQ score at first visit (≥1 out of 3).** An HAQ score at the first visit of ≥1 out of 3 is associated with disability at 4 years (OR=3.0) (Pincus, 1985). For each HAQ unit over 0 at the baseline visit, the OR for disability increases by 1.6 to 2.9 (Wolfe, 1998b). In patients with a baseline HAQ of at least 2.5, the relative risk of developing disability is 2.2 (Wolfe, 1991b).

- **Early involvement of large joints (≥2).** Early involvement of 2 or more large joints is associated with the presence of erosions at 1 year (OR=2.0) (Brennan, 1996).

- **Rapid appearance of erosions (≥2/year).** Rapid appearance of erosions is associated with poorer prognosis.

- **Presence of extra-articular manifestations (rheumatoid nodules, vasculitis, scleritis, or others).** In general, these extra-articular manifestations are associated with RF seropositivity, therefore their prognostic value by themselves is unclear. The presence of extra-articular manifestations is particularly associated with increased mortality (Gordon, 1973).

- Treatment-dependent factors

- **Duration of treatment.** Longer treatment with DMARDs is associated with improved functional prognosis in the long term. For example, the difference between patients treated with DMARDs 100% of the time and those never treated is 0.53 HAQ units (Fries, 1996).

- **Delayed treatment with DMARDs.** Patients who delay initial treatment with DMARDs have a poorer functional prognosis than those who initiate early treatment. The longer the delay in beginning treatment, the lower the probability of achieving a satisfactory response (OR=5.6), which in turn implies a poorer functional prognosis (with a mean increase of 0.12 HAQ units for each visit at which a 50% improvement was not achieved (Tsakonas, 2000).

- Psychological and social factors

- **Depression.** Patients with depression have higher mortality (Ang, 2005).

- **Social support.** Patients with social support from their partners, family or friends have a better prognosis (Treharne, 2005).

Treatment evaluation

IV.1.3. Objective of RA treatment

The objective of treatment of RA is to induce complete remission [3.c]. In patients with a longer history, the objective of treatment may be to achieve low disease activity [1b, A].

RA patients who evolve with spontaneous or drug-induced remissions have a better medium-term prognosis than those who evolve with persistent clinical activity (Eberhardt, 1998). However, complete remission rates with DMARDs and/or corticosteroids are low (18-25%) (Eberhardt, 1998; Wolfe, 1985; Prevoo, 1996; Harrison, 1996) and do not last over time. Thus it is necessary to define criteria for clinical improvement that can be used to evaluate patient evolution and to aid the clinician in making treatment decisions. Complete disease remission, or at least achieving the smallest possible degree of inflammatory activity, is the only way to improve the prognosis and assure the most favorable evolution for the patient.

IV.1.4. Treatment-response criteria

Treatment-response criteria should be applied to each patient individually, therefore they should take into account the change in disease activity and the current degree of activity. [5, D]

In 2010, the results of the "Treat to Target" initiative (Smolen 2010a) were published. The objective of this initiative was to reach a consensus on a definition of recommendations that improve management of RA in clinical practice using objective-based treatment. The working approach involved an expert panel formed by rheumatologists and nurses who formulated a series of recommendations after an exhaustive systematic review of the literature. These recommendations were later discussed in order to reach some degree of agreement. The results were structured as 4 general principles and 10 recommendations, for each of which the level of evidence, the strength of the recommendation, and the degree of agreement between the experts were established. Similarly, an objective-based treatment algorithm was drawn up based on the 10 recommendations.

The expert panel almost unanimously agreed that remission should be the final therapeutic objective in RA, although no supporting evidence is provided. There is evidence, however, on the beneficial effect of treatment whose objective is minimal clinical activity based on a strategic approach as opposed to non-structured treatment. However, the experts agree that reduced disease activity is a more important objective that can only be applied in patients with long-standing RA whose disease could be refractory to treatment. In early RA, minimum activity should be an intermediate stage on the road to remission.

IV.1.4.a. ACR response criteria

The ACR criteria do not take current disease status into account, therefore the following modification proposed by the SER is recommended if they are applied. [5,D]

The ACR criteria for improvement (Felson, 1995) define a dichotomous outcome (response/no response) according to the following criteria:

- ✓ Improvement of 20% or more in the tender joint count and in the swollen joint counts.
- ✓ Improvement of 20% or more in at least 3 of the following parameters: ESR or CRP, physician global assessment of disease activity, patient global assessment of disease activity, patient pain assessment, physical disability.

These criteria have come to be known as the ACR20, reflecting the need for 20% improvement in each of the parameters, a value considered a clinically relevant cut-off point. Some authors have proposed raising this requirement to 50% (ACR50) or 70% (ACR70). The ACR criteria for improvement use the core variables proposed by the ACR itself, which can be applied with little problem in daily practice (Felson, 1993b). However, the failure to consider current disease activity limits their application in daily clinical practice unless they are adapted to take this factor into account. The ACR response criteria are likely to be modified in the near future; meanwhile, the following adaptation is proposed: (http://www.ser.es/)

- ✓ Satisfactory response: fulfillment of the ACR20 criteria, fewer than 6 swollen joints, and absence of any patient circumstance that results in intolerable loss of functional capacity in the opinion of the patient or physician.

- ✓ Unsatisfactory response: failure to meet the criteria for satisfactory response.

IV.1.4.b. EULAR response criteria

The EULAR response criteria take into account both the degree of improvement and the patient's current situation, and have been shown to have comparable validity to the ACR response criteria in clinical trials of RA patients.

These criteria use the DAS scale of disease activity, which combines different clinical information in a single index that can be used to classify patients in different categories. Although some confusion exists due to the proliferation of modified DAS (Van der Heijde, 1998), there are basically two validated formulas (Van Gestel, 1998) that are applicable to the EULAR criteria for improvement: the original DAS (Van der Heijde, 1990; van der Heijde, 1992a), which uses the Ritchie joint index (Ritchie, 1968) and a 44-joint count for inflammation, and the DAS28, which uses the ungraded count of 28 joints (Appendix 2).

Contrary to the ACR criteria, the EULAR definition takes into account both the degree of improvement and the patient's current situation, and its validity has been shown to be comparable to the ACR response criteria in clinical trials of RA patients (van Gestel, 1999). The definitions of satisfactory and unsatisfactory response by applying the original DAS or the DAS28 are shown in Table 13 and Table 14.

Table 13. EULAR definition of response (original DAS)

	DAS decrease		
Current DAS	**>1.2**	**1.2 - 0.6**	**<0.6**
<2.4	**Satisfactory**		
2.4 - 3.7	**Unsatisfactory**		
>3.7			

Table 14. EULAR definition of response (DAS28)

	DAS28 decrease		
Current DAS28	**>1.2**	**1.2 - 0.6**	**<0.6**
<3.2	**Satisfactory**		
3.2 – 5.1	**Unsatisfactory**		
>5.1			

IV.1.4.c. Subjective physician assessment of disease activity

The subjective physician assessment of disease activity is the clinical criterion most commonly used in daily practice. It is not advisable to use it as the only response criterion. [5, D]

This is the most commonly used criterion in daily practice. Its use as the only response criterion is not advisable. If physician assessment of disease activity is the only criterion used to judge response to treatment, the assessment must fit the treatment objectives (complete disease remission or achievement of the best possible response) and should be a synthesis of objective and quantifiable parameters that analyze disease activity, joint damage, and health status, with a final classification of the results into the categories of satisfactory and unsatisfactory response.

IV.1.5. Frequency of check-ups

RA patients should be followed indefinitely: cases of established RA and in complete disease remission should be evaluated every 6-12 months; those with frequent outbreaks or with persistent activity and those who have recent-onset disease should be assessed "on demand" (in general, every 1-3 months) until remission is achieved or until reaching and maintaining the least possible inflammatory activity. [5, D]

Frequent and continued evaluation of RA inflammatory activity and its consequences is critical to meeting the treatment objective of achieving remission or, alternatively, maintaining the patient with the least possible inflammatory activity. No treatment has been shown to cure RA, therefore all patients who suffer this disease should have medical check-ups indefinitely.

It has now been clearly demonstrated that close and careful management of inflammatory activity, together with a proactive treatment approach, are required to achieve either remission or the least possible inflammatory activity in the shortest possible time.(Grigor, 2004).

Patients with established RA and those in complete disease remission can be seen every 6-12 months, depending on their characteristics. To avoid overburdening the service, patients in complete remission can be seen in primary care during the periods between rheumatologist visits, in order to assure clinical control and appropriate laboratory tests, and to permit rapid referral to the specialist in case of disease reactivation and/or adverse effects.

Patients with recent-onset disease, frequent outbreaks or persistent activity should be seen, in general, every 1-3 months (at the same time as the laboratory tests), depending on the treatment used and disease activity, until achieving remission or reaching and maintaining the least possible inflammatory activity.

The frequency of visits should be modified as required in the presence of complications, side effects or comorbidity.

IV.1.6. Nursing consultations

The active incorporation of nursing staff is recommended from the outset to assist in the evaluation of disease inflammatory activity, facilitate early detection of side effects and comorbidity, and improve health education. [5, D]

In recent years nursing consultations have been established in some centers, with notable advantages. In essence, the objectives covered with regard to periodic patient control are: to facilitate the evaluation of inflammatory activity, b) early detection of side effects and comorbidity, and 3) to provide education on subjects related with the patient's disease.

The basic characteristic of the nursing consultation is holistic or integral patient care; that is, considering not only the disease, but also other factors like psychological distress, manifested as anxiety and depression, family and social relationships, and employment problems. The role of the nurse should include a liaison function, with the ability to detect problems, rapidly refer the patient to other health professionals and, in turn, inform the patient about the existence of potentially helpful associations or organizations.

The nursing consultation can be considered a supportive tool in the patient's periodic checkups. Visits to the nurse for follow-up tests and even for periodic patient evaluation, besides resolving uncertainties or simple questions, can avoid overburdening the appointment schedule.

The nurse specialist can do joint counts and collect other parameters included in the systematic clinical evaluation of the patient. The nurse acts as a facilitator in filling out questionnaires and monitoring the adverse effects of DMARDs and biological treatments, thus becoming a fundamental component in continuing patient evaluation.

IV.1.6.a. Periodic check-ups and administration of questionnaires

Joint counts and other parameters included in the systematic clinical evaluation of the patient should be carried out in the nursing consultation. [5, D]

Joint evaluation can be carried out by previously trained nurses (Palmer, 2000). In this way, a patient who is starting or modifying a prescribed treatment with DMARDs or biologics can be evaluated previously by the nurse. Taking into account that not all patients treated in the nursing consultation require a joint assessment, this evaluation could be included without the need for an excessive amount of time, since the systematic assessment of 28 joints (including evaluation of pain and swelling) can be performed on average in 3 minutes and 30 seconds (Batlle-Gualda, 2002).

The administration of generic and specific questionnaires, as well as the patient's pain assessment and global assessment gives information on different relevant aspects of the disease. Although most of the questionnaires currently used are theoretically self-administered, at times the nursing staff need to help patients understand them. Likewise, with respect to the patient's pain assessment and global assessment, it should be mentioned that, of the four types of scales classically used – visual analogue (VAS), visual analogue with numeric descriptors (VASn), numeric (NS) and Likert (LS) – the numeric scales are the most highly recommended despite the fact that all four are similar in terms of efficiency.

However, if there are difficulties in comprehension, the Likert is a good alternative, whereas the VAS is the most complicated for the patient (de la Torre, 2002).

IV.1.6.b. Monitoring the adverse effects of DMARDs and treatment with biologics.

It is recommended that adverse treatment effects be monitored in the nursing consultation. The rheumatologist who is responsible for the patient should be informed of any possible adverse effect, whether objective or subjective. [5, D]

Monitoring adverse effects of treatment in the nursing consultation encourages treatment compliance and increases the patient's perceived ability to copy with RA (Ryan, 2006). The objective of monitoring is early detection of possible adverse cutaneous, renal, hepatic, pulmonary and gastrointestinal effects or symptoms of myelosuppression (White, 2002).

All possible adverse effects, whether objective or subjective, should be made known to the patient's rheumatologist.

IV.1.6.c. Patient education

A patient education program should be implemented that includes at least the following aspects: 1) Monitoring and control of the adverse effects of DMARDS and biologic treatments; 2) Exercise; 3) Pain control; 4) Joint protection. [5, D]

Patient education (PE) includes all those structured activities aimed at increasing knowledge of subjects related with RA and designed to improve the patient's health-related behaviors, and thus his/her coping skills or self-sufficiency. The objective is not only to obtain knowledge, but also to know what to do when faced with particular situations.

PE is not considered a treatment "per se", but is an important instrument to increase the potential benefits of treatments since it facilitates compliance and encourages the adoption of healthy habits (Hill, 1997). Given the high prevalence of psychological distress related with RA, patient education programs should also be considered to improve the patient's psychosocial environment since a small improvement in the indices of depression analyzed has been shown (Riemsma, 2002).

To date, the literature has not established what programs or interventions are most effective in improving patients' ability to cope with chronic disease (Cooper, 2001). The Cochrane review conducted by Riemsma et al (Riemsma, 2002) compared three different methodologies of patient education: information only, both oral and written; counseling, where, patients were allowed to express their problems in addition to receiving information; and behavioral treatment, which included techniques to achieve changes in the patient's attitudes and behavior. According to the conclusion of the review, only the last format showed significant differences in the following parameters: depression, disability and patient's global assessment. However, these programs did not achieve any lasting benefits: 12 months after the intervention, no significant differences were evident (Brus, 1998); and the change in attitudes cannot always be related with the intervention (Lorig, 1989). Booster or reminder sessions slightly prolong the beneficial effect of the intervention (Riemsma, 2002).

PE is a complex process; to be effective, the following elements should be considered (Hill, 1997):

- ✓ The patient's need for information.
- ✓ An individualized program in accordance with those needs.
- ✓ Appropriate pace, format and time for the intervention.

After being diagnosed with a chronic disease, all patients enter an indefinite period of mourning. PE programs are not recommended during this period since they may hasten the onset of depression (Donovan, 1989). First, patients need to accept their disease. When they begin to ask questions about the disease process, this is the time to include them in the program.

Most PE programs conducted currently in Anglo Saxon countries include the following subjects (Hill, 1997):

- ✓ RA and the disease process.
- ✓ Medication: expected and adverse effects, recommended doses.
- ✓ Exercise: expected effects, what exercise to do and when.
- ✓ Joint protection: use of preventive splints, postural hygiene, use of assistive devices.
- ✓ Fatigue: causes of fatigue and how to save one's strength so as not to become overtired.
- ✓ Pain control: drugs and use of relaxation and other techniques.
- ✓ Diet: its general effects on health.
- ✓ Relaxation: techniques and how to do it.
- ✓ Alternative treatments: acupuncture, massage, homeopathy.
- ✓ Communication with other professionals related with the disease process.
- ✓ Self-help organizations.

Of the previously mentioned subjects, four are considered very important and are thus recommended for inclusion in a PE program.

1. *Monitoring and control of adverse effects of DMARDs and biologic treatments:* previously described.

2. *Exercise:* Exercise should initially be designed in accordance with the patient's characteristics and should be performed under supervision. It should include, on the one hand, low-impact aerobic exercise from activities like cycling, water exercises or swimming, initially for 25 minutes, which can gradually be increased up to 1 h 15 min, from one to three times a week; and, on the other hand, a muscular toning program that works all the muscle groups once a week by contraction for 30 seconds, followed by relaxation for 30 seconds, repeating this 3-5 times for each muscle group (Pedersen, 2006b).

3. *Pain control:* Teaching different relaxation techniques such as distraction, visualization or music therapy, in addition to use of the prescribed drugs. The patient must know what drugs to use and what dose to take to avoid undesired effects.

4. *Joint protection:* Teaching the patient the benefit of using assistive devices to avoid overburdening the joints and to facilitate the basic activities of daily living, thus achieving greater independence.

RA comorbidity

The rheumatologist is responsible for controlling the inflammatory process and should monitor RA-associated comorbidity with the support of the primary care physician and with recourse to other specialists when needed. [5, D]

It is not easy at present to discern what comorbidity is due directly to RA inflammatory activity (disease complication) and what is not (associated comorbidity) because persistent inflammation is the pathogenic mechanism of many diseases that have been found in association with RA.

Control of the inflammatory disease will in many cases affect control of comorbidity. The rheumatologist is a health provider for RA patients and should monitor the different comorbidities associated with RA, with the support of the primary care physician and with recourse to other specialists when needed.

IV.1.7. RA complications

IV.1.7.a. Amyloidosis

Secondary amyloidosis should be suspected in RA patients who develop proteinuria, renal failure, gastrointestinal symptoms, myocardiopathy and/or hepatomegaly, and in those who have elevated APR concurrent with little clinical activity. [5, D]

Treatment should be preventive and should aim to suppress the inflammatory activity of RA. There is no single clear standard for the treatment of established amyloidosis. Several published case series have shown important improvements in proteinuria and renal function in patients with amyloidosis secondary to RA treated with anti-TNF, which, given its lower toxicity, is a good treatment alternative. [4, C]

A much closer and more careful control is recommended in RA patients with amyloidosis, with MTX or anti-TNF.

Amyloidosis is a syndrome characterized by the presence of insoluble deposits of normal serum proteins in the extracellular matrix of one or more organs. Amyloidosis secondary to RA, the same as in other chronic inflammatory diseases, is produced by deposition of serum amyloid A, an acute phase reactant, which is produced in greater quantities in the inflammatory response. Amyloid is degraded by macrophages into smaller fragments that are deposited in the tissues.

Its prevalence varies widely according to the case series consulted, depending on the characteristics of the subjects included (time of disease evolution, post-mortem studies, geographic area, etc.), but only represents a complication in less than 10% of patients. In the EMECAR cohort of AR (*Sociedad Española de Reumatología*, 1999-2005), the prevalence of amyloidosis is 0.6% (95% confidence interval: 0.1-1.2) (Sanmarti, 2004).

- Clinical suspicion

Amyloidosis should be suspected in RA patients who develop proteinuria or renal failure since these are the most frequent initial clinical manifestations. It should also be suspected in RA patients who develop changes in intestinal habits, myocardiopathy and/or hepatomegaly, as well as in those with persistently elevated acute phase reactants with little clinical activity (Okuda, 1994).

- Clinical description

Clinical manifestations vary depending on the organ affected. In order of frequency, the most common manifestation is renal (proteinuria with or without reduced renal function), followed by gastrointestinal (malabsorption syndrome, intestinal motility disorders, digestive tract bleeding or protein-losing gastroenteropathy), hepatomegaly and myocardiopathy (Hazenberg, 2000).

- Diagnosis

Diagnosis is made by demonstrating the presence of extracellular deposits with green birefringence when stained with Congo-red under polarized light. Abdominal fat and rectal mucosa are the recommended sites for biopsy due to their accessibility and low risk. Scintigraphy with serum amyloid P component is a reliable alternative to biopsy which allows quantification of the amount of amyloid deposited in the tissues and evaluation of evolving changes (Jager, 1998; Hachulla, 2002).

- Treatment

Given the mechanism of production, treatment should be preventive and should aim to suppress RA inflammatory activity. There is no single clear standard for the treatment of established amyloidosis. Before anti-TNF came into generalized use, case reports and case series with acceptable results were published of patients treated with methotrexate (Fiter, 1995), cyclophosphamide alone (Chevrel, 2001) or with prednisone (Maezawa, 1994), and clorambucil (Berglund, 1993). Several published case series (Gottenberg, 2003; Fernandez-Nebro, 2005) have now demonstrated important improvements in proteinuria and renal function in patients with amyloidosis secondary to RA treated with anti-TNF, which, given its lower toxicity, is a good alternative treatment.

IV.1.7.b. Anemia

Periodic blood cell counts and general liver and kidney function tests are recommended. [5, D]

Chronic anemia in conjunction with RA does not usually require treatment. Oral iron supplements are not indicated, except in cases of ferropenic anemia. The use of erythropoietin is controversial. [5, D]

Anemia is the blood disorder than most frequently accompanies RA. It is generally a moderate normocytic normochromic asymptomatic anemia, mediated by the RA chronic inflammatory process, which improves as disease activity is controlled.

Anemia is usually asymptomatic, therefore periodic blood cell counts should be obtained including erythrocyte, leukocyte and platelet counts, calculation of mean corpuscular volume, reticulocyte count and general liver and kidney function tests.

There is no specific treatment for anemia in RA. It should be taken into account when considering possible changes in RA treatment guidelines.

This kind of anemia may be aggravated by adverse effects related with treatment. The use of NSAIDs may induce ferropenia due to blood loss in the digestive tract leading to microcytic anemia; methotrexate may give rise to folate deficiency, leading to megaloblastic anemia, and any drug, but especially azathioprine, cyclophosphamide and methotrexate, can induce anemia and even aplasia mediated by a toxic mechanism.

- Clinical suspicion

The anemia that generally accompanies RA is moderate and asymptomatic. The development of typical symptoms (asthenia, progressively reduced capacity for physical exertion, tachycardia and pale skin or mucosa) should lead to suspicion of the existence of causes other than RA itself.

- Diagnosis

Diagnosis is based on the existence of low hemoglobin levels in the blood count.

RA-associated anemia is characteristically normochromic, but can be slightly hypochromic and even somewhat microcytic; serum iron levels are usually reduced, but ferritine is normal or elevated; transferrine is usually slightly reduced, although the transferrine saturation index is normal.

Any deviation from this typical pattern should prompt the prescription of the appropriate tests to evaluate other causes of anemia.

- Treatment

Chronic anemia accompanying RA does not generally require treatment. Oral iron supplements are not indicated, except in cases of ferropenic anemia. The use of erythropoietin alone or in conjunction with iron supplements as treatment for anemia continues to be debated (Wilson, 2004) since, although it can improve the anemia, there are contradictory results about its effects on the course of RA itself (Pincus, 1990; Pettersson, 1993; Murphy, 1994; Peeters, 1996; Nordstrom, 1997; Peeters, 1999). It has proved useful in patients who require surgery and desire to donate their own blood for autologous transfusion (Mercuriali, 1996; Mercuriali, 1997).

IV.1.7.c. Cardiological complications

The two most frequent cardiological complications are pericarditis and myocarditis.

RA-related cardiac involvement should be suspected in the presence of pericardial pain, heart failure or conduction abnormalities. [5, D]

Pericarditis should be treated initially with full doses of NSAIDs (150 mg/day of indomethacin); if this is not effective, prednisone (1mg/kg/day); the rare cases of cardiac tamponade should be treated with evacuation by pericardiocentesis. [4, C]

In addition to treatment for heart failure, myocarditis requires treatment with high-dose prednisone. [4, C]

Independently of the increased risk of sudden death and ischemic cardiopathy in RA patients' due to the increased incidence of arteriosclerosis in this population, there are two main types of cardiological complications directly related with RA: pericarditis and myocarditis; although they are frequently found in post-mortem studies (Bonfiglio, 1969), they generally have little clinical expression and are mild alterations that do not require treatment.

Pericarditis is treated with full doses of NSAIDs (150 mg/day of indomethacin). If this treatment is not effective, prednisone (1mg/kg/day) is useful for symptom control. Myocarditis is treated with high dose steroids, diuretics, digitalis, vasodilators and anti-arrythmics.

- Clinical suspicion

The appearance of pericardial-type pain, signs or symptoms of heart failure or conduction abnormalities in an RA patient should lead to suspicion of cardiopathy, even though this is generally due to causes other than RA.

Involvement of the coronary arteries or intramyocardial vessels that may be produced as a consequence of a rheumatoid vasculitis usually has no clinical repercussions, thus the presence of signs of ischemia is almost always due to associated coronary arteriosclerosis.

Pericarditis

Clinical description. It is no different from pericarditis due to other causes. It is the most frequent cardiological complication in the course of RA. Echocardiographic studies in RA patients have shown pericardial effusion in 30% of patients, but less than 10% have an episode of clinical pericarditis. It is more frequent in men with positive RF. Massive pericarditis leading to cardiac tamponade occurs only in exceptional cases.

Diagnosis. By echocardiographic demonstration of pericardial effusion.

Treatment. Initially, full dose NSAID (150 mg/day of indomethacin); if this is not effective, prednisone (1mg/kg/day); in the rare cases of cardiac tamponade, evacuation by pericardiocentesis.

Myocarditis

Clinical description. Infrequent in RA. From the histological point of view, may be granulomatous — highly specific for RA — or interstitial, which is much less frequent. Presents clinically as slow-onset heart failure with progressive asthenia and dysnea. The physical examination typically shows tachycardia, reduced differential arterial pressure and a

third heart sound. The presence of granulomatous involvement of the endocardium may also lead to valve insufficiency, affecting, in decreasing order of frequency: the mitral, aortic, tricuspid and pulmonary valves.

Diagnosis. Echocardiographic demonstration of reduced cardiac contractility. Definitive confirmation is made by histological study of right ventricle biopsy.

Treatment. In addition to treatment for heart failure, the use of high-dose prednisone is indicated.

IV.1.7.d. Pulmonary complications

Pulmonary disease should be suspected if there is pleuritic pain, progressive or recent-onset dysnea, or hemoptysis. [5, D]

In the case of pleural involvement, thoracocentis is recommended to obtain an exudate and rule out other diseases (infection or neoplasia). [5, D]

Pleural involvement should be treated with full-dose or medium-dose steroids (10-20 mg/day of prednisone). [4, C]

Rheumatoid nodules do not require treatment in the absence of complications. [5, D]

Recent-onset (acute) interstitial involvement is treated with prednisone (1-1.5 mg/kg/day). If there is no response, patients may be treated with cyclophosphamide or azathioprine. Bronchiolitis obliterans organizing pneumonia (BOOP) is treated with prednisone (1.5 mg/kg/day). [4, C]

The prevalence of different types of pulmonary disease associated with RA is difficult to estimate precisely, since the various case series published differ substantially as to type of patients selected for each series, ranging from autopsy studies of asymptomatic patients, to early stage patients and to long-term patients, with and without symptoms of pulmonary disease.

Irrespective of these difficulties, it seems clear that interstitial pulmonary disease and pleural involvement are the most frequent of these diseases, while bronchiolitis obliterans, adverse drug reactions and infectious pulmonary disease have the most impact on patient survival; rheumatoid nodules are the pulmonary complication most specific to RA.

Pleuritic pain, dysnea (either progressive or recent-onset), or hemoptysis suggest pulmonary disease in RA patients. Pulmonary complications may be pleural involvement, rheumatoid nodules, interstial fibrosis or BOOP.

Treatment of pleural involvement includes thoracocentesis to obtain an exudate and rule out other diseases (infection or neoplasia), full-dose NSAIDs or medium-dose steroids (10-20 mg/day of prednisone). Rheumatoid nodules do not require treatment unless there are complications. Recent-onset (acute) interstitial involvement is treated with prednisone (1-1.5 mg/kg/day). If no response is achieved, it can be treated with cyclophosphamide or azathioprine. BOOP is treated with prednisone (1.5 mg/kg/day).

The appearance of pulmonary symptoms in an RA patient makes it necessary to rule out concomitant neoplasia, infectious disease or drug reaction, in addition to pulmonary disease associated with the process.

- Pleural effusion

Clinical description. Even though residual pleural lesions are frequently present in RA patients (20%), pleural effusion is infrequent (0.6%) (Jurik, 1982), and it is estimated that less than 5% of patients have an episode of clinical pleuritis (Kelly, 1993) manifested as pleuritic pain and pleural effusion with our without fever.

Diagnosis. By radiologic demonstration of the presence of pleural fluid and biochemical and bacteriological testing. The pleural fluid of RA patients characteristically presents a low cell count (<5000 leukocytes/mm^3), a low glucose level (<40 mg/dL), low complement level, and high protein level. The culture must be negative.

Treatment. Full-dose NSAIDs (150 mg/day of indomethacin) or medium-dose corticosteroids (10-20 mg/day of prednisone). The role of intrapleural corticosteroids has been discussed, with contradictory results (Russell, 1986; Chapman, 1992). Pleurodesis with tetracyclines is indicated in cases of recurrent effusion.

- Rheumatoid nodules

Clinical description. The prevalence of intrapulmonary rheumatoid nodules is highly variable depending on the techniques used for their detection, from less than 0.4% in radiologic studies, to 32% by pulmonary biopsy in RA patients with suspected pulmonary disease (Yousem, 1985). Alone or in groups, they are more frequent in the upper than lower lobes and are usually asymptomatic unless there are complications (cavitation, superinfection, fistulization, etc.), in which case they evolve with the corresponding clinical manifestations. One variant of these pulmonary nodules is Caplan's Syndrome, characterized by rapid development of multiple nodules together with moderate airway obstruction in RA patients exposed to inorganic dust (coal, asbestos, silica).

Diagnosis. Firm diagnosis of rheumatoid nodules is made by histology. The presence of neoplasia should be ruled out by fine-needle puncture (cytology) or by biopsy (histology).

Treatment. Rheumatoid nodules do not require treatment unless complications occur (superinfection, pneumothorax, etc.). Radiologic monitoring is advisable, especially in the case of a single nodule.

- Interstitial fibrosis

Clinical description. This is the most frequent pulmonary manifestation in RA (Tanoue, 1998): 3.7% (95% confidence interval 2.4-5.0%) in the EMECAR RA cohort (*Sociedad Española de Reumatología*, 1999-2005) (Carmona, 2003a); smoking is the most important risk factor (Saag, 1996a). Its clinical presentation is similar to that of idiopathic pulmonary fibrosis (progressive dysnea, non-productive cough), which generally appears at advanced stages of the disease. The physical examination is normal in the early stages, with the subsequent appearance of basal crepitations, acropachy and signs of pulmonary hypertension.

Diagnosis. If interstitial pneumonitis is suspected, blood gas analysis and respiratory function tests, including diffusion test, should be requested, in addition to simple radiology.

High-resolution computerized axial tomography has a high diagnostic sensitivity and specificity and often makes it possible to avoid biopsy, which is necessary in cases showing atypical patterns in the tomographic examination.

Treatment. It is advisable to follow the consensus guidelines proposed by the American and European societies of pulmonary diseases (American Thoracic Society, 2000).

- Bronchiolitis obliterans organizing pneumonia (BOOP)

Clinical description. BOOP is an infrequent proliferative bronchiolitis, generally idiopathic in character, whose presentation has been associated with several infectious and toxic agents as well as with RA (Yousem, 1985; Rees, 1991; Ippolito, 1993). The clinical picture of RA-associated BOOP is similar to that produced by other causes: cough, dysnea, general discomfort, loss of weight and fever. Basal crepitations are found on physical examination.

Diagnosis. The sedimentation rate is generally very high. The chest radiograph shows bilateral consolidation of parenchymal foci without loss of volume. High-resolution axial tomography reveals a patchy unilateral or bilateral pattern of consolidated foci of pulmonary parenchyma, generally peripheral (Tanaka, 2004). The definitive diagnosis is made by pulmonary biopsy, in which intraluminal plugs of immature fiberblasts can be observed in the bronchioles, with or without involvement of the perialveolar space (Yousem, 1985; Rees, 1991; Ippolito, 1993).

Treatment. Oral prednisone (1.5 mg/kg/day) in a single daily dose, to be maintained for 4-6 weeks, then slowing reducing the dosage until discontinuing the drug in 4-6 months.

In cases of serious and rapidly progressive disease, it is recommended to begin treatment with prednisone pulses (125-250 mg/6h) during the first 3-5 days.

IV.1.7.e. Felty's syndrome

Treatment for Felty's syndrome requires comprehensive control of RA inflammatory activity. As a specific measure, the use of filgastrim is recommended when the absolute neutrophil count is lower than 1,000/mm^3 and the patient has a history of severe infections associated with the disease. [5, D]

Felty's syndrome is an infrequent but serious extra-articular manifestation of RA. Its prevalence in the EMECAR AR cohort (*Sociedad Española de Reumatología*, 1999-2005) is 0.3% (Carmona, 2003a). The clinical picture is characterized by the presence of splenomegaly, leukopenia (<3,500/mm^3) and neutropenia (<2,000/mm^3), in a patient who fulfills the RA criteria. The main determinant of its prognosis is the higher incidence of systemic manifestations, mainly bacterial infections. This higher incidence is due both to neutropenia and to defective neutrophil function.

- Treatment

There are no controlled studies showing the efficacy of any specific treatment in Felty's syndrome. Thus these patients should be managed the same as for RA, together with

measures for the prevention of infections and empirical treatment of fever, similar to those used in patients with secondary neutropenia. Given that these guidelines vary depending on the frequency with which certain germs are isolated and their antibiotic resistance, the treatment guidelines recommended in each center should be followed.

Granulocyte colony stimulating factor and granulocyte-macrophage colony stimulating factor are indicated in patients with absolute neutrophil counts of less than 1,000/mm^3 and recurrent infections, once bone-marrow biopsy has ruled out the existence of a myeloid process that may simulate Felty's syndrome. A good clinical response is usually obtained, and treatment can be continued for a long period of time when drug treatment fails. Cases of failure to respond and of serious adverse effects have been reported in some patients (exacerbation of arthritis and leucocytoclastic vasculitis) as a consequence of their use. (Stanworth, 1998; Hellmich, 1999).

In refractory cases surgical splenectomy or partial embolization of the spleen have been used, but there are no conclusive data about their usefulness (Laszlo, 1978; Nakamura, 1994).

IV.1.7.f. Secondary Sjögren's syndrome (SSS)

There are no specific recommendations for modifying the course of SSS in RA. The recommendations in this guideline include symptomatic treatment of xerophthalmia and xerostomia. Dental and ophthalmological examinations at least every 6 months are recommended. [5, D]

- Clinical history and diagnosis

A patient with RA is considered to have SSS if there are signs and symptoms of xerophthalmia together with signs and symptoms of xerostomia.

Objective signs of xerophthalmia are considered to be an abnormal Schirmer's test result together with a diagnosis of keratoconjunctivitis sicca by staining with rose Bengal or fluorescein.

Objective signs of xerostomia are considered to be reduced production of saliva determined by Lashley cup or other methods, together with a positive minor salivary gland biopsy and a lymphoid foci count of 2 or higher, based on the average of four evaluable salivary gland lobules.

A differential diagnosis should be made in patients with sarcoidosis, lymphoma, AIDS, hepatitis, autonomous neuropathy, and salivary gland hypertrophy.

- Treatment

There are no specific recommendations for modifying the course of SSS in RA.

Dryness of the eyes should be treated with:

- ✓ Withdrawal, if possible, of drugs that produce ocular dryness, such as drugs for hypertension, diuretics, and psychotropic drugs
- ✓ Use of artificial tears

- ✓ Avoidance of dry areas, those that are excessively warm, or contain irritating gases, including tobacco smoke

- ✓ Temporary or permanent surgical occlusion of the tear duct.

Dryness of the mouth should be treated with:

- ✓ Withdrawal, if possible, of drugs that produce mouth dryness, such as drugs for hypertension, diuretics, and psychotropic drugs

- ✓ Use of artificial saliva

- ✓ Use of sugar-free lemon drops

- ✓ Use of oral pilocarpine (5 mg/6 h).

Multidisciplinary teams should be created consisting of 1 rheumatologist, 1 dentist, and 1 ophthalmologist. Dental and ophthalmological examinations are recommended every 6 months.

IV.1.7.g. Vasculitis

Palpable purpura should be treated with full-dose NSAIDs and medium-low doses of prednisone (15-30 mg/day). [4, C]

Polyarteritis nodosa is treated initially with high-dose steroids (40-120 mg/day of prednisone). If there is no response, cyclophosphamide should be added (2-3 mg/kg/day orally or 0.5-1 g/m2 in intravenous pulses of 2 to 4 weeks). [4, C]

Rheumatoid vasculitis is understood to be a set of vascular processes (periungual splinter hemorrhages, palpable purpura, polyarteritis nodosa) with variable prognosis and treatment.

Rheumatoid vasculitis is an infrequent extra-articular manifestation of RA. It appears in RA of long evolution, often with little or no joint inflammation. Risk factors for rheumatoid vasculitis are male gender, positive RF, the presence of other extra-articular manifestations of RA, and time of disease evolution.

- Palpable purpura

Diagnosis: Diagnosed clinically. Systematic skin punch biopsy is not recommended for histopathological confirmation, unless a vascular process other than small vessel leukocytoclastic vasculitis is suspected. Recently prescribed drugs should be reviewed to identify a possible pharmacological cause of the palpable purpura.

Treatment: Generally disappears spontaneously. The most important factor in treatment is rest. If it does not disappear, palpable purpura should be treated with full-dose NSAIDs and medium-low doses of prednisone, beginning with 15 to 30 mg/day and progressively reducing the dosage depending on disease evolution.

- Polyarteritis nodosa-type rheumatoid vasculitis

Diagnosis. This is the most severe form of rheumatoid vasculitis and is life threatening in many patients. Histopathological confirmation is recommended whenever possible, since treatment of this form of vasculitis is frequently accompanied by severe adverse effects. Nevertheless, the physician can initiate treatment without histopathological confirmation in the most common and typical clinical presentations such as distal necrosis, skin ulceration, or multiple mononeuritis. Depending on the clinical manifestations, various complementary studies should be made, such as liver and kidney tests, arteriography, electromyogram-electroneurogram, skin biopsy, subcutaneous tissue biopsy, or biopsy of the sural nerve.

Treatment. Initial treatment is with high-dose steroids: from 40 to 120 mg of prednisone or its equivalent, in single or divided doses. The dosage selected for a particular patient will depend on the severity of the process and the threat to life. If clinical manifestations are not controlled with high-dose prednisone or if they reappear during the attempt to reduce the dosage, cyclophosphamide should be added, either 2-3 mg/kg/day orally or 0.5 to 1 g/m^2 in intravenous pulses every 2 to 4 weeks, depending on the clinical evolution and dose used. If there is a risk to life, treatment should begin with methylprednisolone IV, 15 mg/kg/day in a single daily infusion for 3 consecutive days, together with 0.75 gr/m^2 of cyclophosphamide IV in a single infusion the first day. Beginning on the fourth day, 1 mg/kg/day prednisone or its equivalent in divided doses, with dose and timing of next pulse of cyclophosphamide adjusted to the patient's clinical evolution.

- Periungual splinter hemorrhages

Although periungual splinter hemorrhages are traditionally included in the vascular manifestations associated with RA, they are not histologically related with vasculitis.

Diagnosis. They are diagnosed clinically and do not require complementary examinations.

Treatment. No specific treatment is required. Close clinical monitoring is recommended for the early identification and treatment of vascular phenomena that may develop in the future.

IV.1.8. Comorbidity not directly related with RA

IV.1.8.a. Infections

Extreme precautions should be exercised in RA patients to prevent infections. Recommended measures include receipt of routine vaccinations, but never with attenuated microorganisms if the patient is receiving immunosuppressive treatment [4, C], avoiding contacts with tuberculosis patients and receiving chemoprophylaxis with isoniazid as needed [2.b, B], and practicing scrupulous dental hygiene. [2.b, B]

When taking the clinical history of an RA patient, it is important to investigate risk factors for infections, such as parenteral drug use, transfusions or previous history of tuberculosis.

It is important to explore the presence of conjunctivitis in patients with recent-onset arthritis, and to perform a hepatic and serologic profile if there is suspicion of exposure to hepatitis virus C or B.

Evaluation of dental hygiene and basic recommendations for maintaining good dental care will allow easy control of a factor that can lead to poor outcome.

RA patients should be included in vaccination schedules, especially for influenza and pneumococcal vaccines, due to the high prevalence of respiratory diseases.

In patients who will receive treatment with biologic therapies, especially with anti-TNF, a complete examination should be performed for latent tuberculosis (history of previous infections or frequent contacts, intradermal reaction test, repeated one week later if negative, and chest radiograph). If any of these parameters are abnormal (the skin test is considered abnormal if greater than or equal to 5 mm), the patient should receive chemoprophylaxis with isoniazid for 9 months.

Patients with RA have twice the risk of developing serious infections, even after adjusting for risk factors such as age, smoking, leukopenia, steroid use and diabetes (Doran, 2002a). The most frequent locations are the musculoskeletal system, skin and respiratory tract (Doran, 2002a). Nevertheless, the rate of infections is not much different from that of other polymedicated patients with chronic diseases, including those who have other musculoskeletal diseases (van Albada-Kuipers, 1988).

This increase in infections could be explained by the immunodepression to which these patients are subject, due both to the disease itself and to treatment. However, close control with DMARDs, usually with MTX, is not related with increased infections after adjusting for other clinical variables and for comorbidity (Doran, 2002b).

Joint surgery in RA patients can also be a source of infections. Approximately 2% of RA patients who undergo surgery become infected; the type of surgery is more important than the DMARD the patient is using in determining susceptibility (Hamalainen, 1984).

An association has been seen between periodontal infection and the severity of rheumatoid arthritis, which is reversible with control of the infection (Ribeiro, 2005).

An SR (SR 7) was performed to study the safety of anti-TNF use in patients who have suffered a severe infection or an infected prosthesis. No new articles were found, thus, the conclusion was:

- There is no evidence either for or against the safety of anti-TNF use in patients who have suffered a severe infection and/or infected prosthesis.

- Viriasis

Several viruses have been related with the pathogenesis of RA. The Epstein Barr virus has been associated with the development of RA or the abnormal lymphocyte response in RA (Becker, 1989), although not all studies have observed a direct relation between the virus and the disease (Saal, 1999; Niedobitek, 2000). Other viruses that have been associated with RA are the parvoviruses, although the association was not consistent in twin analysis (Hajeer, 1994). No association has been seen with retroviruses such as the AIDS virus (Pelton, 1988) o el HTLV-1 (Sebastian, 2003).

Hepatitis B virus and HBV vaccine have sometimes been related with triggering of autoimmune diseases, RA among them.

The prevalence of HCV antigens in European RA patients is approximately 0.65%, not very different from the prevalence in the general population (Maillefert, 2002), which is contrary to the idea that HCV is related with the pathogenesis of RA.

Nevertheless, HCV infection may sometimes be associated with an arthritis that is indistinguishable from RA and which also responds to the usual treatment for RA (Lovy, 1996). Thus, it is important to take a history of risk factors for hepatitis virus infections, such as parenteral drug use or transfusions. It is important to explore the presence of conjunctivitis in patients with recent-onset arthritis, and to perform a hepatic and serological profile if there is suspicion of exposure to HBV or HCV.

Although the use of treatments that produce greater immunodepression in the patient could be contraindicated, it has not been demonstrated that concurrent use of anti-TNF agents is associated with greater replication of latent viruses such as HCV (Peterson, 2003; Parke, 2004) or of lymphotropic viruses such as herpes (Torre-Cisneros, 2005).

- Vaccines

RA patients' susceptibility to respiratory tract infections like influenza and its serious complications make vaccination a necessity. The influenza vaccine has been demonstrated to be safe and sufficiently immunogenic (Chalmers, 1994; Fomin, 2006).

The pneumococcal vaccine is also recommended in these patients due to the risk of infection and its proven efficacy and safety (Elkayam, 2002a). However, anti-TNF agents may reduce the immunogenic response to this vaccine (Elkayam, 2004), therefore the vaccine should be administered before beginning treatment with these therapies.

The response to vaccination against hepatitis B may be reduced in very elderly patients. It produces a response in 68% of patents with RA (Elkayam, 2002b).

Vaccination with attenuated viruses is contraindicated in RA patients receiving immunosuppressive treatment.

- Tuberculosis

Spain has a high rate of tuberculosis compared with other countries in our part of the world. RA has been seen to increase the frequency of tuberculosis up to 4 times higher than expected in the non-affected population (Carmona, 2003b). The cause of this could be related with abnormal response of rheumatoid arthritis lymphocytes to granuloma, or with multiple morbidity, or with the use of glucocorticoids (Jick, 2006). Anti-TNF agents clearly predispose the patient to TB reactivation, which increases the risk even more (Gomez-Reino, 2003).

The following recommendations of the Spanish Society of Rheumatology and the Spanish Medicines Agency (AEME in Spanish) (

Table 15 and Table 16), have made it possible to reduce the risk of tuberculosis activation in patients undergoing anti-TNF treatment to nearly normal levels (Carmona, 2005):

Table 15. SER and AEME recommendations to control the risk of TB in patients with anti-TNF treatment

Clinical history should include:	History of tuberculosis
	Recent contacts with tuberculosis patients
Should also perform:	Chest radiograph to rule out active tuberculosis or radiographic signs consistent with old tuberculosis infection
	Tuberculin skin test (PPD) (see following table)

Table 16. SER and AEME recommendations according to PPD results

If PPD is positive (induration ≥ 5 mm at 48-72 hours), patient is considered to have latent tuberculosis infection.
If anergy or induration less than 5 mm is detected, a new tuberculin test (booster) should be performed, 1-2 weeks afterwards, especially in persons over age 50.
If induration is ≥ 5 mm at 48-72 hours after booster, patient is also considered to have tuberculosis infection.
In individuals vaccinated with BCG it is impossible to know whether a positive PPD is a consequence of the vaccine or indicates latent tuberculosis infection, therefore the same recommendations should be followed as for those who are not vaccinated.

All patients with latent tuberculosis infection, as shown by residual lesions on the chest radiograph and/or positive PPD, should institute specific treatment before beginning therapy with biologics. The minimum interval needed between initiation of treatment for latent tuberculosis infection and anti-TNF treatment is not known. Although the previous recommendation was to begin tuberculosis treatment one month before, a much shorter interval of only days is probably sufficient, or the two treatments may even be initiated at the same time. The treatment of choice for tuberculosis infection is isoniazid (5 mg/kg/day up to a maximum of 300 mg/day) with vitamin B_6 supplements for 9 months, since treatment for 6 months has been shown to be less effective. In case of isoniazid intolerance, rifampicin is recommended at doses of 10 mg/kg/day (maximum of 600 mg/day) for 4 months. Because of its greater risk of liver toxicity, treatment with rifampicin at the same dose plus pirazinamide (15-20 mg/kg/day) for 2 months is not currently recommended.

IV.1.8.b. Cardiovascular complications

Individual risk factors for cardiovascular (CV) complications should be identified and treated: age, male sex, highly active arthritis, smoking, arterial hypertension, hypercholesterolemia and history of CV episode. [1.b, A]

RA patients have accelerated arteriosclerosis that depends, among other factors, on the chronic inflammatory process. These patients have more extensive CV complications than in the general population, which manifest in a less typical form and are accompanied by higher

mortality after the first CV event. Effective treatment of the inflammatory process is accompanied by a significant reduction in morbidity and mortality from CV causes.

Less primary and secondary prevention of CV disease is common in RA patients. However, strict control of CV risk factors can have very positive repercussions on RA outcome.

Each RA patient's individual risk of suffering CV complications should be established and the resulting treatment implemented. It is particularly important to keep in mind the factors associated with higher risk: age, highly active arthritis, smoking, male sex and history of a previous CV event.

All RA patients should discontinue the use of tobacco.

Unless there are contraindications, platelet inhibitors should be used prophylactically in RA patients who have suffered a previous CV event.

Strict control and monitoring of arterial pressure, especially in patients treated with drugs that can elevate blood pressure (NSAIDs, steroids, leflunomide), is also important.

Hyperlipidemias should be treated in accordance with general recommendations, not forgetting the possible positive influence of the statins on the inflammatory process in RA. A systematic literature review including 3 studies (no new studies) was performed to evaluate the "Efficacy and safety of statins in RA patients" (SR 4). The conclusions were:

- Atorvastatin, and it is not known if other statins, has a moderate effect on inflammation in RA patients **[1.b].**
- The statins (**atorvastatin and simvastatin**) are effective in the short term in improving the clinical parameters of thrombosis in RA patients **[1.b].**
- The statins can slightly improve bone mass in RA patients **[5].**
- Evidence for the safety of statins in RA is inconclusive.

Homocysteinemia is easy to combat by assuring an optimal level of folic acid (and also of Vitamin B12), especially if the patient is taking MTX.

It has been known for decades that RA patients have an increased mortality rate (Sattar, 2003; Boers, 2004). The most important cause of mortality in RA patients is of cardiovascular origin (Boers, 2004) – a CV mortality that is not completely explained by the traditional CV risk factors, and which has clearly been related with RA activity and, consequently, with the accompanying chronic inflammatory process (del Rincon, 2001). In this regard, it is assumed that the decreased mortality observed in case series of patients with a more recent diagnosis (Goodson, 2002a) is due partly to better control of the inflammatory process by the more effective therapeutic agents used in recent decades (Choi, 2002).

Sufficient evidence now exists to suggest that mechanisms different from these risk factors and depending mainly on RA are going to be key in the accelerated arteriosclerosis that occurs in these patients. Moreover, the importance of inflammatory mechanisms in the development of CV events is supported by the finding that the serological and clinical markers of inflammation are clear predictors of CV disease. Patients with more serious disease have higher mortality. Thus, the most important predictors of mortality in RA are the presence of rheumatoid factor (RF), the score on the Health Assessment Questionnaire (HAQ) and the

presence of extra-articular manifestations (Goodson, 2002b). Logically, patients with more serious disease of longer duration have a higher probability of developing vascular complications. Most of the studies made in tertiary hospitals have confirmed an increased CV risk in RA patients, which may reflect a bias towards a population with more serious disease. However, it has also recently been reported that patients treated in primary care have more frequent CV complications than those in the general population (Turesson, 2004). It has also been shown that, in patients with inflammatory polyarthritis treated in primary care, elevated levels of C reactive protein (CRP) are a clear predictor of CV mortality (Goodson, 2005a). The presence of a large number of swollen joints is also a clear predictor of DV mortality (Jacobsson, 2001). Furthermore, an increased risk of acute myocardial infarction (AMI) and silent AMI has been shown in patients before the ACR criteria-based diagnosis of RA (Maradit-Kremers, 2005a). In this regard, it has been shown that signs of systemic inflammation and serological abnormalities (autoantibodies) exist years before the development of full-blown clinical arthritis (Nielen, 2004b). Thus, there may be a preclinical phase before the development of frank RA in which a higher risk of CV disease is also observed.

- Manifestations of CV disease

Ischemic heart disease. Ischemic heart disease has traditionally been considered the most frequent manifestation of accelerated arteriosclerosis in RA patients. However, it is possible that RA patients experience less pain or interpret anginal pain differently, that they do not go to specialty services and that they more frequently suffer unrecognized (silent) AMI and sudden death (Maradit-Kremers, 2005b). In addition, RA patients with ischemic heart disease more often have multi-vessel disease compared with individuals without arthritis (Warrington, 2005).

Heart failure. The risk of congestive heart failure (CHF) in RA patients is twice as high as in the population without arthritis, an increase that cannot be explained by the traditional CV risk factors or by increased ischemic heart disease (Wolfe and Michaud, 2004a; Nicola, 2005). In these patients, CHF is associated with markers of disease activity and severity, and adequate control of RA activity is associated with a lower frequency of CHF, especially in patients treated with anti-TNF (Wolfe and Michaud, 2004a). However, the use of anti-TNF is contraindicated in patients with New York Heart Association (NYHA) class III/IV CHF (Sarzi-Puttini, 2005).

A systematic review (SR 5) was made to evaluate the "Incidence of heart failure in RA with or without anti-TNFs". It included 2 systematic reviews, 7 case-control studies and 3 cohort studies. In the up´date, 14 additional articles were selected. The conclusions, with their level of evidence, were as follows:

- RA patients show echocardiographic evidence of sub-clinical ventricular dysfunction that is associated with age, late-onset RA and extra-articular manifestations, but not with disease duration, sex, RF, radiological index, total prednisone dose, HLA-DRB1 genotype or treatment with MTX **[1.b].**
- The incidence of CHF in RA patients is 22% higher than in controls, especially in women and in patients with positive rheumatoid factor **[1.b].**
- Although the analysis of studies published to date shows a protective effect of biologic therapies against development of CHF, at least in short term **[2.b],** there are

other arguments in favor of maintaining a cautious approach and not using these therapies in patients with CHF **[4].**

Non-cardiac ischemic accidents. Although increased CV mortality in RA has been attributed mainly to ischemic heart disease, RA patients have accelerated arteriosclerosis that not only affects the coronary arteries, but also produces generalized vascular involvement, as shown in recent studies (Popa, 2005a, Popa, 2005b). Thus, several studies have shown increased arterial stiffness and increased vascular resistance in RA patients. Moreover, an increase in the frequency of distal vascular obstruction and vascular stiffness has also been shown in the peripheral arteries of RA patients, especially in cases of more progressive disease, which suggests a relation between the intensity of the inflammatory process and vascular damage (del Rincon, 2005).

- Cardiovascular risk factors

Tobacco. Tobacco has traditionally been considered a risk factor for the development of RA, and smoking has been associated with poorer disease outcome (Wolfe, 2000). The recently discovered relation between the shared epitope, anticitrulline antibodies and tobacco clearly supports the role of this environmental agent in the pathogenesis of RA (Klareskog, 2006).

Dyslipidemia. Patients with untreated active disease have an abnormal lipoprotein profile characterized by a reduction in HDL-cholesterol and an increase in the LDL/HDL-cholesterol ratio, which can increase the risk of atherogenesis (Munro, 1997a; van Halm, 2006). Control of the disease's inflammatory activity with the classical DMARDs is accompanied by substantial improvement in the lipid profile (Park, 1999; Park, 2002). On the other hand, some of the drugs used to treat dyslipidemia have been shown to have several beneficial effects in RA patients (Klareskog and Hamsten, 2004a; Tikiz, 2005). The paradigm is the statins, which obviously improve the lipid profile, may also help decrease the incidence of osteoporotic fractures, and have shown a modest beneficial effect on disease activity in these patients (McCarey, 2004).

Arterial hypertension. Ra patients have a heightened risk of developing arterial hypertension (AHT), and this risk seems to increase particularly after developing the disease (Kroot, 2001). The use of certain drugs like NSAIDs, steroids and, more recently, leflunomide, may contribute to this increased frequency of HTA.

Hyperhomocysteinemia. RA patients have elevated levels of homocystein, especially those treated with MTX (and/or sulfasalazine) who do not receive folic acid supplements (Goodson, 2002). Since hyperhomocysteinemia is an independent, but modifiable, risk factor for CV disease, all patients receiving treatments that can increase homocystein should receive appropriate vitamin supplements.

Diabetes mellitus. Although RA patients do not appear to have a heightened prevalence of diabetes, there is an increase in insulin resistance that is related with the inflammatory activity of the disease (van Doornum, 2002)

Reduced physical activity. Uncontrolled inflammation in RA can lead to a marked reduction in physical activity in many patients, which in turn may result in significant weight increase. Both factors are accompanied by an increase in CV risk. Accordingly, adequate control of RA activity that permits the most suitable physical activity possible and the control of obesity by combining diet and physical exercise, can help reduce the CV risk.

- Influence of treatment

Treatment of CV disease and the traditional risk factors. Cardiovascular risk factors should be strictly controlled in RA.

It has been shown that treatment of a chronic disease substantially reduces the probability of treating comorbidity, due both to poor compliance of the prescribing physician with recommendations (Colglazier, 2005) and to poor compliance of polymedicated patients (Kulkarni, 2006).

RA Treatment. Control of chronic inflammation in RA, both by using effective medication and by ensuring good patient follow-up, improves CV and joint outcome. The more intensive treatment approach to achieving the therapeutic goal that has been observed in recent decades is reflected in lower AMI mortality (Krishnan, 2004).

The antimalarials, especially hydroxychloroquine (HCQ), appear to have a beneficial effect on the lipid profile, as well as certain antithrombotic properties (Vazquez-Del, 2002).

A recent study has shown that, after correcting for different variables (including length of follow-up and severity of RA), RA patients treated with biologics had a lower rate of first ischemic CV event compared with those who had not received biologic treatment (Jacobsson, 2005). This suggests that the possible beneficial effect of the anti-TNFs on the inflammatory process may also have a protective effect on the development of CV events.

In contrast, some part of this CV comorbidity could be related with certain RA treatments. The NSAIDs, whether coxibs or not, are related with AMI incidence, especially when they are taken for prolonged periods of time, which happens quite frequently in RA (García-Rodríguez, 2005). The glucocorticoids favor the development of atherosclerotic plaque by different mechanisms, an effect that can be stronger than their beneficial anti-inflammatory action (del Rincon, 2004). MTX produces an increase in homocysteinemia unless folic acid is administered the day before taking it; following this guideline may even reduce CV mortality (Choi, 2002).

IV.1.8.c. Osteoporosis

When RA is first diagnosed, the principal risk factors for fracture and loss of bone mass should be analyzed; if any are present, bone densitometry is indicated. [5, D]

The first-line treatment options for osteoporosis are alendronate and risedronate, with cyclic etidronate or calcitonin as alternatives. [5, D]

Hormone treatment is not indicated. [5, D]

A large percentage of RA patients have low bone mass in the axial and peripheral skeleton. These patients are thought to have double the risk of developing fragility fractures of the vertebrae and femur as compared to the general population, with a relative risk of 2.1 for vertebral fracture and 1.5-2.1 for fracture of the femur, rising to 4.4 in patients with marked alteration of functional capacity.

Numerous risk factors are involved in the development of osteoporosis: age, post-menopause (in women), disease activity, functional capacity, immobilization, and influence of the drugs

used in treatment, especially the glucocorticoids. An important loss of bone mass has been described in the initial phases of RA. Despite this evidence, no CPG has yet been developed on the treatment of osteoporosis in RA.

Osteoporosis should be suspected in the presence of vertebral or peripheral fractures not due to trauma. When RA is first diagnosed, all patients should be evaluated for the main risk factors for fracture and loss of bone mass, both independent factors and those related with RA (Tables 23 and 24).

For the specific treatment of osteoporosis, the first-line treatment options are alendronate and risedronate, with cyclic etidronate or calcitonin as alternatives. Hormonal treatment is not indicated as treatment for osteoporosis.

Control of inflammatory disease may have a beneficial effect on the bone (Torikai, 2006)

- Clinical suspicion

Vertebral or peripheral fractures, excluding those caused by trauma.

- Diagnosis

At the initial examination an analysis should be made of the main risk factors for fracture and loss of bone mass, both independent risk factors and those that are associated with RA (Table 20). If one or more of these factors is present, a bone densitometry of the lumbar spine and femur is indicated.

Since a large percentage of vertebral fractures are asymptomatic, a lateral radiograph should be made of the dorsal and lumbar spine to evaluate the existence of vertebral fractures in accordance with the following criterion for fracture: a 20% or greater reduction of the anterior, mid, or posterior height of the vertebral body. Routine laboratory tests should also be obtained to rule out associated processes that may be causing the osteoporosis.

Table 20. Risk factors for osteoporosis

Factors independent of RA
Age over 65 years
History of fragility fracture after age 40
Body weight less than 58 kg
Fragility fractures in first-degree relatives
Smoking
Early menopause
Prolonged amenorrhea
Male hypogonadism
Other predisposing diseases for osteoporosis
Factors associated with RA or its treatment
Active disease

HAQ >1,25
Treatment with glucocorticoids: >7.5 mg/d for more than 3 months, continuous treatment with >2.5 mg/d, or cumulative dose over 30 g.

In accordance with the WHO criteria for the diagnosis of osteoporosis in post-menopausal women, osteopenia or osteoporosis is considered to exist when the T-scale value is between -1 and -2.5, or is less than -2.5, respectively. Although there is no official consensus, these diagnostic criteria appear to be valid in men.

- Treatment

Since all RA patients are at risk for osteoporosis, the following recommendations are made for preventive treatment:

- ✓ Discontinue smoking and excessive alcohol consumption.
- ✓ Maintain physical activity.
- ✓ Take the necessary precautions to avoid falls.
- ✓ Administration of calcium supplements sufficient to reach a daily intake, including diet, of 1,500 mg, plus 400-800 IU of vitamin D3.
- ✓ If hypercalciuria is present, thiazides should be administered.

Specific treatment for osteoporosis should be begun if:

- ✓ There is a history of fracture of the vertebra or femur.
- ✓ The patient is a post-menopausal woman with a bone mineral density of less than -1.5 on the T scale.
- ✓ The patient is over 65 years of age and is being treated with glucocorticoids.
- ✓ The glucocorticoid dose is more than 7.5 mg/day of prednisone for more than 6 months, and there are other risk factors(Table 20).

Treatment is with alendronate or risedronate.

At the time of writing of this guideline, no information is available on the efficacy of raloxifene or strontium ranelate in secondary osteoporosis. Teriparatide is approved for treatment of post-menopausal women with severe osteoporosis and high risk of fracture; however, it is not approved specifically for the treatment of secondary osteoporosis.

IV.1.8.d. Neoplasias

Discontinuation of all tobacco use is indicated in all RA patients. [5, D]

Anti-TNFs are not recommended in patients with a personal history of lymphoma. [4, C]

In patients with a personal history of lymphoma, the risk/benefit ratio should be carefully evaluated before deciding to use a TNF antagonist. [5, D]

History of a malignant solid tumor in the last 5 years is a contraindication for the use of anti-TNF agents. [5, D]

If there is history of a malignant solid tumor longer than 5 years previously, the physician should consult the specialist in oncology about the biopathology of the tumor. [5, D]

An RA patient who develops a tumor should discontinue all DMARDs except antimalarials, gold salts, and sulfasalazine. [5, D]

There is an association between RA and cancer, not so much in the overall cancer rate, as it is not clear whether or not this is higher, but with regard to specific types of cancer (Prior, 1984; Gridley, 1993; Mellemkjaer, 1996).

It is primarily the rate of hematological neoplasias that has been seen to increase, although there is disagreement about the subtype and the magnitude of the association (Macfarlane, 1996; Baecklund, 2004; Ekbom, 2005; Zintzaras, 2005; Geborek, 2005; Smedby, 2006). The hypotheses that support this association are related with the chronic abnormal immunostimulation that occurs in RA, which may lead to a malignant transformation of lymphocyte clones (Baecklund, 1998; Ehrenfeld, 2001).

With respect to solid cancers, the available information is even more heterogeneous, with the possible exception of an increase in lung cancer, particularly in men, and a reduction in breast cancer in women (Gridley, 1993; Kauppi, 1996a). Some studies point to a reduced rate of colorectal cancer (Kauppi, 1996b).

Some drugs have been related with the association between cancer and RA. Cancer of the bladder, epidermoid skin cancer and hematological cancers have been related with cytotoxics like azathioprine or cyclophosphamide (Kinlen, 1985; Beauparlant, 1999). Studies of the relation with MTX are contradictory (Bologna, 1997; Feng, 2004). A relation between NSAIDs and a reduced risk of colorectal cancer has been reported in patients who have taken these drugs over prolonged periods (Kauppi, 1996b). In general, the anti-TNFs are not related with increases in cancer. The rate of lymphomas is higher than expected in RA, both in those treated and those not treated with anti-TNFs. Although the rate appears to be somewhat higher in those treated with anti-TNFs, the data currently available are not totally conclusive (Mikuls, 2003; Symmons, 2004; Wolfe, 2004b; Balandraud, 2005; Geborek, 2005; Chakravarty, 2005; Askling, 2005a). Definitive conclusions will have to await the availability of longer term use of anti-TNFs (Askling, 2005a).

For this reason, the anti-TNFs are not indicated in patients with a personal history of lymphoma, and their use should be carefully evaluated in RA patients with a family history of lymphoma. Although the evidence in regard to other types of cancers is debatable, in general the use of anti-TNFs is not recommended when there is a history of a malignant solid tumor in the last 5 years, and consultation with the specialist in oncology about the biopathology of the tumor is indicated when the solid tumor occurred more than 5 years previously.

- Lung cancer

Lung cancer is increased in RA, although the main risk factors for its appearance are the expected ones: being a male smoker (Kauppi, 1996a). Tobacco is related with the appearance of RA, with its severity, with the detection in serum of anti-CCP antibodies and rheumatoid factor; it is also related with a higher cardiovascular risk and, finally, with lung cancer. Besides tobacco there are no other factors related with RA or its treatment that explain the increased rate of lung cancer. Lung cancer is expressed in RA patients no differently than in other persons (Chen, 2005).

- Lymphoma

Hematological neoplasias, while infrequent, are increased in RA, especially the lymphomas. There seems to be a relation among lymphomas in RA, HLA genetic markers and infection with Epstein Barr virus (Van Haarlem, 2000; Ehrenfeld, 2001; Feng, 2004; Ekbom, 2005; Smedby, 2006).

RA sufferers have an increased risk of developing lymphoma, regardless of the presence or absence of concomitant treatment with anti-TNFs (Askling, 2005a, Baecklund, 2006). Although being a first-degree relative of an RA patient increases the risk of suffering a lymphoma (Ekstrom, 2003), it is not known if an RA patient with a family history of lymphoma has a higher risk. The risk of developing a lymphoma in RA patients is related with the inflammatory activity of the disease (Baecklund, 2006).

Cohort studies have not been able to demonstrate a higher risk of developing a lymphoma in RA patients treated with anti-TNF compared with patients with RA of similar severity who are not treated with anti-TNF (Askling 2005a); however, reports of case series in which the interval between initiation of anti-TNF and the development of lymphoma was very short, with explosive and occasionally lethal clinical courses, in RA patients with a history of lymphoma (Brown 2002), call for a cautious attitude, and advise against the use of anti-TNFs in RA patients with personal histories of lymphoma.

IV.1.8.e. Mental health problems

Psychological disorders (anxiety and depression) may frequently appear, and are a factor predictive of disability in RA patients.

Psychological disorders (depression and anxiety) are very frequent in RA from the time the disease begins (van der Heijde, 1994), due to the impact of confronting its diagnosis and evolution. Depression, anxiety and chronic pain are closely related. This can impede the evaluation (VAS pain score by the patient and by the physician) and should be kept in mind when planning treatment. In addition, anxiety and depression appear to play a determining role in the appearance of disability (Escalante, 1999).

It is currently believed that some of the patient's psychological characteristics (perceived level of helplessness, coping ability, self-management ability) play an important role as factors predicting disability and health status. A high level of helplessness makes for a poorer outcome, while a higher capacity for coping and self-management improves it (Scharloo, 1999).

V. PHARMACOLOGICAL TREATMENT

To facilitate reading of the text, the abbreviations listed below for the DMARDs used in RA treatment will generally be used in the chapters that follow.

Table 17. DMARD abbreviations

PHARMACEUTICAL	ABBREVIATION
ABATACEPT[a]	ABT
ADALIMUMAB[a]	ADA
ANAKINRA[a]	ANK
AZATHIOPRINE[b]	AZT
CERTOLIZUMAB PEGOL[a]	CZP
CYCLOPHOSPHAMIDE[b]	CTX
CHLOROQUINE[c]	CLQ
CYCLOSPORINE[c]	CSA
D-PENICILLAMINE[d]	DPE
ETANERCEPT[a]	ETN
GOLIMUMAB[a]	GLM
HYDROXYCHLOROQUINE[c]	HCQ
INFLIXIMAB[a]	IFX
LEFLUNOMIDE[c]	LEF
METHOTREXATE[c]	MTX
ORAL GOLD[d]	AUR
INJECTABLE GOLD[c]	IG

a= Biologic agents ; b= Chemical agents used occasionally ; c=Chemical agents used frequently; d= Chemical agents used very infrequently.

PHARMACEUTICAL	ABBREVIATION
RITUXIMAB[a]	RTX
SULFASALAZINE[c]	SSZ
TOCILIZUMAB[a]	TCZ

Pharmacological treatment of recent-onset rheumatoid arthritis.

All RA patients should be treated with a DMARD as soon as the clinical diagnosis of the disease is established, regardless of whether they meet the ACR classification criteria. [1a, A]

The time between symptom onset and initiation of treatment with DMARDs is one of the few variables that the physician can modify. Early treatment is associated with a higher probability of favorable response (Egsmose, 1995; van der Heide, 1996; Tsakonas, 2000; Anderson, 2000; Landewe, 2002; Mottonen, 2002; Genovese, 2002; Choy, 2002). A certain dose-response effect has also been found, with greater efficacy and improved outcomes (reduced clinical activity, less disability and better radiographic score) in patients treated with the strategy that includes more powerful and faster-acting DMARDs (van Jaarsveld, 2000a). Three double-blind placebo-controlled randomized clinical trials (Borg, 1988; The HERA study group, 1995; van der Heide A, 1996) have shown that treatment with a DMARD, in addition to NSAIDs, is beneficial in patients with early RA. A meta-analysis by Anderson et al. (Anderson, 2000) of 14 double-blind controlled randomized clinical trials including a total of 1,435 patients concluded that there was a significant relation between RA duration and the probability of response to a DMARD. More recently, Nell et al. showed in an observational case-control study that initiating DMARD treatment within the first 3 months of the disease reduces radiologic damage after 36 months follow-up, as compared with beginning the DMARD at 3 to 12 months of RA evolution (Nell, 2004). The 2010 EULAR recommendations on management of RA (Smolen, 2010b), which are based on 5 systematic reviews, state that treatment with DMARDs should begin as soon as the diagnosis of RA is confirmed. A meta-analysis by Finckh et al (Finckh 2006), which included 6 follow-up studies and 6 cohorts, revealed reduced radiological progression in patients with early RA treated quickly with DMARDs compared with patients treated later. The benefit was greater for patients with more aggressive disease. Consequently, all RA patients should initiate DMARD treatment as soon as possible in the course of the disease.

The initial treatment recommended in all patients who have not been previously treated with a DMARD is MTX, due to its excellent safety and efficacy profile. [1a, A]

MTX should form part of initial therapy in patients with active RA, since it has proven to be more efficacious than other DMARDs (Gaujoux-Viala, 2010). In this meta-analysis, the results were comparable for MTX and LFN at the doses of MTX evaluated (7.5-15 mg/wk). The advantages of MTX as opposed to other DMARDs with similar short-term efficacy are: an extensively known safety profile, ease of administration, and a lower rate of treatment dropout in the medium to long term (De La Mata, 1995; Galindo-Rodriguez, 1999). For all these reasons, this guideline recommends it as the drug of choice.

For optimal use of MTX as a remission-inducing agent in early RA, a rapid step-up dose to 20 or 25 mg weekly is recommended by 3-4 months after initiation of MTX. In refractory cases, MTX bioavailability should be assured by subcutaneous administration. [1a, A]

MTX remains the cornerstone of disease-modifying drug treatment in early RA. A systematic review (Visser 2009) on the route of administration and optimal dose of MTX showed that the initial dose should be 15 mg/wk orally, with escalation at 5 mg/mo up to 30 mg/wk or the maximum tolerable dose. The authors state that subcutaneous administration should be used

when the response to treatment is insufficient. This systematic review was incorporated into the EULAR recommendations on management of RA (Smolen, 2010b). Similarly, a meta-analysis (Gaujoux-Viala, 2010) compared the efficacy of synthetic DMARDs with placebo or other DMARDs in the treatment of RA and concluded that monotherapy with MTX is more efficacious with respect to signs, symptoms, disability, and structural damage than other non-biologic DMARDs, although the results were comparable for MTX and LEF at the doses of MTX evaluated (7.5-15 mg/wk). MTX bioavailability after oral administration is variable, therefore subcutaneous administration is recommended before concluding that the RA is refractory to MTX. The systematic review cited above (Visser 2009) showed that evidence from retrospective studies suggests greater efficacy and less gastrointestinal toxicity with parenteral MTX than with oral MTX. Therefore, unless it is contraindicated, MTX is the DMARD of choice, based on its safety and efficacy profile.

Nonetheless, given the clinical complexity of RA, the panel considers that, in some clinical situations, initial DMARD treatment may consist of using other drugs that have also been shown to control signs and symptoms of the disease and to delay radiologic progression. [5, D]

– The efficacy of all the DMARDs in Table 18 has been shown to be superior to placebo. However, no clinical trials have compared all possible drug combinations in monotherapy or combined therapy. SR 6 summarizes the comparative efficacy of the different DMARDs in monotherapy or combination therapy, updating the review in the previous edition of GUIPCAR to 2006. The result of the synthesis of the evidence is presented in evidence tables 23 to 26.

According to the conclusions of SR 6, in regard to treatments in monotherapy:

- The DMARDs are effective long-term agents in established RA **[1a].**
- LEF **[1b]** and CSA **[2b]** in monotherapy are as effective as MTX.
- LEF is clinically more effective than SSZ, although it has no radiologic benefits **[1b].**

To investigate the existence of significant differences in retention time (no withdrawal) of the different DRMARD treatments, especially in **advanced RA**, an update of the previous review (RS9) identified a 59 studies. The conclusions were as follows:

- Among the factors influencing the length of time that the same DMARD is maintained (duration of treatment or retention time) are: the rheumatologist, early disease activity and the number of previous DMARDs **[1b].**
- MTX has very good retention time, especially when it is supplemented with folic acid and at high doses, but also because it is often administered in combined treatment **[1b].**
- LEF and the anti-TNFs also have high retention time **[1b].**
- AUR, the anti-malarials, and ANK are notable for their low retention time **[1b].**
- Survival of ABT and TCZ does not seem to differ from that estimated for anti-TNF agents, at least in the short term **[2b].**

In early RA with no markers of poor outcome (radiologic erosions, RF, anti-CCP antibodies, absence of extra-articular disease, HAQ over 1 or high inflammatory burden), it is acceptable to begin treatment with other DMARDs that have a lower toxicity profile

or are easier to monitor for side effects; typical examples of these are the anti-malarials or SSZ. [5, D]

In clinical practice it is common to be confronted with a chronic polyarthritis of more than 6 weeks duration that meets RA classification criteria, but does not have radiologic erosions or extra-articular manifestations, and is not positive for either RF or anti-CCP. In these cases, and in the absence of high inflammatory and/or functional burden, it is acceptable to use DMARDs that have lower toxicity (Felson, 1990) and that can be monitored more easily.

In early RA that is expected to be especially incapacitating due to characteristics of the disease, the patient, or the patient's type of employment, initial combination therapy with MTX and an anti-TNF agent may be indicated; the objective of this treatment is to induce rapid remission and try to withdraw the anti-TNF agent and maintain RA remission with MTX in monotherapy. [5, D]

Two recent reviews (Kingsley 2010; Kuriva, 2010) compared the combination of MTX and an anti-TNF agent with MTX in monotherapy in patients with active early RA (less than 3 years). Both concluded that combination of MTX with a biologic (IFX, ETA, ADA, ABAT) is more efficacious than MTX in monotherapy. These data cannot be extrapolated to patients with established RA.

As concluded in SR 6, in regard to the use of combination treatment in **early RA**:

- The most frequently used combination in studies of early RA is MTX+CSA. This combination has higher efficacy than CSA in monotherapy and is moderately better than MTX **[1b].**
- In early RA, the combination of CSA+CLQ does not appear to be more beneficial than monotherapy with CSA **[1b].**

There are other combinations with proven efficacy in early RA, some of which have been treated in the systematic reviews supporting this guideline. In SR 10 there is a comparison of combination treatment with DMARDs, according to the COBRA guideline, with "rapid step-up" MTX as the remission-inducing regimens in recent-onset RA. SR 11 addresses the question of whether the clinical and radiologic effectiveness of combined anti-TNF+MTX vs. rapid step-up MTX is sufficiently important to recommend anti-TNF+MTX as initial therapy in early-onset RA. The objective of SR 12 was to evaluate the efficacy of combined treatment with classical DMARDs by systematically reviewing the randomized controlled trials, randomized clinical trials and controlled trials comparing this therapeutic option with monotherapy in initial RA treatment.

The conclusions of SR 10, in which only one randomized controlled trial met the inclusion criteria, were:

- The COBRA guideline cannot be compared with MTX "rapid step-up" monotherapy due to the lack of studies treating the latter regimen as a distinct way of using MTX in the treatment of RA.
- Combination treatment in accordance with the COBRA guideline is an alternative treatment of recent-onset RA that provides better clinical and radiologic control than SSZ in monotherapy **[1b]**. The benefit observed is significant only while prednisolone is maintained.
- Long-term differences between the groups are associated with safety **[2c]**.

The results of SR 11 are based on 9 studies that meet the minimum requirements; its conclusions were:

- Combination therapy with IFX or ADA + MTX in patients with recent-onset RA shows a moderate benefit compared with rapid step-up MTX in regard to improved physical function (-0.27 HAQ points between groups) and prevention of radiologic damage (-5 points on the van der Heijde score) **[1b]**.

- Combined biologic therapy with MTX, compared with MTX in monotherapy, provides better clinical and radiological improvement after at least 1 year of treatment. The effect is of moderate intensity **[1b]**.

- In MTX-naive patients, combination of MTX with other agents (IFX, ADA, ETA, GLM, ABT) has proven to have greater clinical efficacy. With respect to radiological improvement, MTX in combination (IFX, ADA, ETA, ABT) has also proven superior to MTX in monotherapy **[1b]**.

- In patients with a poor response to MTX, combination with other agents (IFX, ADA, ETA, GLM, ABT, CZP, TCZ, RTX, ANK) has proven more efficacious than MTX in monotherapy. Combination of MTX with other agents (IFX, ADA, ABT, TCZ CZP) is also more efficacious than MTX in monotherapy in terms of radiological improvement at 12 months **[1b]**.

The meta-analysis identified in SR 11 bis (Nam 2009), which served as the basis for the EULAR recommendations for treatment of RA (Smolen, 2010b), provided an exhaustive review of the evidence available to date on the safety and efficacy profile of biologics in patients with RA. The meta-analysis concluded that all currently available biologics (IFX, ADA, ETA, GLM, ABT, CZP, TCZ, RTX, ANK) are efficacious in patients whose DMARDs failed **[1b]**. Similarly, RTX,TCZ, ABT, and GLM have proven to be efficacious in patients whose anti-TNF has failed **[1b]**. Lastly, the combination of biologics with MTX is more efficacious than biologics in monotherapy **[1b]**.

SR 12 included 15 studies, concluding that:

- Combination therapy (not including biologics) in early arthritis has higher efficacy than monotherapy **[1b]**.

- The DMARD combination with the highest efficacy in the control of recent-onset RA is a triple therapy that includes SSZ + MTX associated with HCQ or "step-down" corticosteroids (COBRA guideline), but always compared with SSZ in monotherapy. **[1b]**. It is not yet clear in the literature what patients will benefit most from this treatment alternative, or whether these regimens continue to have higher efficacy in comparison with initial monotherapy with MTX rather than SSZ.

- Initial combination treatment with a biologic (MTX + IFX) does not provide better clinical or radiologic control than the COBRA guideline at 12 months **[2b]**.

The systematic review included in the new review 12 bis (Gaujoux-Viala 2009) revealed a meta-analysis comprising 19 studies (Katchamart 2009) that compared the efficacy of DMARDs in monotherapy with combinations of various DMARDS. The meta-analysis concluded that, in DMARD-naive patients, the balance between efficacy and toxicity favors MTX in monotherapy

and that, in patients with an insufficient response to DMARDs, the evidence is not conclusive, indicating that studies comparing current doses of MTX with combination therapy with DMARDs are necessary.

ADA, ETN and IFX and GLM have been compared with MTX in the clinical and radiologic control of short-duration RA in double-blind randomized clinical trials (ERA, ASPIRE, PREMIER, GO-Before). The results of these studies have demonstrated a marginal benefit of the anti-TNF agents compared with MTX. ABT combined with MTX was compared with MTX in monotherapy in patients with recent infection and poor prognostic factors (erosions and positive titers of RF or anti-CCP) and proved to be both clinically and radiologically efficacious (Westhovens 2009).

The BeSt study, which compares different management strategies for early RA, has also shown that the combination of MTX and IFX is superior to sequential monotherapy and to step-up combination therapy in the prevention of radiologic damage (Goekoop-Ruiterman, 2005).

A systematic review (SR 15) was also made to determine, among other things, if it is possible to discontinue a biologic drug after achieving a significant response and to maintain this response with a classic DMARD. Two studies were found with a subgroup of patients with early RA (less than 2 years evolution), without previous DMARD treatment, in whom a sustained therapeutic response was achieved with IFX and MTX, after which IFX was withdrawn and the response was maintained over time. Thus, the conclusion of this review was:

- In early RA patients without previous treatment with DMARDs, and after achieving and maintaining a therapeutic response with IFX + MTX, the response can be maintained over time after withdrawing IFX **[2b]**.

V.1.1. Disease-modifying anti-rheumatic drugs: dosage and commercial names

The following table summarizes the recommended doses and commercial names of the principal DMARDs, in alphabetical order.

Table 18. Recommended doses and commercial names of DMARDs

DRUG	DOSAGE	COMMERCIAL NAMES
ABATACEPT[a]	Dosage adjusted to body weight: <60 kg: 500 mg from 60 to 100 kg: 750 mg >100 kg: 1,000 mg Intravenous infusion during 30 minutes. Additional doses to be administered 2 and 4 weeks after first infusion, with one dose every 4 weeks thereafter. Can be used in monotherapy or in combination with another DMARD, except for TNF antagonists.	ORENCIA®, Lyophilized vials of 250 mg to be reconstituted
ADALIMUMAB[a]	40 mg/14 days, in subcutaneous injection In some patients the interval between infusions needs to be shortened to every 7-10 days instead of the recommended 14 days. The addition of methotrexate may improve the therapeutic response in selected patients.	HUMIRA®, Preloaded syringes, 40 mg HUMiRA ® , preloaded 40-mg pens
ANA-KINRA[a]	100 mg/day, in subcutaneous injection	KINERET®, Preloaded syringes, 100 mg
AZATHIO-PRINE[b]	✓1.5 – 2.5 mg/kg/day, orally ✓Begin with low doses around 1 mg/kg/day and increase by 4-6 weeks to maintenance dose of 100-150 mg/day	IMUREL® Coated tablet, 50 mg IMUREL® Lyophilized vial, 50 mg
CERTOLIZUMAB PEGOL[a]	✓400 mg during weeks 0, 2, and 4, followed by a maintenance dose of 200 mg every 2 weeks. ✓When appropriate, patients should continue to use MTX during treatment with Cimzia.	CIMZIA ® preloaded 200-mg syringes
CYCLO-PHOS-PHAMIDE[b]	✓1.5 – 2,5 mg/kg/day, orally ✓Begin with 50 mg/day and increase dose every 4-6 weeks until response is obtained, without exceeding 2.5 mg/kg/day.	GENOXAL® Amp. IV 1000 mg GENOXAL® Amp. IV 200 mg GENOXAL® Tab. 50 mg

a= Biologic agents ; b= Chemical agents used occasionally ; c= Chemical agents used frequently; d= Chemical agents used very infrequently.

DRUG	DOSAGE	COMMERCIAL NAMES
CHLORO-QUINE[c]	✓250 mg/day, orally ✓Do not exceed 4 mg/kg/day.	RESOCHIN® Tab. 250 mg
CYCLO-SPORIN[c]	✓2.5 – 5.0 mg/kg/day, orally ✓The initial dose can be increased by 0.5 mg/kg/day every 2 weeks up to 5 mg/kg/day.	SANDIMMUN NEORAL® 100 mg SANDIMMUN NEORAL® 50 mg SANDIMMUN NEORAL® 25 mg SANDIMMUN NEORAL® Oral sol. 100 mg/ml
D-PENICILLA-MINE[d]	✓125 – 500 mg/day, orally ✓Begin treatment with 125-250 mg/day and if there is no improvement, increase dose at 8 weeks by 125 mg/day. Dose can be increased gradually every 8 weeks up to 500-750 mg/day. Should be administered 2 hrs before the main meal.	CUPRIPEN® Caps .250 mg CUPRIPEN® Caps .125 mg CUPRIPEN® Comp.50 mg SUFORTANON® TAB. 250 MG
ETANER-CEPT[a]	✓25 mg in subcutaneous injection twice a week (at intervals of 72-96 hours) or 50 mg once a week.	ENBREL® Vial, 25 mg ENBREL® 50-mg vials
GOLIMU MAB[a]	✓50 mg once per month, on the same day every month. ✓Should be administered in combination with MTX	SIMPONI ® preloaded 50-mg syringe SIMPONI ® preloaded 50-mg pen
HYDRO XYCHLO ROQUIN E[c]	✓400 mg/day, orally ✓Do not exceed 6.5 mg/kg/day.	DOLQUINE® Tab. 200 mg
INFLIXIMAB[a]	✓3 mg/kg in intravenous perfusion for 2 hours ✓Then administer additional doses of 3 mg/kg in perfusion at weeks 2 and 6 after the first week, and one dose every 8 weeks thereafter. Dose may be increased to 5 mg/kg if ineffective or in case of relapse. Some patients require a shorter interval of infusion of 4-6 weeks, instead of the 8 weeks recommended for maintenance. ✓Infliximab should be administered together with methotrexate or other immune modulator (such as leflunomide or azathioprine).	REMICADE® Lyophilized vial, 100 mg

🗁DRUG	DOSAGE	COMMERCIAL NAMES
LEFLUNOMIDE[c]	✓20 mg/day, orally ✓Begin with 100 mg/day for 3 days and then 20 mg/day continuously. ✓Elimination of the loading dose notably improves initial tolerance to the product, therefore it is acceptable to begin directly with the dose of 20 mg/day.	ARAVA® Tab.100 mg ARAVA® Tab.20 mg ARAVA® Tab.10 mg
METHOTREXATE[c]	✓7.5-10 mg/week, orally for 4 weeks, 15 mg/week for the following 4 weeks and then increase up to 20-25 mg/week. If ineffective or if there is gastrointestinal toxicity, parenteral administration should be considered. ✓Folic acid should be administered (5-10 mg/week) 24 hours after the administration of methotrexate.	METHOTREXATE ALMIRALL® Inj. sol. Vial 50 mg, A.D.1000 mg, 5000 mg, and 500 mg METHOTREXATE LEDERLE® Tab. 2.5 mg; Inj. sol. 25 mg/ml (2, 20, 40 and 200 ml); Lyophilized vial 50 and 500 mg METHOTREXATE WASSERMANN® Inj. sol. 25 mg/ml (2 and 20 ml) EMTHEXATE® Vial 50 and 500 mg/2ml
ORAL GOLD[d]	✓6 mg/day, orally ✓2 tablets daily	RIDAURA® Tab. 3 mg CRISINOR® Tab. 3 mg
INYECT-ABLE GOLD[c]	✓50 mg/week in intramuscular injections ✓Increasing doses of 10, 25 and 50 mg/week, maintaining the dose (from 6 to 24 months) or adjusting it depending on clinical response or adverse effects	MIOCRIN® Inj. sol. IM 10 mg MIOCRIN® Inj. sol. IM 25 mg MIOCRIN® Inj. sol.. IM 50 mg
RITUXIMAB[a]	✓Two doses of 1000 mg, in IV infusion, 2 weeks apart, in combination with MTX ✓To reduce the incidence and severity of infusion reactions, the administration of 100 mg IV of methylprednisolone (or equivalent) 30 minutes before each infusion is recommended.	MABTHERA® single-use vials of 100 AND 500 mg
SULFA-SALA-ZINE[c]	✓2-3 g/day, orally	SALAZOPYRIN® Tab. 500 mg

🗁 **a= Biologic agents ; b= Chemical agents used occasionally ; c= Chemical agents used frequently; d= Chemical agents used very infrequently**

🗁DRUG	DOSAGE	COMMERCIAL NAMES
TOCILIZUMAB[a]	✓ 8 mg/kg of body weight, administered once very 4 weeks. ✓Doses greater than 800 mg are not recommended for individuals whose body weight exceeds 100 kg	ROACTEMRA® . 4-ml vials. (20 mg/ml) ROACTEMRA® . 10-ml vials. (20 mg/ml) ROACTEMRA® . 20-ml vials. (20 mg/ml) ***V.1.2.***

🗁 **a= Biologic agents ; b= Chemical agents used occasionally ; c= Chemical agents used frequently; d= Chemical agents used very infrequently**

Changes in treatment

Once any kind of treatment has begun, the response must be evaluated using DAS28 (see chapter III) and its toxicity must be monitored (see chapter VI).

Therapeutic failure or toxicity should be evaluated no later than 3 months after starting therapy; if necessary, a change in treatment should be considered. The objective of treatment should be clinical remission of disease [3b, C] or, when this is not possible, low disease activity [1b, A].

The primary objective of treatment of RA should be to obtain a satisfactory response (see chapter IV 2.1), that is, clinical remission or, if this is not possible, low disease activity, especially in patients with established disease (Smolen, 2010b; Knevel, 2010). Until this objective is reached, pharmacological treatment should be adjusted every 3 months.

Regardless of the initial treatment chosen, the patient must be monitored closely. If a satisfactory response is not obtained in 3 months or if DMARD-related toxicity occurs, the physician should evaluate the possibility of changing treatment by adding a new drug or modifying the dosage. It is essential that a patient with RA who has not responded to a particular DMARD treatment in monotherapy or combination therapy have the option of other treatments of proven efficacy as quickly as possible.

The strict use of objective response criteria, together with prompt changes in the prescribed therapy to achieve predefined objective responses, improves the clinical and radiologic outcome of AR in the medium term (Grigor, 2004).

If response to MTX is unsatisfactory after reaching the maximum dosage and assuring the bioavailability of the agent, the panel recommends the use of LEF or SSZ or an anti-TNF agent as the second step in the treatment ladder, either replacing or in addition to MTX. If MTX toxicity is such as to oblige its withdrawal, the panel recommends using LEF or SSZ or an ant-TNF agent as the second step on the treatment ladder. [5, D]

The efficacy of the anti-TNF agents infliximab, etanercept, adalimumab, anakinra, abatacept, and rituximab was reviewed in SR 17. For those drugs approved after 2007 (golimumab, tocilizumab, and certolizumab pegol), Cochrane reviews and the most recent studies were used (Singh JA 2010, Singh JA 2010-b, Ruiz Garcia V 2011). In addition, data on rituximab have been updated with the reviews performed for the consensus on use of RTX in RA (Martín Mola 2011); data on abatacept have been updated with a Cochrane review performed after 2007 (Maxwell 2009). The conclusions of these reviews according to the drug concerned are as follows:

INFLIXIMAB

- The efficacy of IFX is higher than placebo, both in the short and long term, using the ACR 20, 50 and 70 efficacy criteria **[1b].**
- IFX moderately but significantly improves the radiologic evolution of the disease after 54 weeks **[1b].**

- In comparison with placebo, there are no differences with regard to the occurrence of serious adverse events, nor are there differences in the occurrence of serious infections, tumors or deaths. However, the total number of infections is significantly greater in patients treated with IFX compared with placebo **[1a].**

- No clear differences were found in the ACR clinical efficacy variables or in radiologic evolution between the usual doses of 3 mg/kg and doses higher than 6 mg/kg **[2b].**

ETANERCEPT

- ETN sc. in monotherapy has higher clinical efficacy than placebo **[1b].**

- ETN sc. in monotherapy has the same clinical efficacy as MTX after 12 months of treatment **[1b].**

- ETN sc. + MTX vo. in combination treatment has higher short-term clinical efficacy than MTX in monotherapy **[1.b].**

- ETN sc. + MTX vo. in combination treatment has higher long-term clinical efficacy than MTX in monotherapy **[2.b].**

- It is not clear whether ETN sc. in monotherapy slows radiologic progression after 12-24 months of treatment. **[4].**

- In general, ETN is a well tolerated treatment compared with MTX in parameters such as asthenia, cephalea or diarrhea **[1.b].** The most common adverse effect compared with placebo or MTX is injection site reaction.

- Evidence with regard to increased number of infections is lacking or contradictory.

ADALIMUMAB

- ADA + MTX is efficacious and safe in the treatment of RA, in both early disease and that of long evolution **[1.a].**

- ADA 20 mg every 2 weeks + MTX slows radiologic progression after 52 weeks of treatment. ADA 40 every 2 weeks + MTX slows radiologic progression after 52 weeks and after 104 weeks of treatment **[1.b].**

- ADA + other DMARDs different than MTX is also efficacious and safe **[2.a].**

- ADA in monotherapy is efficacious and safe in RA and slows radiologic progression in patients with early RA who have not previously used MTX. However, the differences as compared with MTX are not significant, unless ADA is combined with MTX **[2.a].**

ANAKINRA

- ANK is an efficacious alternative for the short-term treatment of RA, with a modest efficacy profile and an acceptable toxicity profile **[1.b].**

- The long-term safety and efficacy of ANK is unclear **[3.b].**

- ANK + MTX in the short-term treatment of AR has higher clinical efficacy than MTX in monotherapy and is no more toxic **[1.b].**

- ANK + ETN in no more beneficial than monotherapy with ETN; furthermore, it significantly increases the incidence of serious infections **[2.b].**

RITUXIMAB

- RTX + MTX is efficacious and safe in the treatment of RA with positive rheumatoid factor in patients who do not respond satisfactorily to DMARDs **[2.b].**

- The use of RTX as monotherapy is not supported by studies made to date.

- The most appropriate dose is 1,000 mg of RTX in two doses 15 days apart. This dose provides the best clinical response according to the ACR criteria, without a significant increase in side effects **[2.b].**

- At the recommended dose, RTX delays structural damage in patients who have not previously taken MTX **[1.a]**

- RTX is efficacious in patients with an insufficient response to TNF antagonists **[1.c]**. Its efficacy is reduced when it is used in later stages of therapy **[2.a]**.

- The absence of RF and ACPA does not rule out a response to RTX. If this agent is administered in this population, the therapeutic response is poorer than that obtained in patients with positive RF and/or ACPA titers **[1.c]**.

- Treatment with RTX seems to be more efficacious if combined with MTX and other DMARDs, especially leflunomide. **[2.b]**.

ABATACEPT

- ABT + MTX is efficacious and safe in the treatment of RA **[1.b].**

- ABT + DMARDs other than MTX is also efficacious and safe **[2.b].**

- ABT + MTX is efficacious and safe in the treatment of RA with unsatisfactory response to biologic therapy **[1.b].**

GOLIMUMAB

- GLM + MTX is safe and efficacious for treatment of RA in patients who do not respond to DMARDs **[1.a]**.

- GLM + MTX is safe and efficacious for treatment of RA in DMARD-naive patients **[1.a]**.

- GLM + MTX is safe and efficacious in patients with an insufficient response to other anti-TNF agents **[1.a]**.

TOCILIZUMAB

- TCZ + MTX is safe and efficacious for the treatment of RA in patients who do not respond to DMARDs **[1.a]**.
- TCZ + MTX is safe and efficacious in patients with an insufficient response to other anti-TNF agents **[1.a]**.
- In comparison with DMARDs, monotherapy with TCZ leads to a moderate but significant radiological improvement after 52 weeks **[1.b].**

CERTOLIZUMAB-PEGOL

- CZP + MTX is safe and efficacious in the treatment of long-standing RA **[1.a]**.
- CZP in monotherapy is safe and efficacious in the treatment of long-standing RA **[1.a]**.
- CZP leads to a moderate but significant radiological improvement of RA at 54 weeks **[1.b].**
- Adverse events were more common in patients treated with CZP than in those treated with placebo. An increase was observed in the number of severe infections, especially tuberculosis **[1.a]**.

Even though the medium-term efficacy of drugs like D-penicillamine or aurothiomalate has been shown to be similar to that of MTX and SSZ in a randomized, open-label clinical trial comparing management strategies (van Jaarsveld, 2000), the speed of action of a DMARD is an added value when there is a need to closely monitor a significant response to treatment. Thus, in case of MTX failure or intolerance, the use of a quick-acting and efficacious DMARD is recommended.

In patients for whom the previously described guidelines are not useful due to lack of efficacy, toxicity or other reasons, use of any of the DMARDs, combinations or other biologic agents is recommended; if these fail, experimental treatments should be tried. [5, D]

RA has a long natural history, and no treatment has been shown to be curative in all patients. Thus, notwithstanding the recommendations in the preceding paragraphs, alternative treatments with proven efficacy in a CT may be introduced. SR 6 synthesized the results of CTs conducted to date comparing the efficacy of non-biologic DMARDs in monotherapy and in combination therapy (see tables 23 and 24); [the level of evidence ranges between 1a and 2b].

According to the conclusions of SR 8, which aimed to determine the efficacy of combining biologic therapies with DMARDs other than MTX:

- The combination of IFX with LEF **[1.b],** AZT **[5.d]**, or CSA **[4]** and the combinations of ADA or ETN with LEF **[1.c]** may be as efficacious as combinations including MTX.

- The combination of ETN with SSZ is more efficacious than SSZ alone, although it presents more adverse events **[1.c]**

- The combination of ADA or TCZ with DMARDs is more efficacious than DMARDs, although it can lead to greater toxicity **[1.b]**

- These combinations may be limited by the presence of considerable adverse effects, particularly serious infections. The combination with LEF, besides infections, may be strongly associated with the emergence of skin reactions and vasculitis **[1.b]**

Currently available data do not permit a decision as to whether the best treatment alternative if the first anti-TNF fails is a second anti-TNF or to block another pathogenic route (IL-1, T-lymphocyte co-stimulation, depletion of CD20-positive B lymphocytes).

The second part of SR 15 was prepared in order to answer the question of whether treatment should be started with the same anti-TNF or with a different anti-TNF in the case of a symptomatic recurrence of RA. Similarly, this question was evaluated in Cochrane reviews on abatacept, tocilizumab, and certolizumab (Singh JA, 2010, Singh JA, 2010-b, Ruiz Garcia V, 2011). The conclusions of these reviews are as follows:

- In patients previously treated with a biologic drug, who are not currently receiving that treatment and who experience a relapse, no controlled RCT could be found to answer the question raised, but in one open-label study it was found that reinfusion of IFX in case of disease relapse may be efficacious and safe **[4].**

- In patients receiving treatment with a biologic drug considered ineffective because of disease relapse:

  - ABT has proven efficacy in patients with insufficient response to ETN or IFX **[1b].**
  - ADA may be efficacious in case of failure of IFX or ETN **[3b].**
  - IFX may be efficacious in case of failure of ETN **[3b].**
  - ETN may be efficacious in case of failure of IFX **[4].**
  - ANK does not appear to be efficacious in case of failure of IFX or ETN **[4].**

SR 16 was conducted to determine if a new biologic agent is efficacious in RA patients who have not responded to the usual doses of another biologic agent. The review concluded that changing from one anti-TNF to another is efficacious under the following conditions:

- If IFX or ETN has failed, the change to ABT is efficacious **[1b].**

- If IFX or ETN has failed, the change to ADA is efficacious **[1b].**

- If ETN has failed, the change to IFX is efficacious **[1b].**

- IF IFX has failed, the change to ETN is efficacious **[1b].**

- IF IFX or ETN has failed, the change to ANK is not efficacious **[4].**

- if ADA fails, switching to IFX is efficacious **[3b].**

- if ADA fails, switching to ETN is efficacious **[3b].**

- if an anti-TNF agent fails, switching to ABT is efficacious **[1b].**

- if an anti-TNF agent fails, switching to GLM is efficacious **[1b].**
- if an anti-TNF agent fails, the switch to RTX is efficacious **[1b].**
- if an anti-TNF agent fails, the switch to TZM is efficacious **[1b].**
- Based on indirect comparisons, no biologic has proved to better than another (ABT, RTX, TCZ) in patients with active RA and an insufficient response to an anti-TNF **[1b].**
- In patients for whom anti-TNF agents are inefficacious, switching to RTX is more effective than switching to another anti-TNF agent **[2a].**

Other biologic agents such as ABT or RTX are reasonable alternatives in patients who have not responded to or who have experienced toxicity with one or more anti-TNF agents.

If the disease cannot be controlled with any of the proposed treatments, experimental treatments (new drugs or new combinations of existing ones) can be explored to assure that the patient is never without some type of potentially disease-modifying treatment.

Treatment with glucocorticoids

In recent-onset RA the use of low-dose oral glucocorticoids (GC) is the recommended disease-modifying therapy, always in combination with a DMARD. [1.b, A]

Corticoids are frequently employed in the treatment of RA, but their use is controversial, especially in the long term. The corticoids are better than placebo, and similar to or better than NSAIDs or CLQ in the control of RA activity (Saag, 1996b; Saag, 1997; Criswell, 2000; Gotzsche, 2000b).

Several authors have studied the role of the corticoids in RA management, from different perspectives. Their role has been studied, on the one hand, as disease modifiers (see below) and, on the other, as "bridge" therapy while waiting for the DMARDs to take effect (Harris, 1983; Van Gestel, 1995; Caldwell, 1991)

Since 1995, several double-blind placebo-controlled RCTs have shown that the use of low-dose glucocorticoids in recent-onset RA (from 1 to 3 years' evolution) delays the appearance of radiologic lesions **[1b]** (SR 14). Table 20 presents a summary of the main characteristics and conclusions of these studies. The update of this review and an SR on corticosteroids (Porter, 2010) on which some of the EULAR recommendations on the management of RA are based (Smolen, 2010b), states the following:

- there is direct and indirect evidence that corticosteroids can be used as bridge therapy **[1b]**
- addition of corticosteroids to DMARDs being taken in monotherapy is beneficial in terms of signs, symptoms, and radiologic progression **[1a]**
- addition of corticosteroids to combinations including DMARDs is beneficial in terms of signs, symptoms, and radiologic progression **[2b]**
- corticosteroids must be tapered very slowly in order to avoid clinical recurrence **[4]**

In no case can the corticoids be substituted for DMARD treatment. Their use without a DMARD should be considered only in RA in the elderly with seronegative, non-erosive, pseudopolymyalgia rheumatica or similar to remitting symmetrical synovitis with pitting edema syndrome.

In RA of long duration, the use of low-dose oral glucocorticoids is recommended as anti-inflammatory therapy for symptom control while waiting for the DMARDs to take effect. [5, D]

Oral corticoids at low doses (<10 mg/day of prednisone or its equivalent) are an effective anti-inflammatory treatment in RA. Dosage should not exceed 10 mg/day of prednisone and should be used during the least possible time.

The use of corticoids has been associated with increased mortality, and their chronic use, at low doses, is related with increased morbidity. However, it is difficult to separate the effect of corticoid use from the fact that the patients receiving them usually have more serious disease that cannot be controlled with NSAIDs alone.

There is no evidence that one corticoid preparation is superior to any other, therefore they can be used indistinctly at equivalent doses.

There is no evidence to date that the most commonly used preparations (prednisone, prednisolone, methylprednisolone and deflazacort) are significantly different with regard to efficacy or adverse effects when used at equivalent doses.

The dosage of the glucocorticoids will always depend on the underlying disease for which they are prescribed and on their clinical and biologic activity. Whenever possible, a single daily dose should be prescribed first thing in the morning. The dose should progressively be reduced (going from fractionated doses to a single dose before decreasing the dosage) until the medication is withdrawn.

Table 19. Classification of the corticoids by duration of action

Duration of action	Corticoid
Short-acting	Hydrocortisone, prednisone and prednisolone
Intermediate-acting	Methylprednisolone, paramethasone, triamcinolone and deflazacort
Long-acting	Betamethasone and dexamethasone

Given the association between glucocorticoid use and rapid loss of bone mass, it should at a minimum be used jointly with Vitamin D and calcium, and other preventive treatments for osteoporosis should be evaluated (see section III.3.2.c.) if treatment is expected to exceed 3 months. [5, D]

The use of intra-articular glucocorticoids is essential in the management of joints that are persistently inflamed despite good therapeutic response to the DMARD regimen.

As part of the overall strategy of strict control of inflammatory activity in RA, the use of intra-articular infiltrations in joints with persistent clinical activity despite adequate response to DMARDs has demonstrated efficacy in reducing radiologic damage (Grigor, 2004).

Table 20. Evidence tables on the effect of the glucocorticoids on radiological progression in RA.

Reference	Type of study	Comments
van Everdingen AA, et al. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med, 2002;136:1-12.	Multicenter, randomized, double-blind clinical trial - Prednisone (10 mg/day)/placebo. After 6 months SSZ can be added - RA of less than 1 year - Study duration 2 years - Sharp index modified by van der Heijde - Number of patients with erosions - Number of joints affected	Quality: Excellent. Jadad: 4 The index is initially somewhat better in the placebo group (not statistically significant). Rescue sulfasalazine at 6 months in both groups (corticoids and placebo). Analysis was not made in the subgroup of patients with sulfasalazine according to whether they were assigned to the control or placebo group. At 6 months, 39 of the 71 patients who completed the study were receiving sulfasalazine (20 in the placebo group and 19 in the prednisone group). Authors do not indicate what percentage of patients were taking it at 24 months. Conclusion: Less radiologic progression in the steroid group. The improved evolution is maintained at 2 years. In any case, authors advise combining with DMARD.
Kirwan, JR The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med, 1995; 333:142-6.	Multicenter, randomized, placebo-controlled, double-blind clinical trial - Prednisone (7.5 mg/day)/placebo but DMARDs permitted - AR of less than 2 years - Study duration 2 years - Larsen index	Quality: Moderate. Jadad 5 There are baseline differences with regard to radiologic indices. Only radiographs of the hands. Little said about concurrent DMARDs. In subsequent comments authors note that patients in the placebo group were worse off. Conclusion: Treatment with low-dose prednisone reduces radiologic progression.
Harris ED Jr, et al. Low dose prednisone therapy in rheumatoid arthritis: a double blind study. J Rheumatol, 1983;10:713-21.	Double-blind non-randomized clinical trial - Prednisone 5 mg/day or placebo in addition to gold salts or D-penicillamine - AR of more than 1 year evolution - Study duration 32 weeks (prednisone 24 weeks) - Own index for radiographs	Quality: Moderate. Jadad 3. This is a clinical trial, but with little validity: a) Very superficial radiologic assessment (before current indices); b) Degrees of progression are not defined; c) No statistical data on progression is provided; d). Small number of patients. Conclusion: Greater radiologic progression in the placebo group.
Rau R, et al; LDPT-Study Group. Low dose prednisolone therapy (LDPT) retards radiographically detectable destruction in early rheumatoid arthritis--preliminary results of a multicenter, randomized, parallel, double blind study. Z Rheumatol. 2000;59 Suppl 2:II/90-6.	Multicenter, randomized, double-blind controlled clinical trial - Prednisone (5 mg/day)/placebo parallel with introduction of a DMARD - AR from 6 months to 2 years - Study duration 2 years - Ratingen and Sharp index modified by van der Heijde	Quality: Poor (negative response to item 3, preliminary report) Jadad: 1 196 patients (192 in results), 76 meet inclusion and exclusion criteria and did not break protocol, although intention to treat in 80 in the prednisone group and 86 in the placebo group. Subgroup analysis not made for methotrexate/gold with/without corticoids. Conclusion: Prednisone prevents radiologic progression in the first 6 months. Thereafter, evolution is very similar, although somewhat better in the prednisone group. Authors support use of prednisone during first year as bridge treatment until detectable DMARD effect is achieved. Since progression during second year continues to be somewhat better in the prednisone group, long-term treatment with prednisone could be recommended, although sufficient date are not available.
Zeidler HK, et al. Progression of joint damage in early active severe rheumatoid arthritis during 18 months of treatment: comparison of low-dose cyclosporin and parenteral gold. Br J Rheumatol, 1998;37:874-82.	Multicenter, randomized, controlled, open trial Cyclosporin is compared with parenteral gold, although stratified by prednisolone (no more than 10 mg/day)/placebo. - AR less than 3 years - Study duration 18 months - Larsen-Dale index - Number of erosions - Number of eroded joints	Quality: Poor. Jadad 1, not blinded, low compliance, use of rescue medication. Study at 18 months, 375 patients (187 cyclosporin; 188 gold). Compliance 52%. Assignment by minimization technique. Not clear who was given steroids, although it seems to have been predetermined. Neither patients nor physicians were blinded. Blinded radiologic assessment. Conclusion: The corticoids delay radiologic progression when used jointly with other treatments.

Reference	Type of study	Comments
Svensson B, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum, 2005; 52(11):3360-70.	Multicenter randomized clinical trial, not placebo controlled and not blinded - Prednisolone 7.5 mg/day vs no prednisolone. Use of DMARDs permitted (at the physician's discretion) - No differences in DMARD use (either at the beginning or end) - RA of less than 1 year evolution - Initial DAS28 >3 - Study duration 2 years - Sharp modified by van der Heijde (chronological reading)	Quality : good, Jadad: 3, treatment not blinded, but radiographic readings were blinded. 2-year study with 250 patients (119 in prednisolone group, 131 in placebo group). The groups are comparable in all except age, with those in placebo group slightly older (59 ± 13 vs 51 ± 14). Intention-to-treat analysis. Fewer NSAIDs taken and fewer infiltrations in the prednisolone group. Significantly greater reduction in the DAS28, HAQ and CRP in the prednisolone group. Simulates usual clinical practice. Conclusion: The combined use of prednisolone and DMARDs delays radiologic progression in patients with rheumatoid arthritis of less than 1-year evolution.
Wassenberg S, et al. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum, 2005; 52(11):3371-80.	Multicenter randomized placebo-controlled clinical trial (recruitment between January 1995 and December 1995) - Prednisolone 5 mg/day vs placebo - Initial treatment with MTX or intramuscular gold - AR of less than 2 years' evolution - Study duration 2 years - Sharp modified by van der Heijde and Ratingen (chronological reading) - Patients in the prednisolone group slightly older, and larger percentage of women Same as Rau study (Z Rheumatol, 2000;59 Suppl 2:II/90-6) published in another journal.	Quality: Good. Data presented more clearly than in the Rau study (Z Rheumatol. 2000;59 Suppl 2:II/90-6), so can be classified 5 on Jadad scale. 196 patients(192 in results). 94 randomized to prednisolone group and 98 to placebo group. Two analyses: – By protocol: 76 (34 prednisolone group vs 42 placebo) – By intention to treat (80 prednisolone group vs 86 placebo) DMARD changes in the two groups were similar. In both analyses, there are significant differences with regard to radiologic progression, in favor of the prednisolone group, something that was not clear in the Rau study. No significant differences in the clinical variables, there is a trend favoring the prednisolone group. No subgroups methotrexate/gold with/without corticoids. Conclusion: A 5 mg daily dose of prednisolone combined with DMARDS substantially reduces radiologic progression in early RA.
Capell HA, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomized controlled trial. Ann Rheum Dis. 2004 Jul; 63(7):797-803.	Randomized, double-blind, placebo-controlled clinical trial - Prednisolone 7,5 mg/day vs placebo - Salazoprine administered concurrently up to doses of 40mg/Kg. - No previous DMARD use (except for hydroxychloroquine) - AR of at least 3 years' evolution - Study duration 2 years - Sharp modified by van der Heijde and Ratingen (chronological reading) - Primary outcome, radiologic assessment; secondary outcome. clinical improvement	Quality: Good. Jadad 3 167 patients: 84 prednisolone group vs 83 placebo group. No significant differences between the groups with respect to radiologic or clinical variables. Conclusion: Low doses of prednisolone do not reduce radiologic progression.
Suponitskaia EV, et al. Effect of small-dose glucocorticoids on the course of early rheumatic arthritis. Klin Med (Mosk). 2004; 82(9):39-42.		The article was not accessible because it is in Russian. It is not possible to evaluate the quality or the conclusions from the abstract, although it states that the group randomized to corticoids had fewer erosions.

Treatment with non-steroidal anti-inflammatories (NSAIDs)

The NSAIDs are used to modify the symptoms of RA. The use of NSAIDs is recommended at disease onset, when a new DMARD is introduced, and occasionally when uncontrolled isolated symptoms persist despite good response to a DMARD. [5, D]. The need for continuous use of NSAIDs in a patient with RA should be interpreted as inadequate control of inflammatory activity and should, therefore, lead to reassessment of the DMARD regimen. [5, D]

Regardless of DMARD treatment, patients may on occasion require temporary treatment with symptom-modifying drugs (NSAIDs and/or corticoids and/or analgesics), while the disease-modifying regimen induces RA remission.

The NSAIDs are used to modify the symptoms of RA. They have not been shown to have any additional effect on disease outcome.

The use of NSAIDs is recommended when a new DMARD is introduced. NSAIDs should be used until the disease and its symptoms can be controlled with the DMARD alone. NSAIDs should be used for 2-12 weeks, depending on the time needed for the DMARD to reach effective therapeutic levels. The period of combined use may occasionally be prolonged until the DMARD dose is adjusted.

NSAIDs should not be used without first trying other analgesics such as acetaminophen for mechanical pain (pain that worsens with exercise and improves with rest, becomes worse during the day, with no joint stiffness after rest).

It is important to weigh the benefit-risk relation for the patient whenever an NSAID is used. The side effects and interactions of the NSAIDs used should be known. The recommendations on the use of NSAIDs in the SER consensus document should be followed (Bori G, 2009).

All NSAIDs should be used at the full dose for at least 1 week before considering the treatment to have failed. Once symptoms have been controlled, the minimum effective dose should be used. [5, D]

When the NSAIDs are withdrawn after prolonged use (over 3 months), they should be discontinued gradually to avoid the effects of rebound pain. No guidelines for withdrawal have been shown to be more effective than others.

Length of treatment with NSAIDs is a risk factor for gastric erosion.

Table 21. Usual dosage of NSAIDs.

FÁRMACO	TOTAL DOSE (mg/24 h)	INTERVAL BETWEEN DOSES
AAS	3,000 – 6,000	6-8 h.
Ibuprofen	1,200 – 2,400	8 h.
Flurbiprofen	200 – 300	12 h.
Flurbiprofen Retard	200	24 h.
Mefenamic acid	750 – 1,500	8 h.
Meclofenamate Na	200 – 400	8 h.
Diflunisal	500 – 1,000	12 h.
Tolmetin Na	800 – 1,200	6-8 h.
Naproxen	500 – 1,000	12 h.
Ketoprofen	200	8-12 h.
Ketoprofen Retard	200	24 h.
Aceclofenac	200	12 h.
Diclofenac	150 – 200	8-12 h.
Diclofenac Retard	100	24 h.
Phenylbutazone	200 – 400	12-24 h.
Indomethacin	75 – 150	8 h.
Sulindac	200 – 400	12 h.
Piroxicam	20	24 h.
Tenoxicam	20	24 h.
Meloxicam	7,5 – 15	24 h.
Nabumetone	1,000-2,000	12-24 h.
Celecoxib	200 – 400	12-24 h.
Etoricoxib	90	24 h

There is no evidence that some NSAIDs are better than others, therefore the one that best fits the patient characteristics should be used. [5, D]

There is no evidence that the efficacy of combined NSAIDs is greater than each NSAID alone. In a recent review of various meta-analyses and trials comparing the efficacy of the NSAIDs, it was not possible to show that some NSAIDs are more efficacious than others, although it was shown that they have different safety profiles, in favor of ibuprofen [Gotzsche, 2000a]. No controlled clinical trial of sufficient size has compared the efficacy of the NSAIDs to acetaminophen.

There are no convincing studies showing that specific patients benefit more from some NSAIDs than from others. Generally, different NSAIDs are tried until symptom control is reached. A large number of different NSAIDs is available in Spain, thus it is important to know them all,

especially their different pharmacokinetic profiles, in order to adapt them to the patient's needs. Some NSAIDs, such as naproxen or acetylsalicylic acid (ASA) have more rapid uptake (about 20 minutes), and thus would be indicated for acute pain. Others with delayed uptake and prolonged action (retard forms) can be administered at night so they will act when the patient wakes up.

In certain clinical situations, some NSAIDs may have a more favorable safety profile, as in the case of sulindac in renal failure, diflunisal or nabumetone in chronic liver disease, or diclofenac in patients being treated with oral anticoagulants.

Selective cyclooxigenase inhibitors of the COX-2 isoenzyme, or coxibs, have not been shown to have a significantly better safety profile than other NSAIDs, except in the gastrointestinal system [Schnitzer, 1999; Simon, 1999; Emery, 1999; Langman, 1999]. Patients with cardiovascular disease can benefit from the platelet-inhibitory action of the NSAIDs, which is not shared by the coxibs. The SER guidelines for the rational use of coxibs are recommended [SER, 2000a].

The need for co-treatment with gastric protectors should be evaluated on an individual basis. [5, D]

Since the NSAIDs are associated with a high frequency of gastrointestinal adverse effects and are often used for prolonged periods, the need for a gastric protector should be evaluated in accordance with other existing risk factors for gastroduodenal ulcers.

Treatment for pain

Analgesics are indicated to control pain. If there is no response, surgical treatment can be considered, especially to restore function and mobility. [5, D]

Pain control treatment should be prescribed if pain persists despite the adoption of previous disease-control measures. Simple analgesics (e.g., acetaminophen, ASA) should be used first, increasing to the maximum dose of 3-4 g/day in the case of acetaminophen and up to 4 g/day for ASA. If pain persists, dipyridamole, NSAIDs, or codeine can be used.

If pain is due to neuropathy, tricyclic antidepressants (amitryptiline or duloxetine) and some anticonvulsants (gabapentine, pregabalin or carbamazepine) can be used.

When pain is very localized, local analgesics such as capsaicin cream can be used. The ideal dose is 0.75 mg of cream.

Surgical treatment should be considered when pain does not respond to pharmacological treatments and is due to joint destruction, producing an alteration in the patient's functional capacity (Dunbar, 1998).

If pain is intense, there is no response to previous analgesic treatments, and surgery is not an option, opiate analgesics may be administered (Schur, 1999; Hazes, 1994).

V.1.3. Elderly patients

V.1.3.a. Monitoring kidney and liver function

Kidney and liver function should be monitored in elderly patients, and the dosage intervals of the drugs eliminated by these routes should be adapted accordingly. [5, D]

Aging may be accompanied by changes in various organs, especially those responsible for metabolizing and excreting different drugs. This means that the pharmacokinetic and pharmacodynamic properties of a large number of drugs used in elderly patients may be different than in younger individuals (Bird, 1990; Morgan, 1986). Optimal pharmacological treatment in a particular patient depends on a variety of factors, which are frequently not well known or are difficult to determine. This may contribute to the large variability among different individuals in the response to the same drug, a phenomenon that is especially notable in the elderly (Bird, 1990).

The dosage of drugs eliminated by the renal route should be adjusted so that it is similar to what is used in patients with renal failure (decreasing the dose and/or lengthening the intervals between doses). Even in the absence of kidney disease, renal clearance in elderly individuals is decreased by 35-50%. The elderly, and especially those who suffer RA, have reduced muscular mass, which produces a decline in the production of creatinine. Thus, an elderly individual may have a normal creatinine value even though creatinine clearance is altered (Oates, 1998).

Aging may also produce alternations in hepatic function, thus the metabolization of drugs broken down in the liver may also be reduced (Morgan, 1986).

V.1.3.b. Monitoring adverse effects and drug interactions

The possible appearance of adverse effects and interactions among drugs taken regularly should be monitored in elderly patients. [5, D]

Adverse drug effects have traditionally been considered more frequent in elderly individuals (Dahl, 1990; Hurwitz, 1969), although little information is available about most drugs in this age group, including those used in RA patients. The lack of data is due to the frequent exclusion of extreme age groups in clinical trials. For this reason, unexpected side effects are not uncommon in individuals with late onset RA, once the drugs have come into generalized use (Morgan, 1986; Dahl, 1990).

In general, elderly patients have more than one disease and need treatment with multiple drugs. This means there is an increased probability of drug interactions and contributes to a larger number of side effects (Buchan, 1991). The use of multiple drugs in elderly patients is often accompanied by lack of treatment compliance, which is estimated at 10% (Bird, 1990).

The DMARDs and the immunosuppressors have a similar efficacy and safety profile in young and old individuals, although, for the reasons mentioned above, toxicity should be monitored more closely in the elderly (O´Callaghan, 1986).

V.1.4. Pregnancy and breastfeeding

V.1.4.a. Prevention

Women of childbearing age should be informed of the possible effects of RA on pregnancy, in particular, because of the implications for treatment. [5, D]

There is no evidence that RA has a negative effect on pregnancy outcome. However, treatment with DMARDs can have negative consequences on pregnancy, the fetus, and breastfeeding. Thus, women of childbearing age should know the risk so they can act accordingly.

The manifestations of RA disappear during pregnancy in 70% of cases, to reappear early in the postpartum period (Nicholas, 1988). When there is improvement, this usually occurs in the first trimester. Nevertheless, the disease commonly fluctuates and, at the very least, cycles of analgesics will be required. The disease almost always recurs early in the postpartum period, and this does not seem to depend either on breastfeeding or on the return of menstruation. Most patients need full doses of NSAIDs in the postpartum period.

Children of mothers with Sjögren's syndrome with Ro antibodies have an increased risk of neonatal lupus.

V.1.4.b. Drug management during pregnancy and breastfeeding

The use of NSAIDs during pregnancy and breastfeeding should be avoided insofar as possible. Corticosteroids can be used under controlled conditions. DMARDs should be managed on an individual basis, and should preferably be continued during pregnancy. [5, D]

Teratogenic effects in the early weeks of pregnancy have been observed in animals receiving larger than pharmacological doses of NSAIDs. In both humans and animals, premature closure of the ductus arteriosus has also been observed in the last trimester. NSAIDs are not recommended near the time of delivery due to their inhibitor effects on platelets and the uterine musculature. All NSAIDs are transmitted, in greater or lesser measure, to the mother's milk. For these reasons, the NSAIDs should be avoided in the first and last trimester and during breastfeeding. If necessary, NSAIDs with a short half-life (ibuprofen or ketoprofen) should be used. During breastfeeding, NSAIDs should be taken while the baby is feeding to avoid elevated concentrations in the milk.

There is no evidence that the corticoids produce serious adverse effects at average doses during pregnancy, except for promoting glucose intolerance, fluid retention, and hypertension. Consequently, they should be administered under controlled conditions.

If it is necessary to use a glucocorticoid during pregnancy, prednisone or methylprednisolone should be given since neither drug crosses the placental barrier.

Table 25 shows the considerations to be taken into account with regard to DMARD use during pregnancy and breastfeeding. The decision to withdraw continuous treatment during pregnancy should be made on an individual basis. If the disease is aggressive, it is preferable not to withdraw the DMARD (unless it has been shown to affect the embryo, fetus, or infant) and to leave it at the minimum effective dose. Total withdrawal of the drug could provoke

disease recurrence during pregnancy and a poorer outcome. Thus, for women of childbearing age, treatment involving the least risk for the fetus should be proposed to avoid drastic, last-minute decisions.

As for biologics, the recommendations of the SER consensus document on management of risk with biologics should be followed. The document includes guidelines on use during pregnancy and breastfeeding (Gomez Reino, 2011).

Table 25. Use of anti-rheumatic drugs in pregnancy and breastfeeding.

Drug	FDA category*	Effects on the fetus	Breast-feeding	Recommendations
NSAIDS	B	✓ Risk of fetal hemorrhage ✓ Premature closure of the ductus	Yes, but possible increased risk of jaundice and kernic-terus	Discontinue 6-8 weeks before childbirth; preferably discontinue at week 32.
ANAKINRA	B	✓ **ID** ✓ No toxicity in studies of reproduction in mice or rabbits	✓ ID ✓ No	Use during pregnancy only if needed to suppress RA activity
ANTI-TNF	B	✓ **ID** ✓ VACTERL association has been suggested	✓ ID ✓ No	Caution if used during pregnancy
AURANO-FIN	C	✓ **ID**	Yes**	Use with caution if needed to suppress RA activity
AUROTHIO-MALATE	C	✓ **ID** ✓ Complex CNS malformation has been described in animals.	Yes**	Use with caution if needed to suppress RA activity
AZATHIOPRIN E	D	✓ **IUGR**; neonatal leukopenia, lymphopenia and ypogammaglobulinemia; infections (CMV and gram-negative)	No	✓ Use with caution if needed to suppress RA activity. ✓ Consider reducing dosage after week 32.
CYCLOPHOS-PHAMIDE	D	✓ Embryopathy with growth deficiency; developmental delay; craniosynostosis; craniofacial malformations; and malformations of the extremities	No	Avoid during pregnancy, especially during the first trimester

Drug	FDA category*	Effects on the fetus	Breast-feeding	Recommendations
CYCLO-SPORINE A	C	✓ Altered development and maturation of the T, B and NK lymphocytes	No	Use with caution if needed to suppress RA activity.
COXIBS	C	✓ Risk of fetal hemorrhage; premature closure of the ductus	ID	Discontinue 6-8 weeks before childbirth; preferably discontinue at week 32
D-PENICILLA-MINE	D	✓ Abnormalities of the conjunctiva, cutis laxa	✓ ID ✓ No	Avoid during pregnancy
GLUCOCORTI-COIDS	B	✓ Cleft palate with exposure in first trimester	✓ Yes ✓ Breast-feed 4 hours after the last dose	Evaluate need for stress dose; avoid during the third trimester
HYDROXY-CHLORO-QUINE	C	✓ Probably none	✓ Yes***	Can be used during pregnancy
METHO-TREXATE	X	✓ Cranial malformations; malformations of extremities; CNS alternations	✓ No	Discontinue 4 months before conception; supplement with folic acid during those 4 months and during pregnancy.
MYCOPHEN-OLATE MOFETIL	C	✓ Teratogenic; craniofacial distal extremity and other malformations.	✓ No	Avoid if possible during pregnancy.
LEFLUNOMIDE	X	✓ Embryotoxic	✓ No	Cholestyramine 8 g/8 hours x 11 days with plasma levels < 0,02 mg/L in 2 separate tests 2 weeks apart and wait 3 menstrual cycles before conception.
SULFA-SALAZINE	B, D	✓ Probably none	✓ Yes****, with caution (AAP)	Can be used during pregnancy

Drug	FDA category*	Effects on the fetus	Breast-feeding	Recommendations
RITUXI-MAB	C	✓ **ID**; isolated cases of granulocytopenia and lymphopenia	✓ ID ✓ No	If possible, avoid during pregnancy
TOCILIZUMAB	C	✓ ID	✓ ID ✓ No	If possible, avoid during pregnancy

Abbreviations: AAP, American Academy of Pediatrics; NSAID, non-steroidal anti-inflammatory drug; CMV, cytomegalovirus; IUGR, intra-uterine growth retardation; ID, insufficient data; CNS, central nervous system.

***FDA classification of teratogenic drug risk:**

Category A: Adequate and well controlled studies have not shown fetal risk in the third trimester, and there is no evidence of risk in subsequent trimesters.

Category B: Indicates one of the following possibilities:

a) Animal studies have shown no teratogenic effects, but this has not been confirmed in humans.

b) Animal studies have detected potential teratogenic risk, but this has not been confirmed in humans.

Category C: Indicates one of the following possibilities:

a) Animal studies have detected teratogenic effects, but no data in humans is available.

b) No studies have been made (either in animals or in humans).

Category D: Studies have shown teratogenic effects in the human fetus, but on occasion the benefit obtained with the use of these medications may exceed the expected risk (use in situations where the mother's life is at risk).

Category X: Medications that have clearly been shown to have teratogenic effects and whose risks by far outweigh the possible benefit to be obtained..

**20 % of the dose administered is excreted in the milk. Skin rashes, hepatitis and blood disorders have been described in breastfed children.

***Between 40% and 60% of the dose administered is secreted in the milk. Bloody diarrhea has been described in breastfed children.

****7% of the dose is secreted in the milk. There is a risk of accumulation in breastfed children with reduced renal excretion.

VI. SAFETY OF PHARMACOLOGICAL TREATMENT

Table 26 shows a summary of the main adverse effects and recommendations for monitoring the DMARDs.

Antimalarials: chloroquine (CLQ) and hydroxychloroquine (HCQ)

***Adverse effects*. The antimalarials are relatively safe drugs when used at the recommended doses. The most frequent side effects are gastrointestinal and skin toxicity, and the most serious are retinopathy and neuromuscular toxicity. Most of these side effects are reversible and do not require discontinuation of treatment (Jiménez-Palop, 2006).**

***Monitoring*. A baseline ophthalmological examination should be made in patients over 40 years of age and/or with a family history of ocular disease (ACR Committee, 1996). All patients should receive a periodic ophthalmological examination including funduscopic and visual field evaluation every 6-12 months. Patients with kidney failure or those who take the drug for more than 10 years need to be monitored more frequently. Laboratory tests to monitor toxicity are not necessary (Sontheimer, 2000). [5, D]**

***Contraindications*.- Allergy to 4-aminoquinoline derivatives. Retinopathy or visual field deterioration. Disorders of the hematopoietic system. Glucose-6-phosphate-dehydrogenase deficiency (hemolytic anemia, favism). Myasthenia gravis. Caution should be taken in patients with G6PD deficiency and reduced kidney function (bloody dyscrasias), as well as in patients with bipolar disorders, epilepsy or in treatment with stimulants (Wallace, 1994) and in patients with diabetes mellitus (Shojania, 1999).**

A large variety of adverse effects with the antimalarials has been described (Jiménez-Palop, 2006); however, these drugs have shown a good safety profile when compared with other DMARDs (Felson 1990; Felson, 1992). Hydroxychloroquine is generally better tolerated and less toxic than CLQ (Finbloom, 1985).

The most frequent contraindication is gastrointestinal toxicity with nausea, vomiting, pain, and bloated abdomen. In these cases, if the patient was taking CLQ, the dosage can be reduced by half or the patient can be switched to hydroxychloroquine. Since its bioavailability is not reduced by taking it with food, it can be administered with meals, which improves tolerance. Taking the drug at night also improves tolerance.

Skin toxicity rarely leads to withdrawal of the medication. Side effects include maculopapular, scaly, or morbilliform rashes, urticaria and pruritus; alopecia and graying of hair; lichenoid reaction; and exfoliative dermatitis. In cases of yellowish hyperpigmentation of the skin and mucosa, which generally appears after periods of prolonged treatment, especially in patients treated with quinacrine, it may be useful to reduce the dose by half.

Ocular toxicity is very infrequent if the recommended doses are not exceeded (Marmor, 2002). It can be detected early if periodic ophthalmological (funduscopic and visual field) examinations are performed (ACR Committee, 1996).

Manifestations of ocular toxicity are of various types:

- ✓ Visual accommodation defects; these are reversible without the need to change the dosage or discontinue the drug. They appear early and are due to muscular dysfunction.
- ✓ Infrequent cases of diplopia due to neuromuscular dysfunction.
- ✓ Corneal deposits, either asymptomatic or with blurry vision, which disappear when treatment is withdrawn.
- ✓ Retinopathy, which may lead to persistent loss of vision and may progress despite withdrawal of treatment.

In recent years various recommendations for ocular control have been published, with the aim of preventing the appearance of retinopathy (Fielder, 1998; Marmor, 2002). The recommendations of the American Academy of Ophthalmology take into account the dosage and type of administration of the antimalarials, as well as the existence of possible risk factors (Marmor, 2002).

Other infrequent side effects are:

- ✓ Central nervous system manifestations: cephalea (usually disappears without interrupting treatment), insomnia, excitability or tinnitus. Convulsions or psychosis may appear in rare cases (special precaution should be taken in patients with bipolar disorders, epilepsy or in treatment with stimulants) (Wallace, 1994; Jiménez-Palop, 2000).

- ✓ Neuromyopathy and cardiomyopathy: these are infrequent manifestations (Avina-Zubieta, 1995; Iglesias, 1993; Stein, 2000). Myopathy affects the proximal musculature and may be accompanied by peripheral neuropathy (Jiménez-Palop, 2000). Cardiomyopathy may manifest with conduction disorders or with congestive heart failure, and some authors propose that electrocardiograms be performed before beginning treatment and periodically thereafter (Cervera, 2001). Muscular weakness, neurological deficits and congestive heart failure resolve several months after discontinuing treatment (Avina-Zubieta, 1995; Ratliff, 1987).

- ✓ In patients with G6PD deficiency, the antimalarials, and especially CLQ, may induce hemolytic anemia (Furst, 1996; Jiménez-Palop, 2000). Cases of aplastic anemia in patients treated with quinacrine have also been reported.

- ✓ Some cases of decreased glycemia have been reported with the antimalarials, in patients with RA and diabetes mellitus treated with insulin or with oral antidiabetic drugs (Shojania, 1999).

Anti-TNFs: Infliximab (IFX), Etanercept (ETN), Adalimumab (ADA)

***Adverse effects*. There is now wide experience with IFX and ETN. No important unexpected side effects have been identified during the first 5 years of observation, but their safety profiles are not yet sufficiently well established, as longer follow-up time is needed. To date, the safety profile of ADA is similar to that of other anti-TNFs.**

***Monitoring*. CBC, general biochemistry, liver serology, chest X-ray, Mantoux and booster at the beginning of treatment. Subsequently, CBC and general biochemistry is**

recommended every 4 weeks during the first 4 months, and every 3-4 months thereafter. If receiving prophylactic treatment against TB: CBC and liver profile every 2 weeks for 2 months, with monthly tests thereafter. These tests are meant to rule out acute or chronic infection before beginning treatment [5, D], as well as to rule out the presence of active or latent tuberculosis [2.b, B]. Patients should also be monitored for neoplasias [5, D] and autoimmune diseases (ANA and DNA every 3 months for the first year, and every 6 months thereafter).

***Contraindications-*. The contraindications for INF, ADA, CMB, and CZM are allergy to the active ingredient or excipients, active TBC, severe infections, and moderate to severe heart failure (NYHA classes III/IV). The contraindications for ETN are allergy to the active ingredient or excipients, sepsis or risk of sepsis, active infections, demyelinating disease, and tumors (Gomez Reino 2011).**

VI.1.1. Adverse effects of the anti -TNFs

Current experience with IFX, ADA, and ETN is extensive. Longer follow-up and more evidence are necessary for GMB and CZM.

The existing data concerning the safety of ADA, ETN and IFX in treating RA come from clinical trials that have included nearly 6,000 patients (Scott, 2006), as well as from wide experience in clinical practice. Treatment with these TNF inhibitors has been studied more extensively, given their early introduction. CZP and GLM have a safety profile similar to that of other TNF antagonists.

Serious or unexpected side effects have been observed with these drugs (infectious, lymphoproliferative, autoimmune, demyelinating diseases...) but in rates which are not completely different from those of the background diseases for which they are used. As yet there is insufficient information about their long-term safety (Listing, 2005).

Information about their long-term safety comes from:

- ✓ Open-label extensions of previous clinical trials (Moreland, 2006; Weinblatt, 2006 a and b)
- ✓ Communication of side effects observed by physicians
- ✓ Prospective observational studies. The creation of databases that include a large number of patients and long follow-up, which already exist in various countries, is the best way to evaluate this issue.

When analyzing the possible toxicity of the anti-TNFs it should be kept in mind that a higher frequency of infections has been observed in RA (Doran, 2002b), as well as a higher frequency of lymphomas (Baecklund, 2006) and cardiovascular disease (Solomon, 2003), in relation with the duration and severity of the disease. Most patients treated with these drugs have moderate to severe disease, of long duration, which makes it difficult to discern whether the side effects are attributable to the disease or to the treatment (Hyrich, 2006a; Schiff, 2006; Hyrich, 2006b).

In 2005 a group of experts reviewed the evidence existing to date about the efficacy and safety of the TNF inhibitors and of interleukin-1 in the treatment of rheumatic diseases (Furst, 2005).

VI.1.1.a. Infections

A subject of continuing controversy is whether patients being treated with anti-TNFs have an important increased risk of infection (requiring antibiotics or hospitalization).

One systematic review of CTs with IFX and ADA (Bongartz, 2006) did find an increased risk of infection. However, two other systematic reviews did not find this effect in patients treated with ADA (Schiff, 2006; Navarro-Sarabia, 2005), although it was found in a clinical trial, with longer follow-up, of ADA and MTX (Keystone, 2004a). In a clinical trial not included in these analyses, the risk in recent-onset RA was found to be somewhat lower with ADA than with ADA combined with MTX (Breedveld, 2006).

Extended studies of ETN and ADA with 7 and 4 years' follow-up (Moreland, 2006; Weinblatt, 2006a) did not find an increased risk of infection with respect to what was initially found in these two CTs.

CTs exclude patients with comorbidities, hence the importance of safety data from registries (which already exist in several countries) that include all patients treated with anti-TNFs, permitting long-term follow-up.

According to data from the BIOBADASER registry (http://biobadaser.ser.es/), patients being treated with anti-TNFs are more disposed to infections (TB and herpes zoster).

Data from the Swiss registry show that the pattern of adverse effects of ETN is similar to what has been found in CTs (Feltelius, 2005).

In the British database, a larger total number of infections has not been found, and no differences in risk have been seen among the three anti-TNFs. A higher frequency of skin and soft tissue infections has been observed, and of intracellular infections exclusively in patients treated with these drugs (Dixon, 2006). In contrast, the incidence is higher in the German database (they analyze ETN and IFX); respiratory, skin, bone and joint infections are the most frequently found type of infections (Listing, 2005).

In the German database the comparison group had a lower frequency of serious infections and in the British data base, it had a higher frequency of respiratory infections, which explains these differences. Additional patient recruitment and longer follow-up will make it possible to obtain more conclusive data.

- Tuberculosis (TB)

After its commercialization, various cases of TB were found in patients treated with IFX and, subsequently, with ADA and ETN as well. An observational study in a Spanish population found a higher risk of TB in patients with RA, which increased with treatment with IFX (Carmona, 2003b; Gomez-Reino, 2003). In most of the cases with IFX, TB appeared 12 months after beginning treatment, which suggests reactivation of latent tuberculosis. With ETN, it occurs an average of 11.5 months after beginning treatment, and with ADA, in the first 8 months (Crum, 2005). It shows an unusual pattern (56% intrapulmonary and 24% disseminated) (Furst, 2005; Dixon, 2006; Crum, 2005; Hamilton, 2003). Given the seriousness of this complication, the following national-level recommendations have been established (Rodríguez-Valverde, 2004):

- ✓ Evaluate the existence of active or latent (inactive) TB before starting treatment with anti-TNF drugs. The evaluation should include previous history of and/or contact with the disease, chest radiograph and tuberculin test, to be repeated 7-10 days afterwards if initially negative (seriously ill or immunodepressed patients may present false negatives). Some authors advise repeating the tuberculin test every year (Furst, 2005; Crum,2005; Cush, 2005).

- ✓ If latent (inactive) TB is diagnosed, preventive measures should be taken and the benefit-risk ratio should be evaluated before starting therapy with anti-TNF. It is not clear how long before starting anti-TNF treatment prophylaxis should begin (Crum, 2005; Rodríguez-Valverde, 2004).

- ✓ In addition, the patient should be instructed to inform his/her physician if signs and/or symptoms of TB appear, for example, persistent cough, weakness/weight loss and low-grade fever. If active disease is suspected, treatment should be discontinued until the diagnosis is ruled out, or the infection has been treated in accordance with standard guidelines.

Institution of these measures has been shown to considerably reduce the number of cases of TB, although this may also be influenced by the fact that physicians try not to treat patients with a higher risk of developing TB with anti-TNF agents (Carmona, 2005).

A larger number of cases has been associated with IFX, which may be due, at least in part, to its earlier introduction and use before the increased risk of this infection was known and prophylaxis was given (Carmona, 2005); however, some authors suggest that the monoclonal antibodies may be associated with a higher risk of this infection than ETN (Dixon, 2006).

- Opportunistic infections

Opportunistic infections have been observed with all three anti-TNFs, as well as intracellular infections (listeriosis, salmonellosis, candidiasis, aspergillosis, histoplasmosis, coccidioidomicosis, and infections from cytomegalovirus, pneumocystis, criptococcus...), but their incidence is low (Furst, 2005; Crum, 2005). Patients should avoid food that carries a high risk of being infected with listeria or salmonella (Crum, 2005; Dixon, 2006).

- Hepatitis B and C infection

The safety and efficacy profile of anti-TNF agents in patients with hepatitis B and C is not well known (Furst, 2005). There have been reports of reactivation of infection and even fulminant hepatic failure in patients with HBV infection taking TNF antagonists (Calabrese 2006; Wendling 2005; Carroll 2010). However, these drugs have no abnormal effect on viral load (Ledingham, 2005), and there are data showing that reactivation can be prevented by using prophylaxis with anti-viral treatment (Furst, 2005; Calabrese, 2006). Lamivudine has proven to be efficacious, although long-term administration has been associated with the emergence of resistance. There are no studies on adefovir administered as prophylaxis for reactivation of hepatitis B in patients with immunosuppressive treatment (Calabrese, 2006).

They appear to be safe in chronic hepatitis C (Calabrese, 2004); a controlled study with ETN, together with interferon and ribavirin, even showed an improvement in symptoms and liver function tests, without affecting viral load (Zein, 2005). Some observational studies have found similar results. However, a case of reactivation has been reported in a patient treated with ETN, therefore they should be used with caution (Ledingham, 2005).

They should not be used in patients with hepatitis B infection, since in recent years various cases of reactivation with IFX and with RTX have been described (Calabrese, 2006). However, their use without producing any change in viral load has also been reported (Ledingham, 2005), and there are data indicating that reactivation can be avoided by using prophylaxis with antiviral treatment (Furst, 2005; Calabrese, 2006). Lamivudine has been efficacious but its long-term administration is associated with the emergence of resistance. There are no studies of Adefovir as prophylaxis against hepatitis B reactivation in patients with immunosuppressive treatment (Calabrese, 2006).

- HIV

The effects of anti-TNF therapy in HIV patients are unknown, since existing data are very limited (Aboulafia, 2000; Gaylis, 2003; Bartke, 2004; Ledingham, 2005). Although TNF antagonists have proven to be efficacious in some case series, an increase in the number of infections has also been reported (Cepeda 2008).

- Infection and Surgery

The risk of infection in the perioperational period is unclear, nor is it known how long before a surgical intervention these drugs should be discontinued (Furst, 2005; Crum, 2005; Cush, 2005; Giles 2006; Corrao 2007; den Broeder 2007), and different scientific societies recommend somewhat different periods of time (Tornero 2010; Ledingham, 2005).

It is not recommended they be combined with ANK or ABT due to the increased risk of infections (Scott, 2006; Weisman, 2002).

- Vaccination

Various publications highlight a favorable humoral response in the use of TNF antagonists to treat infections by microorganisms such as influenza virus and pneumococci and microorganisms containing tetanus toxin (Elkayam, 2004c; Kaine 2007; Tay 2007; Elkayam 2009). Vaccination against pneumococci and influenza is recommended; live vaccines are not recommended (Scott, 2006; Furst, 2005; Crum, 2005; Tornero 2010).

VI.1.1.b. Neoplasias

Whether or not treatment with TNF inhibitors increases the total risk of cancer in RA patients is not well established. There is no current evidence of increased risk of solid tumors in patients taking TNF antagonists (Khanna 2004; Scott 2006), although there does seem to be an increased risk associated with non-melanocytic cutaneous tumors (basal cell) (Chakravarty 2005). It must always be kept in mind that the risk of cancer, especially lymphoproliferative cancer, is higher in this disease, and it is difficult to separate the background risk from that related with treatment for the disease (Setoguchi, 2006; Weyand, 2006).

One systematic review of 9 ECs with IFX and ADA found a higher risk of cancer, including solid and hematological tumors and melanomas (excluding other skin cancers), and the risk was higher in those who received higher doses (Bongartz, 2006).

However, cohort studies of patients included in databases from various countries have not found a higher risk of solid tumors in patients treated with anti-TNFs (Scott, 2006; Setoguchi, 2006; WGET, 2005; Askling, 2005b), or with anti-IL1 (Scott, 2006; WGET, 2005; Setoguchi, 2006).

Patients with Wegener's granulomatosis treated with ETN and CTX have a higher risk of solid tumors, therefore the combination of CFA with an anti-TNF should no longer be used.

Cases of lymphoma have been reported with all three TNF inhibitors (Scott, 2006). As already noted, the risk of tumors is higher in RA patients; one study found that the increased risk of lymphoma was associated with severe disease, with high inflammatory activity (Baecklund, 2006). It is precisely these patients, with high inflammatory activity refractory to other therapies, in whom treatment with TNF inhibitors is most often indicated.

In a series of 26 cases of lymphoproliferative disorders (18 after treatment with ETN and 8 after treatment with IFX), the majority of cases were non-Hodgkin's lymphomas. The interval between initiation of treatment and diagnosis of lymphoma was very short (median 8 weeks), and in 2 patients (1 with each drug) lymphoma regression was observed following discontinuation of treatment. Two patients previously treated for lymphomas and who were in remission rapidly developed a recurrence after starting anti-TNF treatment. (Brown, 2002).

An extended open-label study with 7-years' patient follow-up in a clinical trial of ETN found that the risk of lymphoma was higher than in the general population (Moreland, 2006); however, without a direct comparison group, an association cannot be established (Hyrich, 2006a). Cases were not seen to accumulate with longer follow-up, which suggests that ETN may accelerate the development of pre-existing lymphomas.

A recent study comparing the incidence of lymphomas in a cohort of RA patients who were and were not treated with anti-TNF found a higher risk in those receiving this treatment (Wolfe, 2004b), but the groups were not comparable with regard to disease duration and severity so no causal relation could be established (Hyrich, 2006). In fact, cohort studies that take these variables into account have not found a higher risk of lymphoma in patients treated with anti-TNF (Setoguchi, 2006; Askling, 2005a) or with anti-IL1 (Setoguchi, 2006).

A recent communication has reported 6 cases of highly aggressive hepatosplenic T-cell lymphoma in young patients with Crohn's disease treated with IFX in combination with AZT or 6-mercaptopurine (communication from Centocor).

In the BIOBADASER registry (http://biobadaser.ser.es/), no clear association has been found between the use of anti-TNFs and the appearance of lymphoma.

In general, anti-TNF treatment is not indicated in patients with a higher risk of lymphoma (previous infection with Epstein Barr virus, or family or personal history of lymphomas).

More data with longer follow-up in larger numbers of patients are still needed to clarify whether or not there is an association between the anti-TNFs and tumor development. Meanwhile, extreme caution should be taken in indicating the use of these drugs when there is a history of previous tumors (or not use them at all in these cases), and patients should be advised that the risk of associated cancer is as yet unknown (Scott, 2006).

VI.1.1.c. Other adverse effects of the anti-TNFs

The most frequent mild adverse effects are local reactions at the injection site (erythema, localized pain, edema) with ETN, ADA, GLM and CZP which are generally self-limiting, lasting 3-5 days, appearing in the first month of treatment with no need to interrupt treatment; and infusion reactions with IFX, consisting of non-specific symptoms such as fever, chills, chest

pain, hypertension or hypotension, pruritus/urticaria, cephalea, sinusitis, rhinitis and cardiorespiratory symptoms (Scott, 2006; Furst, 2005).

- Hematological manifestations

Isolated cases of pancytopenia and aplastic anemia have been reported. It is unclear whether there is a causal relationship, although caution must be exercised in patients with a history of hematologic abnormalities, treatment interruption should be considered, and the potential existence of other causes should be evaluated (Furst, 2005; Ledingham, 2005 Keystone 2005).

- Demyelinating disease

More frequent isolated cases of optical neuritis, multiple sclerosis and non-specific demyelination have been reported with ETN (Mohan, 2001; Haraoui, 2006; Simsek 2007; Bensouda-Grimaldi 2007; Fernandez-Espartero 2010). It is not clear if these syndromes occur more frequently than expected in the general population. Treatment should be discontinued. In patients with a history of demyelinating disease, the indication for anti-TNF agents should be evaluated on an individual basis depending on the risks and benefits, although in general it should be avoided (Gomez reino 2011, Tornero 2010)

- Autoimmunity

Syndromes similar to drug-induced lupus may infrequently appear with all three anti-TNFs. Symptoms usually resolve after treatment is interrupted (generally between 6 weeks and 14 months). Antinuclear, anti-DNA and anticardiolipin antibodies may appear, but there is no evidence that they are associated with a greater risk of systemic lupus erythematosus (Furst, 2005; Ledingham, 2005; Haraoui, 2006; Ramos-Casals 2007; Ramos-Casals 2008; Wetter 2009). The presence of ANCA and antithyroid antibodies, vasculitis and other autoimmune complications has infrequently been reported (Haraoui, 2006).

- Heart failure

Increased morbidity and mortality has been observed in RA patients with class 3-4 (NYHA) heart failure treated with high doses of IFX (10 mg/kg), (Furst, 2005; Ledingham, 2005; Curtis 2007; Setoguchi 2008; Singh 2009). There is no evidence that the incidence of mild heart failure, or its mortality, is higher in patients treated with usual doses of TNF inhibitors. It should be kept in mind that RA patients, whether or not they are treated with anti-TNF, have a higher incidence of cardiovascular disease (Wolfe, 2004c).

However, it is recommended that patients with advanced (NYHA class 3-4) heart failure not be treated with anti-TNF, nor should those with mild-moderate (class1-2) heart failure who have a reduced ejection fraction (Desai, 2006).

- Pulmonary disease

In RA patients treated with these drugs some cases of worsening underlying interstitial pulmonary disease have been described, with a fatal outcome in one case (Peno-Green, 2002; Villeneuve, 2006; 2006, Martin 2006; Ostor 2006). This risk could be increased in patients with a history of interstitial lung disease. The worst outcomes have been reported in patients with usual interstitial pneumonitis; therefore, special attention should be paid in patients with a history of this condition (Martin 2006; Ostor 2006). The British Society of Rheumatology recommends that TNF inhibitors be used cautiously and with very close monitoring

(Ledingham, 2005). Some authors advise against their use in patients with significant preexisting pulmonary disease (Villeneuve, 2006).

- Liver disease

Very rarely, cases of liver failure not preceded by altered liver function have been reported with IFX. Elevated liver enzymes have been observed with all anti-TNFs (the etiology and significance is unclear due to other medications and circumstances) and are frequently reversible despite continuing treatment (Furst, 2005). In one study with more than 6,800 patients, elevated liver enzymes were uncommon and related to previous use of DMARD (Sokolove 2010)

- Psoriasis

There have been reports of cutaneous psoriasis, mainly palmoplantar psoriasis, and exacerbation or morphological changes in existing psoriatic lesions with use of these drugs (Sfikakis 2005; Cohen 2007; Wollina 2008).

VI.1.2. Monitoring the anti-TNFs

To reduce the risk of possible side effects with these drugs, it is important to select patients appropriately, excluding those cases with absolute contraindications such as the presence of active systemic or local infection, tumors or demyelinating disease. The possible existence of latent TB should be evaluated and prophylactic treatment should be initiated if indicated. Vaccination against influenza and pneumococcus should be administered. Patients should be advised of what symptoms require consultation, and they should be followed closely (Furst, 2005; Rodríguez-Valverde, 2004; Ledingham, 2005).

VI.1.3. Contraindications of the anti-TNFs

Sepsis or infections; demyelinating illness; tumors; moderate-severe heart failure; and hypersensitivity to components of these drugs.

Azathioprine (AZT)

***Adverse effects*. The most frequent side effects of azathioprine are gastrointestinal intolerance, hematological disorders and infections.**

***Monitoring*. Baseline laboratory tests should be performed, including a CBC (leukocytes, hemoglobin and platelets), creatinine, and liver function tests. A CBC should be performed every 1-2 weeks thereafter while the dosage is being adjusted, and every 1-3 months after a stable dose is achieved (ACR Committee, 1996). Liver function tests are recommended every 6-8 weeks. The dose should be reduced in patients with renal failure. Extreme precaution should be taken if used concurrently with allopurinol. [5, D]**

***Contraindications*.- Known neoplastic disease. Hypersensitivity to the active ingredient 6-mercaptopurine or to one of the excipients.**

About 45% of AZT is excreted in the urine and the rest is metabolized to 6-mercaptopurine (6-MP), which is in turn metabolized via two routes: catabolic oxidation to 6-thiouric acid (by xanthine-oxidase action) and an anabolic route in which two enzymes act (thiopurine methyltransferase [TPMT] and hypoxantine-phosphoribosyl-transferase), transforming it into various metabolites.

VI.1.4. Adverse effects of azathioprine

The toxicity of AZT and 6-MP is predominantly related with TPMT activity. Up to 11% of the population has low TPMT enzyme activity (Lennard, 1989). Analysis of the TPMT gene or enzyme activity before starting treatment may help predict which patients have a higher risk of side effects with AZT (Black, 1998; Marra, 2002; Seidman, 2002). However, as yet there is no agreement about how these analyses should be used, and there is wide variability in clinical practice in this regard (Cuffari, 2004; Lichtenstein, 2004). Moreover, it is important to bear in mind that patients with normal TPMT activity can have important side effects.

The administration of allopurinol (a xanthine oxidase inhibitor) together with AZT also increases the risk of side effects and should be avoided whenever possible. If its use is absolutely necessary, the AZT dose should be reduced by 50 to 75%.

The most frequent side effects at the doses used in rheumatic diseases are gastrointestinal intolerance, myelosuppression and infections (Huskisson, 1984).

VI.1.4.a. Gastrointestinal intolerance

Gastrointestinal symptoms appear in about 20% of patients treated with AZT. The most frequent are anorexia, nausea and vomiting. Less frequent are the development of diarrhea (<1%) or elevated liver enzymes (5%). Although these side effects may require withdrawal of the drug (10%), they usually improve or resolve when the dose is reduced (Huskisson, 1984).

VI.1.4.b. Myelosuppression

Hematological disorders are dose-dependent. The most frequent are leukopenia (25% of patients) and thrombocytopenia (5%), although cases of medullar aplasia have been described. Mild blood disorders can be resolved by reducing the dosage (Huskisson, 1984). Xanthine oxidase deficiency produces an increase in side effects in general, and in hematological effects in particular (Black, 1998). The use of allopurinol should be avoided. If it must be used, the AZT dose should be reduced by 50 to 75%, and more frequent leukocyte counts should be performed. Patients with low TPMT levels have a higher risk of myelosuppression and of macrocytic anemia (Woodson, 1982).

VI.1.4.c. Infections

Infections appear in about 10% of patients treated with AZT. Bacterial infections usually develop in patients with neuropenia. Those of viral origin, especially herpes zoster, occur in up to 6% of patients (Singh, 1989). Reactivations of chronic viral hepatitis may occur (Mok, 2000).

VI.1.4.d. Other adverse effects of azathioprine

A hypersensitive-like reaction has been described in the first weeks of treatment, with fever, general malaise, arthralgias/myalgias, skin lesions, leukocytosis, elevated liver enzymes, and even hypotension and shock (Blanco, 1996).

In RA patients treated with AZT the risk of developing neoplasias appears to be increased (relative risk 2.2-8.7), mainly skin cancers and hematological neoplasias (Silman, 1988; Asten, 1999).

AZT may cause temporary depression of spermatogenesis.

VI.1.5. Monitoring azathioprine

The recommended initial dose is 25-50 mg/day the first week, increasing by 0.5 mg/kg/4-6 weeks until a response is obtained or up to a maximum of 3 mg/kg/day. The dose should be reduced in cases of renal failure. A blood count every 2 weeks is recommended while the dose is being stepped up, and every 4-6 weeks thereafter. If leukocytes are < 4,000 or platelets are < 150,000 the dose should be reduced or the treatment interrupted. If macrocytosis appears, closer control should be made, after ruling out vitamin B12 or folate deficiency.

Liver enzyme tests should be conducted every 6-8 weeks (Furst, 1994b).

Cyclophosphamide (CTX)

***Adverse effects*. Cyclophosphamide has frequent adverse effects, which vary in relation with the dose use and the route of administration (Ortman, 2000). Intravenous administration is recommended. Most side effects are reversible by discontinuing the drug. The most frequent side effects are gonadal, urologic, and bone marrow toxicity, neoplasms, and infections. Other frequent but less important effects are alopecia, nausea, and vomiting.**

Monitoring.- Complete blood count every 1-2 weeks during the first 2-3 months of treatment, then every 2-4 weeks once the dosage has been stabilized (Clements, 1986). In patients with pulsed intravenous therapy, the blood count should be assessed before each infusion of cyclophosphamide, and 1-2 weeks after the infusion. Monthly tests should be obtained for liver enzymes, urinalysis, and urinary sediment. If microscopic hematuria is detected, other, more specific studies are indicated, such as cystoscopy and urinary cytology. [5, D]

Contraindications.- Pregnancy, hypersensitivity, cytopenia, chronic or active infection, liver disease, or history of neoplasia. Renal failure is a relative contraindication that requires adjustment of the dosage.

VI.1.6. Adverse effects of cyclophosphamide

CTX is a useful drug for the treatment of serious complications of RA. It should be used in intravenous pulses since they are as effective as oral administration and have fewer side effects.

VI.1.6.a. Gonadal toxicity

Gonadal toxicity from CTX is produced in women at the level of the primordial and antral follicles, giving rise to oligomenorrhea and amenorrhea (Warne, 1973). In men it affects the epithelial germ layer of the seminal vesicles, causing azoospermia or oligospermia, and testicular atrophy or reduction in size (Watson, 1985).

A review has been made of the epidemiology of ovarian failure produced by CTX and the possible strategies to preserve ovarian function (Slater, 1999). The risk of amenorrhea varies between 11% and 59%. (Mok, 1998; Wang, 1995); it may be lower with administration by intravenous pulses, but the difference is not substantial (Austin, 1986). The risk increases with the patient's age and the cumulative dose (Boumpas, 1993; Gourley, 1996; Mok, 1998; Huong, 2002).

In men the risk of azoospermia varies between 50% and 90% in patients undergoing chemotherapy (Masala, 1997). Less information is available on autoimmune diseases, but they also occur frequently (Fukutani, 1981). The dose causing gonadal toxicity in men may be very small (Rivkees, 1988).

Recovery of ovarian function or of spermatogenesis is unpredictable, and irreversible sterility may occur (Fairley, 1972). Thus, freezing of ova or sperm is recommended before beginning treatment with CTX.

The risk of infertility in women may be reduced by treatment with gonadotropin inhibitors (Blumenfeld, 2000; Somers, 2005; Manger, 2006). One study suggests that contraceptives with high-dose estrogen protects against gonadal toxicity (Chapman, 1981),whereas the low doses used in another study did not show this protective effect (McDermott, 1996). The use of testosterone in men also reduces gonadal toxicity (Masala, 1997).

VI.1.6.b. Urological toxicity

The urologic toxicity of CTX basically consists of the development of hemorrhagic cystitis and carcinoma of the bladder (Talar-Williams, 1996; Knight, 2004).

Hemorrhagic cystitis is present in 15-30% of patients treated with oral CTX. Administration in intravenous pulses is not usually associated with vesical toxicity (Austin, 1986; Boumpas, 1993).

There is a high risk of developing malignant vesicle neoplasm with total doses exceeding 80 g. Tumors may appear early or several years after initiation of treatment. The risk remains even years after discontinuing treatment (Radis, 1995; Hoffman, 1992). The development of carcinoma of the bladder does not appear to be related to pre-existing hemorrhagic cystitis (Knight, 2004; Talar-Williams, 1996).

Abundant oral (2-3 liters in 24 hours) or intravenous hydration and frequent urination are recommended to decrease vesicle toxicity. The use of sodium 2-mercaptoethane sulfonate (MESNA) together with CTX also reduces vesicle toxicity (Reinhold-Keller, 2000; Hellmich, 2004).

If the patient shows signs of reduced vesicular volume (e.g., polakiuria), CTX should be discontinued and cystometry performed. If there is hematuria suggesting the presence of incipient hemorrhagic cystitis or other urological complications, treatment should be discontinued and cystoscopy and urinary cytology should be performed (Talar-Williams,1996).

VI.1.6.c. Medullar toxicity

CTX produces reversible myelosuppression. The degree of leukopenia and neutropenia is dose-dependent. Maximum suppression occurs 8-12 days after intravenous administration (Ortmann, 2000). The leukocyte count should not drop below 3000/mm3 and the neutrophils should not go below 1000/mm3; the doses should be adjusted until the desired levels are regained.

Concurrent treatment with allopurinol should be avoided due to the increased risk of leukopenia (Clements, 1986).

Anemia and thrombopenia are less frequent, and aplasia, if it occurs, is transitory.

VI.1.6.d. Neoplasias

The use of CTX is associated with a higher risk of lymphomas and probably also with leukemias, skin cancer and bladder cancer (Radis, 1995; Vasquez, 1992). The apparent determining factors that condition the development of carcinomas are total dose of CTX and duration of treatment (Radis, 1995; Reinhold-Keller, 2000).

VI.1.6.e. Infections

Upper respiratory tract infections, as well as bacterial, fungal and viral infections, especially herpes zoster, are frequent with the use of CTX. Risk factors are considered to be the involvement of multiple organs, concomitant treatment with high-dose steroids, and leukocyte counts under 3,000 cells/mm3 (Pryor, 1996). S Patients being treated with CTX and high-dose steroids should receive prophylaxis for Pneumocystis jiroveci (Sowden, 2004).

VI.1.6.f. Other adverse effects of cyclophosphamide

Other adverse effects that have been observed are gastrointestinal toxicity (mainly nausea and vomiting) (Singh, 1991), alopecia, nail changes, and hypersensitivity reactions. Pulmonary, cardiac or hepatic toxicity may occur at very high doses (Ortmann, 2000; Fraiser, 1991), as well as inadequate secretion of the antidiuretic hormone (Salido, 2003).

Cyclosporin A (CSA)

Adverse effects. **The most serious and relatively frequent adverse effects are nephrotoxicity and arterial hypertension. Both are dose-dependent and constitute the most important limitation to their use.**

Monitoring. **Before beginning treatment, the following tests should be performed: blood pressure (two measurements), CBC, liver and kidney biochemistry (with special attention to serum urea and creatinine), and urinalysis with sediment. Blood pressure, renal function, and K+ and Mg++ electrolytes should be monitored every 2 weeks during the first 3 months and monthly thereafter. If the dose is changed or if there is an increase in creatinine levels or blood pressure, the patient should be monitored weekly until**

stabilization. If the levels of serum creatinine increase by more than 30% with respect to baseline, the dose should be reduced by 25-50%. If renal function does not improve in 1 month, CSA should be discontinued; it may be resumed if creatinine returns to levels within 10% of the pre-treatment value. If hypertension is detected, treatment with calcium antagonists may be instituted. The drug of choice is nifedipine (which does not increase the levels of cyclosporinemia). [5, D]

***Contraindications*.- Hypersensibility. Patients with autoimmune diseases (RA, psoriasis, nephrotic syndrome, endogenous uveitis, atopic dermatitis), altered renal function (except proteinuria in patients with nephrotic syndrome), or uncontrolled hypertension. Patients with psoriasis who are receiving other immunosuppressors, PUVA, UVB, coal tar, and radiotherapy. Co-existing cancer (except non-melanoma skin cancer), uncontrolled arterial hypertension, renal dysfunction, uncontrolled infections, primary or secondary immunodeficiency (Cush, 1999).**

VI.1.7. Adverse effects of cyclosporin A

VI.1.7.a. Nephrotoxicity and arterial hypertension

The nephrotoxicity produced by CSA may cause acute renal failure, which is usually reversible by reducing the drug dosage, or chronic and progressive disease, which is usually irreversible, (Burdmann, 2003; de Mattos, 2000). It may also produce tubular dysfunction with reduced Mg reabsorption and reduced secretion of K and uric acid (Kahan, 1989).

CSA causes dose-dependent vasoconstriction in the preglomerular vasculature, with reduced renal plasma flow and glomerular filtration (Ruggenenti, 1993). This vasoconstriction, together with an increase in tubular sodium reabsorption and a possible effect on the renin-angiotensin system, also cause AHT. Like acute renal failure, AHT is usually reversible by reducing the dose or interrupting treatment (Lamas, 2005).

Chronic renal disease with irreversible structural changes is rare and usually presents with elevated serum levels of CSA and associated risk factors such as concurrent treatment with nephrotoxic drugs, pre-existing nephropathy, advanced age, diabetes and arterial hypertension (Feutren 1992; Cush, 1999).

The following recommendations should be followed to avoid structural nephropathy:

- ✓ Exclusion of patients with potential risk factors such as renal dysfunction
- ✓ Limitation of the maximum dose to 5 mg/kg/day
- ✓ Administration of the smallest possible maintenance dose, according to the level of serum creatinine
- ✓ Frequent and careful monitoring of renal function
- ✓ Routine clinical examination and laboratory tests (Panayi, 1997; Cush, 1999).

The patient should have normal blood pressure before beginning therapy. If diastolic BP is higher than 95 mmHg or systolic BP is higher than 160, the dose should not be increased. If hypertension is present (diastolic BP >105 mmHg or sustained at more than 95 mmHg) in two

consecutive measurements, antihypertensive treatment should be initiated or the CSA dose reduced (Panayi, 1997). The antihypertensive drugs of choice are some calcium channel blockers (Cush 1999).

VI.1.7.b. Neoplasias

It has not been shown that RA patients treated with CSA have a higher risk of solid tumors or lymphoproliferative processes, although isolated cases of reversible lymphomas on discontinuing the drug have been reported (Cush, 1999; van dem Borne, 1998).

VI.1.7.c. Other adverse effects of cyclosporin A

Besides AHT and nephrotoxicity, the most frequent side effects are gastrointestinal (dyspepsia, nausea, vomiting, abdominal pain and diarrhea), hypertrichosis, gingival hypertrophy, paresthesias and tremor (Thomas, 2000a; Wijdicks, 1995). These are usually dose-dependent and are reversible on reducing the drug dosage. Tremor is usually moderate and well tolerated (Cush, 1999). It can also cause liver disorders (hyperbilirubinemia and hypertransaminemia), hyperuricemia and hyperpotassemia, hypomagnesemia, loss of bone mass… (Landewe, 1994; Thiebaud, 1996).

D-penicillamine (DPC)

Adverse effects. The most frequent adverse effects of DPC are skin lesions, gastrointestinal symptoms and renal involvement.

Monitoring. **Baseline tests should be performed, including CBC, creatinine and urinalysis (including sediment). These tests should be repeated every 2 weeks a stable dose is attained, and every 1-3 months thereafter (ACR Committee, 1996). [5, D]**

Contraindications. **Kidney disease, blood disorders (leukopenia and thrombocytopenia).**

VI.1.8. Adverse effects of D-penicillamine

VI.1.8.a. Skin lesions

All types of skin lesions may appear (25-50%), from morbilliform and pruritic rashes to pemphigus-like lesions (Willemsen, 1990). These generally disappear when medication is withdrawn [Munro, 1997b]. Mucosal lesions, especially mouth ulcers, are less frequent.

VI.1.8.b. Gastrointestinal symptoms

About 30% of patients have gastrointestinal symptoms (nausea, anorexia, abdominal pain, and diarrhea) during the first months of treatment. These symptoms usually disappear even though DPC is continued, although it must sometimes be withdrawn (Munro, 1997b). About one fourth of patients report dysgeusia (altered sense of taste) during the first months of treatment. This symptom usually disappears spontaneously despite continued treatment, or it may improve following the administration of zinc ([Jaffe, 1977).

VI.1.8.c. Renal involvement

Some 30% of RA patients treated with DPC have some type of renal involvement. This most frequently takes the form of proteinuria accompanied by microscopic hematuria [Stein, 1980]. About 7% of patients develop a nephrotic syndrome secondary to membranous glomerulonephritis which disappears completely in a variable period of time after discontinuing treatment [Hall, 1988a]. Much less frequent is the development of acute renal failure secondary to a rapidly progressive "half-moon" glomerulonephritis (Ntoso, 1986).

VI.1.8.d. Other adverse effects of D-penicillamine

Other secondary effects are blood disorders (thrombocytopenia (8-10%) and leukopenia), pulmonary toxicity (bronchiolitis obliterans <1%), breast hyperplasia (Taylor, 1981), development of autoimmune processes, systemic lupus erythematosus (Chalmers, 1982), inflammatory myopathies (Lund, 1983), myasthenia gravis (Andonopoulos, 1994), and Goodpasture syndrome (Munro, 1997b).

Exceptionally, the appearance of the so-called “yellow-nail syndrome” has been described, a condition that presents with dystrophic nails associated with lymphedema of the lower limbs, pleural effusion and bronchiectasis (Leuédé, 2002). It is often reversed when treatment is discontinued.

The low efficacy of DPC and frequent appearance of secondary effects has led to its replacement by other DMARDs, the same as has occurred with gold salts. Nowadays DPC is rarely indicated for RA.

Leflunomide (LEF)

Adverse effects. **The most frequent adverse effects in published clinical trials are gastrointestinal and respiratory. These effects are generally mild, are not dose-dependent, and do not require discontinuation of treatment.**

Monitoring. **Liver enzymes should be monitored every 2-4 weeks during the first 6 months of treatment and every 8 weeks thereafter. If they are elevated to over twice the maximum reference value, the dose should be reduced to 10 mg/day. If a reduction to 1.2 times the maximum reference value is not obtained, LEF should be discontinued and cholysteramine or charcoal administered. In case of persistently elevated transaminases, a liver biopsy should be performed (Weinblatt, 1999b; Arava, 1999). Periodic monitoring for possible anemia and leukopenia is recommended. [5, D]**

***Contraindications*.- Hypersensitivity to the active ingredient (especially in patients with a previous history of Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or one of the excipients, hepatic insufficiency, severe immunodeficiency, significant involvement of bone marrow or marked anemia, leukopenia, neutropenia, or thrombocytopenia due to causes other than RA, severe infections, moderate to severe renal insufficiency, severe hypoproteinemia, pregnancy, and breastfeeding. LEF is also contraindicated in women of childbearing potential who do not use effective contraception during treatment and after finishing treatment while plasma levels of the active metabolite remain above 0.02 mg/l, breastfeeding.**

VI.1.9. Adverse effects of leflunomide

The most frequent adverse effects in published clinical trials are gastrointestinal (diarrhea 17%, nausea 9%, and abdominal pain 6%) and respiratory (upper respiratory tract infections 15% and bronchitis 7%). These effects are generally mild, are not dose-dependent, and do not require discontinuation of treatment (Weinblatt, 1999; Arava, 1999; Smolen, 1999; Strand, 1999; Mladenovic, 1995; van Riel, 2004). Cases of interstitial pulmonary disease have also been reported, much more frequently in Japanese patients (Ito, 2004).

Transitory elevations of transaminases have been described in about 6% of RA patients treated with LEF (van Riel, 2004). These generally do not exceed twice the normal maximum value, and they tend to remit with prolonged treatment (Smolen, 1999; Weinblatt, 1999; Strand, 1999; Mladenovic, 1995; van Roon 2004). Cases of severe liver disease have been reported, some resulting in death, most of which occurred during the first 6 months of treatment. The European Agency for the Evaluation of Medicinal Products (EMEA) has reported 296 cases of liver toxicity and the death of 15 patients due to liver failure (EMEA, 2001). However, a longitudinal study in which 14,997 patients with RA were followed detected no significant differences in liver disorders between subjects treated with LEF and those who received MTX (Wolfe, 2002). According to FDA data, the incidence of elevated liver enzymes ranges between 2% and 4%, although serious liver toxicity is rare (ACR, 2003).

Other less frequent effects are hypertension (10%), cephalea (7%), vertigo (4%), weight loss (4%), and reversible alopecia (1% with a dose of 10 mg/day and 7% with 25 mg/day) (Furst, 1995; Strand, 1999; Mladenovic, 1995). One case of anaphylaxis has been reported. Up to 10% of patients have skin rashes (van Riel, 2004), usually between the first and third month of treatment, and the dose must sometimes be reduced or the drug withdrawn. Pruritus and mouth ulcers are infrequent. Cases of Stevens Johnson syndrome have occasionally been reported, as well as toxic epidermal necrolysis (van Riel, 2004).

In experimental models, treatment with LEF has been associated with anemia and leukopenia (Yuh, 1995). This toxic effect has not been observed in clinical trials in humans, but until long-term pharmacological surveillance data are available, the patient should be monitored periodically for the possible appearance of anemia and leukopenia.

In animal models, LEF has severe teratogenic effects and increases the risk of fetal death (Arava, 1999, Brent, 2001). In a report of 10 women who became pregnant during treatment with LEF, no congenital malformations were found (Chakravarty, 2003). As its safety in humans is unknown, contraceptive measures are recommended before beginning treatment, not only in women of childbearing age, but also in men, due to the possibility of teratogenic effects caused by the paternal route. If pregnancy occurs or if a man wishes to have children, the drug should be discontinued immediately, and the patient should be treated with 8 g of cholestyramine, three times a day, for 11 days. The same treatment should be followed in case of accidental pregnancies, and the patient should be tested until plasma levels of LEF are below 0.02 mg/l in two consecutive tests conducted 2 weeks apart (Product information sheet).

Because it is potentially immunosuppressive, it is assumed to promote or exacerbate infection, but to date no serious infections during clinical use have been reported. Due to its potential immunosuppressive effect, and in the absence of safety and efficacy studies on the concurrent use of LEF and live vaccines, vaccination is not advisable during treatment with this drug.

Most of the adverse effects of LEF are mild and transitory (Van Riel- 2004). Its safety profile is satisfactory and predictable, and new side effects do not usually present with continued treatment (Kalden, 2003, Smolen, 2004).

In 3 large phase III clinical trials [US 301: N=482 (Strand, 1999), MN 301: N=358 (Smolen, 1999) and MN 302: N=302 (Emery, 2000)], LEF showed similar efficacy and tolerability to MTX and SSZ, with a safety profile that was superior to placebo. In an extensive literature review that included the evaluation of previous meta-analyses and trials, the same conclusions were obtained about the safety profile of LEF after 5 years of treatment (Li, 2004).

The incidence of adverse effects is similar in studies of phase II and III clinical trials comparing LEF, MTX and SSZ (Cannon, 2004a)

The safety of LEF has been compared with that of the biologic agents ETN and IFX, finding a similar incidence of liver side effects and a lower incidence of demyelinating diseases and lymphomas (Cannon, 2004b).

With current experience, the combination of LEF and ADA appears to be efficacious and safe, as does the combination of LEF with ANK or ETN based on provisional data (Kaltwasser, 2005), although greater clinical experience is needed.

Methotrexate (MTX)

Adverse effects. **At the doses commonly used in rheumatic diseases, most of the side effects observed with MTX, such as gastrointestinal, mucocutaneous or neurological disturbances, are not serious. The most important adverse effects are pulmonary, hepatic, and hematological toxicity. Some of these effects (stomatitis, nausea, myelosuppression) are dose-dependent and can be prevented with folate treatment. However, the folates do not prevent pulmonary and hepatic toxicity (Goodman, 1994).**

Monitoring. **Before beginning treatment, a complete blood count, liver and kidney biochemistry, serum albumin and chest X-ray should be obtained. If pre-existing liver disease or exposure to liver toxins is suspected, a liver biopsy should be performed before treatment begins. CBC and liver and kidney biochemistry should be obtained every 2 weeks while the dose is being adjusted, and every 4-12 weeks thereafter. Liver biopsy should be considered if the liver biochemistry is persistently abnormal (transaminases 2-3 times more than the upper limit of the normal range) and cannot be attributed to other causes. Other non-routine studies are indicated if symptoms suggestive of specific complications appear (e.g., blood gas analysis and chest X-ray if pneumonia is suspected). [5, D]**

Contraindications.- **Hypersensitivity to MTX or one of its excipients, pregnancy and breastfeeding, alcoholic liver disease, chronic liver disease, alcoholism, hepatic insufficiency if the bilirubin level is greater than 5 mg/dl (85.5 µmol/l), clinical immunodeficiency syndromes or immunodeficiency syndromes confirmed by tests, severe renal insufficiency (creatinine clearance with values below 20 ml/min), pre-existing blood dyscrasia, marked anemia, leukopenia, thrombocytopenia. Relative contraindications are renal failure, chronic pulmonary disease, and active infection not associated with Felty's syndrome.**

VI.1.10. Adverse effects of methotrexate

VI.1.10.a. Most frequent adverse effects

The most frequent side effects are gastrointestinal changes, stomatitis, macular rash predominantly in the limbs, alopecia, fever, and central nervous system symptoms like cephalea, exhaustion and difficulty in concentration.

- Gastrointestinal changes

Some 60% of patients have gastrointestinal toxicity (stomatitis, nausea, vomiting, dyspepsia, abdominal pain, indigestion, diarrhea, anorexia, or weight loss) (McKendry, 1997). These effects are generally reversible by reducing the drug dosage, administering it at night, or changing from the oral to the parenteral route of administration (O´Dell, 1997). They can be prevented and treated with folic acid supplements. Stomatitis is more frequent with higher doses. Studies of whether folate treatment can prevent these effects have yielded conflicting results, but canker sores do improve with this treatment (Ortiz, 1998; van Ede, 2001).

- Neurotoxicity

Neurotoxicity is more frequent at high doses (more than $1g/m^2$). It may manifest as depression, confusion, memory loss, somnolence, cephalea, fatigue or malaise.

Gastrointestinal effects and central nervous system manifestations such as arthromyalgias and fever often appear 24-48 hours after administration of MTX (McKendry, 1997). These "post-dose" effects are the second most frequent reason for stopping MTX treatment (Halla, 1994b).

VI.1.10.b. Pulmonary toxicity

The non-infectious pulmonary complication most frequently associated with MTX is acute interstitial pneumonitis. Other complications that have been described are: pulmonary fibrosis, nodulosis, bronchitis with bronchial hyperreactivity, bronchiolitis obliterans organizing pneumonia, pulmonary edema, pleuritis and pleural effusion (Rosenow, 1992; Cannon, 1997), although in many cases it is not clear if these manifestations, which are less frequent, are due to the drug or to RA (Dawson, 2002).

Mortality in pneumonitis is estimated at around 20% (Imokawa, 2000; Kinder, 2005). Because it presents with fever, eosinophilia, increased CD4 (+) BAL T lymphocytes and pulmonary infiltration by mononuclear cells with granulomatous inflammation, it is thought to be due to hypersensitivity; however, there are cases in which the drug has been reintroduced without recurrence of the pneumonitis, which suggests an idiosyncratic reaction (Barrera, 1994).

Most cases occur in the first 2 years of treatment. Patients with previous pulmonary disease have a higher risk of pneumonitis (Imokawa, 2000; Alarcón, 1997; Golden, 1995). It is characterized by acute or sub-acute onset of dysnea, often with cough and fever, crepitant rales, hypoxia, eosinophilia and pulmonary infiltrates (most often diffuse and bilateral) (Kremer, 1997; Saravanan, 2006). The utility of lung function tests has not been well established (Cottin, 1996; Saravanan, 2006). There is typically a restrictive pattern with reduced lung diffusion capacity (DLCO) (Lynch, 1997). High resolution CT scan usually reveals patchy ground-glass areas with centrilobular nodules and lymphadenopathy (Kim, 2006).

There is no pathognomonic test or finding for this disease. Useful diagnostic criteria have been published, especially in comparing patients in clinical studies (Searles, 1987; McKendry, 1989) The decision to perform invasive studies will depend on the data supporting the diagnosis and the patient's clinical situation. BAL and transbronchial biopsy may be more useful to rule out infections. An open biopsy is often necessary to establish the diagnosis. Treatment consists basically of withdrawing MTX, administering corticosteroids and managing respiratory failure. Given the long half-life of the drug, the concomitant use of folinic acid may be considered (Saravanan, 2004; Saravanan, 2006).

VI.1.10.c. Liver toxicity

MTX can induce a variety of histological change including fibrosis. However, while an increase in transaminases is frequent (Songsiridej, 1990), fibrosis rarely progresses to cirrhosis, even with cumulative MTX doses higher than 5 g (West, 1997). No relation has been established with folate depletion, but supplements with folic or folinic acid reduce the incidence of elevated transaminases (van Ede, 2001). The main risk factors are: diabetes mellitus, alcoholism, obesity, fatty liver, chronic hepatitis B or C virus or other liver disease, age over 60 years, kidney failure, concurrent treatment with NSAIDs, and associated systemic disease (Erickson, 1995; Walker, 1993; O´Dell, 1997). It has been suggested that patients with alpha1-antitrypsin deficiency are more susceptible (O´Dell, 1997). Liver toxicity is reduced by using low doses and administering the drug weekly (Sznol, 1987). Experience with RA has shown that few alterations are seen in serial liver biopsies if the MTX dose is reduced when there are changes in transaminases and serum albumin (Kremer, 1995; Kremer, 1996; Ros, 2002).

Liver biopsy before treatment should be evaluated in patients with a history of excessive alcohol intake, persistent elevation of transaminases or previous liver disease (Kremer, 1992; Kremer, 1994). Treatment is contraindicated if the liver biopsy shows marked fibrosis or cirrhosis (Roegnick stages class III-b or IV). Discontinuation of treatment should also be evaluated in patients who refuse liver biopsy and who have persistent alterations in liver function tests (Kremer, 1994).

Transaminases and albumin should be monitored every 4-12 weeks. Monitoring should be more frequent when other potentially hepatotoxic drugs are associated..

VI.1.10.d. Hematological toxicity

Medullar toxicity is in most cases dose-dependent and responds to the administration of folates. The most frequent manifestations, at the doses used in the treatment of RA, are leukopenia, thrombopenia and macrocytic anemia, which are usually mild to moderate and improve on reducing the dose (Weinblatt, 1989), but severe pancytopenia may also occur (Gutiérrez-Ureña, 1996). Treatment of pancytopenia consists of administering folinic acid and supportive treatment (steroids, transfusions, antibiotics and hematopoietic stimulation factors) (McKendry, 1997). Probable risk factors are considered to be folate deficiency and macrocytosis (Al-Awadhi, 1993), concomitant treatment with other antifolate drugs like SSZ (Morgan, 1993) or trimetropin-sulfametoxazol, concurrent viral infections (Naides, 1995), advanced age, and kidney failure (Al-Awadhi, 1993, Lim, 2005).

VI.1.10.e. Other adverse effects of methotrexate

- Infections

The risk of infections with MTX is not well established. In a publication summarizing the results of various studies, 121 events were observed in 1,700 patient-years, but about 50% of the cases were receiving concomitant treatment with corticosteroids. Most of the infections were non-serious (viral and bacterial) upper respiratory tract infections, herpes zoster, urinary tract infections, and cellulitis (Kanik, 1997). Cases of opportunistic infections have also been published, in which concomitant treatment with steroids was also frequent (Weinblatt, 1996; LeMense, 1994). Vaccination against influenza and pneumococcus is recommended (Gluck, 2006), although MTX may decrease the immune response to vaccines (Kapetanovic, 2006).

- Neoplasias

No clear association between MTX and cancer has been demonstrated (Bologna, 1997). Various cases of B cell lymphomas have been published, often with Epstein Barr virus, which in some patients remitted when MTX was suspended (Mariette, 2002). However, these cases represent a very small number, and it has not been shown that the total risk of lymphomas is increased in RA patients being treated with this drug (Baecklund, 2006).

- Nodulosis

The development or increase, in number or size, of rheumatoid nodules (nodulosis) has been associated with MTX treatment (Kersten, 1992; Karam, 1994), even when the disease is well controlled. It has been suggested that this is due to an increase in adenosine which promotes their formation (Merrill, 1997). The opposite effect has also been seen: a decrease in nodules with this drug.

- Osteopathy

At high doses, MTX produces increased bone reabsorption and decreased bone formation (Pfeilschifter, 2000). This effect has not been observed with the doses used in the treatment of RA (Rozin, 2003).

Gold salts: oral (AUR) and injectable (IG)

***Adverse effects*. The most clinically relevant side effects are hematological and renal toxicity. Both are more frequent with intramuscular treatment and require careful clinical monitoring and immediate suspension of treatment to avoid irreversible sequelae. The most frequent side effects are: dermatitis, stomatitis, transitory hematuria and moderate proteinuria.**

***Monitoring*. CBC, creatinine and urinalysis every 4 weeks during the first 6 months and every 3 months thereafter. If proteinuria is detected, a 24-hour urine quantification should be obtained. If proteinuria exceeds 500 mg/24 h, treatment should be discontinued until it disappears or falls below 200 mg/24 h, after which it may be renewed. If proteinuria is severe (above 1 g/24 h), treatment should be discontinued permanently [5, D]**

***Contraindications*.- Allergy to sodium aurothiomalate and to gold salts or other heavy metals or excipients, severe hepatic or renal disorders, blood dyscrasia, history of agranulocytosis, bleeding diathesis, and, generally, in patients with a history of disorders of the blood or bone marrow.**

VI.1.11. Adverse effects of gold salts

VI.1.11.a. Most frequent adverse effects

The most frequent adverse effects are: dermatitis, stomatitis, transitory hematuria and moderate proteinuria (van Jaarsveld, 2000b). These effects are less common with oral gold (Auranofin); however, diarrhea is much more likely with Auranofin (Abruzzo, 1980). The most important side effects are hematological and renal.

Dermatitis and stomatitis occur in up to 60% of patients (Klinkhoff, 1995). They are less frequent with aurothioglucose than with aurothiomalate (van Roon, 2005; Klinkhoff, 2005). Cumulative doses higher than 10 g may result in a grayish-blue coloration of the skin exposed to the sun, which is called chrisiasis.

VI.1.11.b. Hematological complications

The three main hematological complications are: thrombopenia, agranulocytosis and pancytopenia. Thrombopenia occurs in 1-3%. It may occur suddenly or progressively; treatment should be suspended if the platelet count is less than 100,000 platelets/mm^3. It is generally due to the immune destruction of platelets, while bone marrow is normal (von dem Borne, 1986). Agranulocytosis is infrequent (Lockie, 1985), and the most serious complication is severe pancytopenia or bone marrow aplasia (occurring in < 0.5%) (Yan, 1990). Eosinophilia may be an early warning of hypersensitivity to gold.

VI.1.11.c. Nephrotoxicity

Gold salts may produce transitory proteinuria, microhematuria and nephrotic syndrome. Kidney biopsy usually shows membranous glomerulonephritis, although nephritis with minimal changes may sometimes occur (Hall, 1987). Treatment should be discontinued in case of nephrotic syndrome. Proteinuria requires an average of 11 months to resolve, and may even take 2-3 years. (Hall, 1987). Acute kidney failure may occasionally occur, which is possibly secondary to acute tubular necrosis (Hall, 1988b; Robbins, 1980).

Mucocutaneous toxicity, proteinuria and thrombopenia are associated with HLA DR3 (Wooley, 1980).

VI.1.11.d. Other adverse effects of gold salts

Altered sense of taste (dysgeusia, metallic taste), liver toxicity (jaundice with or without intrahepatic cholestasis) (Edelman, 1983), pulmonary toxicity (hypersensitivity pneumonitis, bronchiolitis obliterans) (Tomioka, 1997; Blancas, 1998), gastrointestinal toxicity (diarrhea, especially with auranofin -47%-, toxic enterocolitis) (Fam, 1980), neurological toxicity (peripheral neuropathy, cranial neuropathy, Guillain-Barré syndrome, encephalopathy) (Fam, 1984), and gold deposits in the cornea or conjunctiva. There are two types of post-injection reaction: a vasomotor type with rapid onset (nitroid reaction) with weakness, nausea, dizziness, vomiting, sweating and facial flushing (Ho, 1997; Arthur, 2001), which is more frequent with concomitant treatment with ACE inhibitors (Nixon, 2006), and another non-vasomotor type, consisting of transitory arthralgias and/or arthritis, fatigue and malaise, which begins hours afterwards and lasts for 1-2 days (Halla, 1977).

Sulfasalazine (SSZ)

Adverse reactions. **The most frequent sites of adverse reactions (33%) to sulfasalazine are the central nervous system and gastrointestinal tract. These are usually mild and do not require discontinuation of treatment. Other less frequent adverse effects are hematological and hepatic toxicity.**

***Monitoring*. CBC and liver biochemistry every 4 weeks during the first 3 months and every 3 months thereafter. [5, D]**

***Contraindications*.- Hypersensitivity to the active ingredient, its metabolites, or an excipient; hypersensitivity to sulfonamides or salicylates; intermittent acute porphyria, intestinal obstruction, or obstruction of the urinary tract.**

VI.1.12. Adverse effects to sulfasalazine

SSZ is a widely used drug in RA, both in monotherapy and in combination treatment with other DMARDs. As a DMARD of first choice, it is similar to MTX in acceptability for British rheumatologists (Jobanputra, 2004). Most of the side effects appear in the first months of treatment, and their incidence declines with continued use.

VI.1.12.a. Most frequent adverse reactions

The most frequent adverse reactions to SSZ (present in 33% of patients) occur in the central nervous system (cephalea, vertigo) and gastrointestinal tract (anorexia, nausea, vomiting, abdominal pain). They are usually mild and do not require discontinuation of treatment (Amos, 1986; Williams, 1988; Farr, 1986).

VI.1.12.b. Hematological toxicity

Hematological toxicity occurs principally in the hematopoietic system: macrocytosis (9%), leukopenia (3.7%), neutropenia (2%), and megaloblastic anemia (<1%). Isolated episodes of aplastic anemia, agranulocytosis, thrombocytopenia, and leukocytosis have been reported. Hematological toxicity may present at any time during treatment, although it usually appears early (between the 5th and 12th week), except for macrocytosis and megaloblastic anemia, which may present after prolonged periods of treatment (Drugex, 1999).

SSZ is a powerful non-competitive inhibitor of the reduced folate carrier, which may cause a marked loss of MTX efficacy when the two drugs are administered together. Folate supplementation should be added when these two drugs are used in combination therapies (Jansen, 2004).

The effects are reversible if the drug is discontinued and treatment is administered (Guillemin, 1989; Canvin, 1993); in the case of megaloblastic anemia treatment consists of folic acid (5-10 mg/day).

Glucose-6 phosphate dehydrogenase (G6-PD) deficiency may produce hemolytic anemia (ACR Committee, 1996).

VI.1.12.c. Liver toxicity

Liver toxicity manifests as acute, febrile episodes, with pruritic skin lesions, lymphadenopathy, hepatomegaly, lymphocytosis, eosinophilia, and elevated transaminases Vyse, 1992; Losek, 1981; Williams, 1979; Boyer, 1989; Marinos, 1992; Michel, 2005). This is a serious situation that can lead to death (Marinos, 1992; Pears, 1989), with mortality estimated at 10% (Michel, 2005). In the pathogenesis of this process, called DRESS syndrome, the implication of an immunoallergic mechanism is postulated, precipitated by an infection mediated by the human herpesvirus 6 (Michel, 2005). Withdrawal of medication is not sufficient to prevent the patient's deterioration, and corticosteroids are needed.

VI.1.12.d. Other adverse effects of sulfasalazine

Continued treatment with SSZ has been associated with lack of fertility in men (spermiogram abnormalities in 86% and oligospermia in 72%) (Birnie, 1981). These abnormalities are reversible after suspending treatment for 3 months (Toovey, 1981). It is usually safe in pregnancy and can be used with caution during breastfeeding (Janssen, 2000).

There have been isolated reports of cases of altered taste (ageusia and metallic taste), skin abnormalities (drug-induced exanthema, pruritic maculopapular rashes, Stevens-Johnson syndrome, toxic epidermic necrolysis), pulmonary disorders (eosinophilic pneumonia, fibrosing alveolitis, subacute hypersensitivity pneumonitis), neurological disorders (motor and sensory neuropathy, aseptic meningitis), muscular disorders (myopathy), and kidney disorders (hemolytic-uremic syndrome, nephrotic syndrome, bilateral kidney stones).

The existence of studies relating the appearance of adverse effects with SSZ metabolization, primarily with slow acetylation but also with glucuronization, leads to the suspicion that the clinical impression that some ethnic groups have more adverse effects may be correct. SR 13 was up-dated to know the susceptibility of the Spanish population to the adverse effects of SSZ; it was concluded that:

- There is no evidence that Spaniards are more susceptible to suffering adverse effects from SSZ. In any event, doses exceeding 2 g/day should be avoided in patients who are slow acetylators or who suffer folate-deficiency anemia **[4b].**

VI.1.12.e. Adverse effects in combinations with other DMARDs

Clinical trials generally confirm that the combination with other DMARDs is well tolerated (Plosker, 2005). However, some studies show increased side effects that are more important in combinations with MTX than in the respective monotherapies. The combination of SSZ with MTX produces a persistent increase in plasma homocysteine concentration, higher than observed with the use of MTX alone and not observed with SSZ in monotherapy. This increase is related with the mutation of the C677T gene of the methylenetetrahydrofolate reductase enzyme and with greater gastrointestinal toxicity, although it does not interfere with clinical efficacy (Haagsma, 1999).

Other studies comparing triple therapy (SSZ, MTX and HCQ) with double therapy (SSZ and MTX or SSZ and HCQ) (O'Dell, 2002), or triple therapy (SSZ, MTX and HCQ) with double therapy (SSZ and HCQ) and with MTX alone (O'Dell, 1996) do not show significant differences in the incidence of adverse effects requiring discontinuation of treatment. Likewise, well known studies like COBRA, which compare the administration of SSZ plus decreasing doses of

prednisolone and MTX with SSZ in monotherapy in recent-onset RA, during 53 weeks (Boers-1997) and FIN-RACo, also conducted in RA of less than 2 years' evolution, treated with SSZ, MTX, HCQ and prednisolone simultaneously versus SSZ with and without prednisolone (Mottonen, 1999), showed a similar frequency of side effects in the different groups.

Anakinra (ANK)

***Adverse effects*. The most frequent adverse effects are injection site reactions. The risk of serious infections is higher in patients treated with this interleukin-1 antagonist. (Fleischmann, 2003). In some patients there is a slight reduction in the leukocyte, neutrophil and platelet count, with isolated cases of neutropenia (Tutuncu, 2005). The combination with ETN increases the risk of infections and neutropenia (Genovese, 2004).**

***Monitoring*. Monitoring of infections. Previous CBC and then every month for 3 months, and every 4 months thereafter for a period of up to one year (Tutuncu, 2005). [5, D]**

***Contraindications*.- Patients with hypersensitivity to proteins of *Escherichia coli* or any component of ANK. Severe renal insufficiency (clearance <30 ml/minute). Chronic or active infection. Not recommended in combination with TNF inhibitors. Administration of live vaccines is not recommended. Its safety in pregnancy and breastfeeding has not been established, nor has its safety in patients with lymphoma, lymphoproliferative diseases or solid tumors (Furst, 2005).**

VI.1.13. Adverse effects of anakinra

Various clinical trials have documented the safety of ANK. Data have recently been published on an open-label expanded clinical trial of 3 years' duration (Fleischmann, 2006), and of a multicenter study evaluating the safety of ANK in clinical practice during 2 years (den Broeder, 2006). In both studies the safety profile is similar to that found in previous clinical trials. Longer-term data are needed.

Injection site reactions are frequent and are generally mild or moderate. They typically occur in the first month of treatment and their intensity and frequency decrease with continued treatment, although in about 5% of cases treatment needs to be discontinued (Bresnihan, 1998; Fleischmann, 2003, Furst, 2005).

An increase in serious infections has been documented. A higher frequency of tuberculosis and opportunistic infections has not been found.

The risk of lymphoma is higher (Fleischmann, 2006), but this is comparable to the increase observed in RA patients in general (Baecklund, 1998; Wolfe, 2004b).

The risk of infections increases when it is combined with anti-TNFs (Genovese, 2004).

Neutropenia occurs in some patients, which is more frequent if it is combined with anti-TNFs (Genovese, 2004).

No differences have been found in the antibody response with tetanus and pertussis vaccination in patients treated with ANK. There are no data on other vaccinations. Live vaccines are not recommended (Furst, 2005).

None of the side effects observed with the anti-TNFs, like demyelinating disease or heart failure, have been observed to date (Tornero, 2010; Rodríguez-Valverde, 2004).

Abatacept (ABT)

***Adverse effects*.- Infusion reactions (uncommon), slight increase in the risk of developing infections (increased and more severe in patients with COPD). These are preliminary data that should be confirmed in post-authorization studies and in studies with a longer follow-up period.**

***Monitoring*. Given the current lack of evidence, no specific monitoring is recommended, although the usual recommendations for testing in RA patients should be followed, or the recommendations established for other DMARDs in patients who use any of the classic DMARDs at the same time. [5, D]**

***Contraindications*.- ABT should not be administered in patients with allergy to the active ingredient or excipients, or in cases of severe uncontrolled infections. Administration of live vaccines is not recommended in patients receiving ABT.**

Abatacept (CTLA-4-Ig) is a fusion protein that consists of the extracellular domain of human CTLA-4 and the Fc fragment of human IgG1. It binds competitively and with great affinity to CD80/86, preventing these molecules from binding with CD28, thus preventing T-lymphocyte activation. ABT has proven clinical efficacy compared with placebo in patients with insufficient response to MTX and with insufficient response to anti-TNF (Kremer, 2006). ABT can be used in monotherapy or combined with other classic DMARDs (Weinblatt, 2006b). The combination of ABT with the anti-TNFs is not recommended.

VI.1.14. Adverse effects of abatacept

Because it has only recently been approved, most of the adverse effects currently attributed to ABT are known from clinical trials. There are no post-marketing safety data (Genovese, 2005; Kremer 2003; Vital, 2006).

As administration is intravenous, infusion reactions may occur. These are generally uncommon and of mild to moderate intensity; therefore, extreme caution should be exercised during therapy with ABT.

Cases of TBC have been detected in patients receiving ABT (Westhovens 2009a). However, the risk of reactivation of latent TBC or developing new TBC is unknown (Furst 2011). Therefore, TBC screening should be performed in all patients starting ABT, according to national anti-TNF guidelines. Although CTs revealed an increase in the number of severe infections compared with placebo, a recent meta-analysis on the use of ABT (12 months) did not detect an association (Salliot 2009). The risk of infections and severe adverse effects seems to be particularly high in patients with RA and COPD (Furst 2011).

ABT has not been associated with an increased risk of lymphoma or solid tumors (Simon 2009).

The decreased response to influenza and pneumcoccal vaccines in patients with RA who are taking ABT is similar to that observed in those taking MTX (Pham 2009).

Although an uncommon finding, patients can develop anti-ABT antibodies. However, the presence of these antibodies does not seem to be accompanied by increased toxicity or reduced clinical efficacy of ABT (Westhovens 2009 b).

Rituximab (RTX)

***Adverse effects*. Frequent infusion reactions, especially with the first infusion. Slight increase in the risk of developing infections, with no increase in the risk of opportunistic infections. Possibility of fatal reactivation of hepatitis B.**

***Monitoring*. Before starting therapy the presence of chronic hepatitis, especially hepatitis B, should be ruled out, and immunoglobulin levels should be determined. In cases of re-treatment, immunoglobulin levels should be determined again. The usual recommendations for testing when monitoring RA patients, or those recommended for other DMARDs in patients who use classic DMARDs simultaneously, should be followed. [5, D]**

***Contraindications*.- Allergy to the active ingredient or excipient. RTX should not be administered in patients with suspected active infection, severe heart failure (NYHA class IV) or severe uncontrolled heart disease. Administration of live vaccines is not recommended.**

Rituximab is a chimeric antiCD20 monoclonal antibody which acts by depleting the B lymphocytes that express CD20 on their surface. RTX (in different treatment modalities, either alone or associated with steroid use) has proven clinical efficacy compared with placebo in patients with insufficient response to MTX or in those with insufficient response to anti-TNF. The currently recommended dose of RTX is generally 2 infusions of 1 g, administered 2 weeks apart, if there are no contraindications, preceded by 100 mg of IV methylprednisolone. RTX can be used alone, or preferably in combination with MTX; it is not currently recommended in combination with CTX in RA patients. RTX is not currently recommended in combination with the anti-TNFs. RTX has been approved by the European Medicines Agency for use in patients with active RA who have an insufficient response to at least one anti-TNF. There are no data from controlled studies on the efficacy and safety of re-treatment with RTX in RA patients.

VI.1.15. Adverse effects of rituximab

Infusion reactions during administration of RTX are the most common adverse event, especially with the first infusion (Cohen, 2006; Emery, 2006; Higashida, 2005). However, its safety profile is better established given the extensive experience with RTX in non-Hodgkin's lymphoma (Rastetter, 2004; Edwards, 2004; Hainsworth, 2003).

Infusion reactions during RTX administration are frequent, especially with the first infusion. The use of methylprednisolone (100 mg IV) before RTX infusion reduces the incidence and severity of infusion reactions. Patients may develop human anti-chimeric antibodies (HACAs) although their clinical importance is not well established. A slight increase in the risk of developing infections has been observed, but no increase has been seen in the risk of opportunistic infections. At present, contrary to other biologic agents, TB screening is not recommended in all patients before receiving RTX. However, based on experience with

lymphoma, chronic hepatitis – especially hepatitis B virus – should be ruled out due to the possibility of a fatal reactivation of this liver disease.

Most data on adverse effects attributable to RTX are from CTs (Cohen, 2006; Emery, 2006; Higashida, 2005). However, owing to the broad experience accumulated with RTX in non-Hodgkin lymphoma, its safety profile is well established (Rastteter, 2004; Edwards, 2004; Hainsworth, 2003).

To date, it has not been possible to demonstrate an increased risk of TBC with RTX. However, it must be remembered that patients in most studies underwent screening and prophylactic treatment, as with TNF antagonists (Furst 2011).

There exists a small increased risk of bacterial infections, but not severe or opportunistic infections (van Vollenhoven 2010; Genovese 2009).

Screening for TBC is currently recommended for all patients before starting therapy with RTX (Gomez Reino 2011). Similarly, and based on experience in lymphoma, the presence of chronic hepatitis should be ruled out, especially HBV, owing to the possibility of a fatal reactivation of liver disease (Evens 2010). Outcome in patients with HCV infection remains unclear (Saadoun 2008; Sene 2009).

There does not appear to be any increased risk of solid tumor or demyelinating disease (Furst 2011).

There does seem to be a reduction in the humoral response, at least to influenza vaccine (Gelinck 2007; Oren 2008).

Patients can develop anti-chimeric antibodies (HACAs), although the clinical relevance of this observation has not been well established.

Tocilizumab (TCZ)

Adverse effects: Upper respiratory tract infections are very common. Hypercholesterolemia, herpes infection, increased transaminases, arterial hypertension, and neutropenia are common. Hypertriglyceridemia and increased total bilirubin are uncommon.

***Monitorización*.- Before starting therapy the presence of: active infection (including TBC), cancer, heart failure, enfermedad desmielinizante, comorbilidad relevante y descartar contatos recientes con pacientes con TBC, should be ruled out. Hemograma, bioquímica general, serología VHB y VHC, Rx de tórax, Mantoux y Booster al inicio del tratamiento. Posteriormente se recomienda hemograma y bioquímica general conperfil lipidico mensual durante los primeroes tres meses y posteriormente cada 3-4 meses**

Contraindications.- Allergy to the active ingredient or excipients; severe and active infections.

VI.1.16. Adverse effects of tocilizumab

Infusion reactions are very uncommon, although isolated cases of erythroderma have been reported (Nakamura 2009a). Neutropenia is also a common adverse event (Nagamine 2009).

TCZ is associated with a greater risk of bacterial infections (Smolen 2008), and opportunistic infections have been reported (Nakamura 2009b). There have also been reports of isolated cases of herpes zoster infection, although no association has been established (Furst 2011).

The cardiovascular risk of TCZ is currently unknown; however, 5-year results have not shown that it is increasing (Nishimoto 2009). Although cases of arterial hypertension and acute cardiovascular accident (ACVA) have been reported, a study with 1.5 years of follow-up did not find increased frequency of ACVA (Furst 2011). TCZ can lead to dyslipidemia (increased total and LDL cholesterol and triglycerides) in up to 20-30% of patients (Smolen 2008); therefore, lipid profile should be monitored 1-2 months after starting treatment and every 6 months thereafter (Furst 2011).

There is no increased risk of solid tumor with TCZ (Maini 2006; Jones 2010).

According to the Summary of Product Characteristics of TCZ, there is a potential risk of demyelinating disease, although it is not clear whether this TCZ really increases the risk of onset of this condition (Gomez Reino 2010).

Use of TCZ can lead to increased liver enzyme levels, although there is no documented evidence of liver damage or failure (Genovese 2008). There may be isolated increases in bilirubin (mainly indirect) that are not associated with other liver abnormalities. There have also been reports of diverticulitis, intestinal perforation, and peritonitis (Roll 2010). Concomitant corticosteroids and non-steroidal anti-inflammatory drugs can increase the risk of these events. TCZ should be administered with caution in patients with a history of intestinal ulcer or diverticulitis (Furst 2011).

Cytopenia may be common as a result of a pharmacodynamic effect (Gomez Reino 2011). A high percentage of patients receiving TCZ present decreased neutrophil counts compared with those receiving placebo. These changes tend to occur at the beginning of treatment and are usually transitory (Furst 2011).

Finally, vaccination against influenza and pneumococci seems to be effective in patients receiving TCZ (Furst 2011).

Table 26. DMARD monitoring, safety and recommendations
Modified from: White, 2002; Rodríguez-Valverde, 2004.

Drug	Previous tests	Periodic tests	Most frequent adverse effects	Special recommendations
METHOTREXATE	✓ CBC ✓ Liver and kidney biochemistry ✓ Albumin ✓ Chest x-ray	✓ CBC and liver-kidney biochemistry every 2 weeks while adjusting the dose, then every 4-12 weeks ✓ Liver biopsy if there is important and persistent alteration of the transaminases ✓ Blood gases and chest X-ray if pneumonitis is suspected	✓ Gastrointestinal (60%) ✓ Liver toxicity ✓ Pulmonary toxicity ✓ Hematological toxicity (myelosuppression) ✓ Rash or mouth ulcers ✓ Neurotoxicity	✓ Avoid ingestion of alcoholic beverages ✓ Annual influenza vaccination ✓ Folic acid the day after receiving methotrexate (prevents a large part of toxicity) ✓ Contraindicated in pregnancy, alcoholism, hepatitis, and cirrhosis
LEFLUNOMIDE	✓ CBC ✓ General biochemistry ✓ BP	✓ Liver enzymes every 2-4 weeks the first 6 months, and every 8 weeks thereafter (reduce dose if transaminases are elevated) ✓ If elevated transaminases persist, perform liver biopsy	✓ Gastrointestinal: diarrhea (17%), nausea (9%), pain (6%) ✓ Upper respiratory infections (15%), and bronchitis (7%) ✓ Liver toxicity (5%) ✓ Mild hypertension (10%), cephalea (7%) ✓ Urticaria, eczema, pruritus (10%)	✓ Avoid ingestion of alcoholic beverages ✓ Strict control of BP on starting treatment, especially if there is baseline arterial hypertension ✓ Contraindicated in immune deficiency diseases, dysplasias and serious infections, and in kidney or liver failure
GOLD SALTS	✓ CBC ✓ General biochemistry ✓ Urinalysis ✓ Liver profile	✓ CBC, creatinine and proteinuria every month during the first 6 months, then every 3 months thereafter	✓ Hematological toxicity (1-3%) ✓ Kidney toxicity ✓ Dermatitis and stomatitis (60%) ✓ Diarrhea (frequent when taken orally)	✓ With proteinuria >500 mg/24 h, discontinue until it falls to <200 mg/24 h ✓ With proteinuria >1,000 mg/24 h, discontinue treatment definitively ✓ Serious kidney or liver alterations

Drug	Previous tests	Periodic tests	Most frequent adverse effects	Special recommendations
AZATHIOPRINE	✓ CBC ✓ Creatinine ✓ General biochemistry	✓ CBC every 1-2 weeks while dose is being adjusted, every 1-3 months thereafter ✓ Liver profile every 6-8 weeks	✓ Dose-dependent hematological alterations: leukopenia (25%), thrombocytopenia (5%) ✓ Gastrointestinal (20%): nausea, loss of appetite, diarrhea ✓ Infections (10%) ✓ Liver toxicity (5%)	✓ Take after food to reduce nausea ✓ Influenza and pneumococcal vaccination ✓ Interacts with allopurinol ✓ Reduce dosage in kidney failure ✓ Contraindicated in known cancer
CYCLOSPORIN	✓ CBC ✓ Biochemistry ✓ Liver-kidney profile ✓ Urinalysis ✓ BP	✓ BP, kidney profile and electrolytes every 2 weeks for 3 months, and every month thereafter ✓ If there are alterations, weekly controls until stabilized.	✓ Kidney toxicity (dose-dependent) ✓ Hypertension (dose dependent) ✓ Gingival hypertrophy ✓ Gastrointestinal ✓ Liver toxicity ✓ Cephalea, confusion, fatigue, tremor	✓ Avoid ingesting grapes and grape juice 1 hour before and 1 hour after treatment ✓ Annual influenza vaccination ✓ If AHT is detected, the treatment of choice is nifedipine ✓ Contraindicated in current cancer, uncontrolled AHT, immune deficiency or chronic kidney disease
ANTIMALARIALS	✓ Ophthalmological examination if over age 40 years and/or with history of eye disease	✓ Ophthalmological checkup every 6-12 months. More frequently if in treatment more than 10 years or in case of kidney failure.	✓ Retinopathy, photophobia ✓ Neuromuscular toxicity ✓ Photosensitivity ✓ Pruriginous rash and dermatitis ✓ Gastrointestinal	✓ Gastrointestinal tolerance improves if administered with food ✓ Use sun glasses and sun protection creams ✓ Contraindicated in retinopathies and visual field deterioration

Drug	Previous tests	Periodic tests	Most frequent adverse effects	Special recommendations
D-PENICILLAMINE	✓ CBC ✓ Kidney profile ✓ Urinalysis	✓ CBC, kidney profile and urinalysis ever 2 weeks until desired dosage is reached, and every 1-3 months thereafter	✓ Gastrointestinal (30%) ✓ Rash or mouth ulcers ✓ Disgeusia (25%) ✓ Kidney involvement (30%), mainly proteinuria ✓ Hematological (leukopenia and thrombopenia)	✓ Take on empty stomach ✓ Do not take drugs or food containing iron, calcium, zinc or antacids for at least 2 hours after taking penicillamine ✓ Contraindicated in kidney disease and blood disorders (leukopenia and thrombopenia)
SULFASALAZINE	✓ CBC ✓ Liver profile	✓ CBC and liver profile every 4 weeks for 3 months, and every 3 months thereafter	✓ Gastrointestinal (33%); ageusia ✓ Cephalea, vertigo (33%) ✓ Hematological toxicity: macrocytosis (9%), leukopenia (4%) ✓ Liver toxicity: DRESS syndrome ✓ Rash or mouth ulcers ✓ Pruritus at beginning of treatment ✓ Infertility in men	✓ Avoid ingestion of iron and antacids for at least 2 hours before and after taking sulfasalazine ✓ Interacts with digoxin ✓ Contraindicated in allergies to salicylates or sulfamides
CYCLOPHOSPHAMIDE	✓ CBC ✓ Liver biochemistry ✓ Urinalysis and sediment	✓ CBC every 1-2 weeks for the first 2-3 months, and every 2-4 weeks thereafter ✓ In IV infusion, CBC beforehand, and repeated 1-2 weeks after each infusion ✓ Liver biochemistry and urinalysis and sediment, monthly	✓ Gonadal toxicity which may be irreversible ✓ Cystitis and bladder cancer ✓ Dose-dependent myelosuppression ✓ Increased risk of lymphomas and some tumors ✓ Gastrointestinal	✓ Contraindicated in pregnancy, chronic or active infection, liver disease, and history of neoplasia ✓ Adjust dose in chronic kidney disease ✓ Contraindicated in association with allopurinol

Drug	Previous tests	Periodic tests	Most frequent adverse effects	Special recommendations
ANTI-TNFs: INFLIXIMAB, ETANARCEPT, ADALIMUMAB	✓ CBC ✓ General biochemistry ✓ Liver serology ✓ Chest X-ray ✓ Mantoux and Booster	✓ CBC and general biochemistry every 4 weeks for the first 4 months, and every 3-4 months thereafter ✓ If receiving TB prophylaxis: CBC and liver profile every 2 weeks for 2 months, and monthly tests thereafter ✓ ANA and DNA every 3 months for the first year, and every 6 months thereafter	✓ Opportunistic and pathogenic infections ✓ TB reactivation ✓ Autoimmune disorders ✓ Not clear whether it increases the incidence of lymphoma ✓ Injection site reactions ✓ Possible worsening of existing heart failure	✓ Annual influenza vaccination and pneumococcal vaccination are recommended before starting treatment. Live vaccines are not advised. ✓ The presence of active, systemic or localized infection is an absolute contraindication for the administration of treatment, especially in TB and hepatitis B ✓ Contraindicated in infections, tumors and heart failure
NEW BIOLOGICS: ANAKINRA	✓ CBC	✓ CBC monthly every 3 months, and every 4 months for 1 year thereafter	✓ Injection site reaction ✓ Increased risk of infections if associated with etanercept ✓ New drug: long-term safety data are lacking	✓ Contraindicated in chronic or active infections ✓ Do not use in association with an anti-TNF ✓ Do not administer with live vaccines ✓ Contraindicated in tumors

Drug	Previous tests	Periodic tests	Most frequent adverse effects	Special recommendations
NEW BIOLOGICS: ABATACEP	✓ Follow usual monitoring for RA patients (evidence for specific recommendations is lacking)	✓ Follow usual recommendations for monitoring RA patients (evidence for specific recommendations is lacking)	✓ Infrequent infusion reactions ✓ Slight risk of infections, mainly in COPD ✓ Some increased risk of lung cancer ✓ New drug: long-term safety data are lacking	✓ Contraindicated in chronic or active infections ✓ Do not administer with live vaccines
NEW BIOLOGICS: RiITUXIMAB	✓ Determine immunoglobulin levels ✓ Liver serology	✓ Follow usual recommendations for monitoring RA patients (evidence for specific recommendations is lacking)	✓ Frequent infusion reactions ✓ Slight risk of infections ✓ Possible fatal reactivation of hepatitis B ✓ New drug: long-term safety data are lacking	✓ Contraindicated in chronic or active infections ✓ Do not administer with live vaccines ✓ Do not administer in case of severe (grade IV) heart failure

Risk management of the use of biologic therapies

Risk management when using any medication is a very important part of pharmacovigilance, which can be defined as the public health activity aimed at identifying, quantifying, evaluating, and preventing the risks of marketed drugs.

More specifically, risk management comprises the set of pharmacovigilance activities and interventions designed to identify, characterize, and prevent or minimize medication risk and to evaluate the effectiveness of these interventions. Risk management is the responsibility of everyone, including regulatory bodies/health authorities, pharmaceutical companies, investigators, and health professionals.

Risks associated with biologics have been identified in recent years. Some of these risks are important, that is, there is evidence of their association with medication. Others are potentially important risks, that is, the risks are suspected although they have not yet been confirmed. It is also important to remember that sufficient information is not available for so-called special situations (eg, pregnancy, breastfeeding).

VI.1.17. Management of the risk of indicating biologic therapy

The risk-benefit balance in the case of a specific patient should be supported by all knowledge available from the time the indication is made.

Monitoring.- Treatment with biologics should be administered by physicians with experience in these drugs and in the management of the diseases for which they are indicated [5, D].

Monitoring.- Professionals should consult the Summary of Product Characteristics of all biologic agents and adhere to their recommendations before administering a drug in clinical practice [5, D].

There is evidence that off-label use can cause more adverse events than the authorized indication. The patient who is to receive the drugs should meet the profile for indication as much as possible (Carmona 2011)

VI.1.18. Management before starting treatment with biologics

These recommendations are based on the evidence presented in the sections on contraindications and adverse events of biologics (see Table 26).

Monitoring.- Any patient about to start treatment with biologics should be evaluated to determine and prevent potential risks. In addition, the patient should be monitored regularly during therapy [5, D].

Before administering the first dose, sufficient information should have been collected on the potential risks for the patient who has been prescribed the medication (eg, concomitant drugs and comorbid conditions). “Regular monitoring” should be adapted to the individual patient’s characteristics and to local departmental organization. At least 1 visit is recommended 1 month after starting treatment and every 1-4 months thereafter, irrespective of the health professional and approach.

Monitoring.- Patients for whom biologic therapy is indicated should be instructed about symptoms warning of a potential risk [5, D].

When a biologic treatment is prescribed, irrespective of the disease involved, the patient should be instructed about the signs/symptoms that should be monitored and how to act if they appear. The patient should be aware of these risks and be able to recognize them, at least the most common ones. Similarly, information should be provided on hygiene and dietary measures that can help to reduce some risks.

Monitoring.- The risks of biologic therapy should be managed by the prescribing physician or by a physician appointed by the prescribing physician; nevertheless, management should involve all health care personnel, including nurses, family doctors, and the hospital pharmacy, as well as the patient. [5, D]

Information provided by the prescribing physician, the attending physician (if different), and the nurse should be consistent; therefore, support must be provided in the form of written information, clearly and accurately defined processes and procedures, brochures, and instruction manuals.

Monitoring.- In the case of a patient who is about to start biologic therapy, the potential existence of active infection should be investigated, since the presence of such an infection is a contraindication for biologic therapy. [2b, B]

Biologic therapy should not be recommended in patients with a history of repeated infections, sepsis, or a high risk of developing infection. Alternatively, the risks and benefits can be assessed and the patient closely monitored. Treatment with biologic therapy should not be started in patients with active, systemic, or localized infection. In this sense, a history of infected joint prosthesis should be appropriately treated before initiation (surgery with complete elimination of the infection and, where indicated, replacement of the infected prosthesis).

Given the increase in the immigrant population and their geographic origin, the possible reactivation of infections that are not common in our region should be evaluated.

Biologic therapy can be started once the infection is resolved.

Monitoring.- The existence of active TBC or recent contact with persons infected by TBC should be ruled out in any patient starting biologic therapy. In addition, the possibility of latent tuberculosis infection should be investigated. Therefore, a history of TBC and recent contact with persons with TBC should be noted in the medical records. A chest x-ray should be performed to rule out active TBC or radiographic signs compatible with a previous tuberculosis infection. A tuberculosis skin test (PPD) should also be performed and repeated (re-test) after 1-2 weeks if the wheal is <5 mm. [2b, B]

A wheal ≥5 mm at 72 hours (PPD or re-test) is considered positive in a patient receiving immunosuppressive therapy. The result should be taken into consideration regardless of previous vaccination against tuberculosis. It is also important to instruct patients about the risk of exposure to persons with active TBC.

Monitoring.- Treatment for latent tuberculosis infection should begin before biologic therapy in the following circumstances: a) recent contact with a patient with documented TBC; b) a history of partially treated TBC; c) positive PPD or re-test; or d) residual lesions on the chest x-ray. The drug of choice for treatment of latent tuberculosis infection is isoniazid (5 mg/kg/d up to a maximum of 300 mg/d) with vitamin B6 supplements for 9 months. [2b, B]

Patients who cannot tolerate isoniazid should receive rifampicin at 10 mg/kg/d (maximum, 600 mg/d) for 4 months. The effectiveness of these recommendations for preventing reactivation of latent TBC is documented (Carmona 2005). Studies with shorter regimens (Ena 2005) and several drugs are emerging, although their efficacy in immunodepressed patients has not yet been confirmed.

Monitoring.- If the patient has received adequate treatment for latent or active TBC infection, neither prophylaxis nor the Mantoux test is necessary. [5, D]

Nevertheless, patients with TBC should be monitored.

Monitoring.- Before initiating biologic therapy, a history of malignant neoplasm should be taken into account. If necessary, tumor biology and behavior should be evaluated, and the risk of recurrence should be discussed with the oncologist and with the patient. Biologic therapy is not recommended in patients with a history of lymphoproliferative disease. [4, C]

In patients with a history of solid tumor, the indication for biologic therapy will be evaluated taking into account risks and benefits.

Monitoring.- The presence of heart failure should be evaluated before beginning biologic therapy. [4, C]

Although available data (TNF antagonists and RTX) are not altogether consistent (see sections on adverse events), patients with mild heart failure should be monitored. Treatment should be suspended if heart failure worsens. Treatment should not be initiated in those patients in NYHA functional class III or IV.

Monitoring.- Biologic therapy should be tailored in patients with underlying interstitial lung disease. [4, C]

The use of biologic therapy in patients with interstitial lung disease may be associated with a risk (albeit poorly studied and defined) of exacerbation and death (Martin 2006, Ostor 2006). In the absence of evidence, biologic therapy should be tailored to the individual patient.

Monitoring.- The presence of cytopenia should be evaluated before initiating biologic therapy. If cytopenia is present, biologic therapy should not be initiated until it has resolved [2b, B].

Monitoring.- The presence of demyelinating disease should be evaluated before initiating biologic therapy. If the patient has a clear history of such processes, then biologic therapy should generally be avoided. [2b, B]

In patients with a history of demyelinating disease, the indication for biologic therapy will be evaluated on an individual basis according to the risks and benefits. However, it should generally be avoided.

Monitoring.- HCV serology testing should be performed and markers for HBV identified. [4, C]

Each case should be treated on an individual basis and the risk-benefit ratio evaluated.

Monitoring.- Patients about to start biologic therapy should be vaccinated against pneumococci and influenza [3b, C].

Live attenuated vaccines are contraindicated. The degree of immunosuppression induced by biologic therapy means that there is a considerable risk of infection; consequently, the use of live vaccines is not recommended.

In the absence of additional risk factors, all other vaccines can be prescribed.

Monitoring.- Patients with a negative hepatitis B test result should be vaccinated before starting biologic therapy. [3b, C]

In any case, it must be remembered that these vaccines may not be effective if the patient is severely immunodepressed. Once biologic therapy has started, live vaccines should not be administered.

VI.1.19. Management of risk during biologic therapy

These recommendations are based on the evidence presented in the sections on contraindications and adverse events of biologic therapy (see Table 26).

Monitoring.- During exposure to the drug, specific events will be systematically monitored at regular intervals. [5, D]

Monitoring.- Risk management during biologic therapy includes a clinical evaluation, complete physical examination, and additional tests (eg, laboratory workup, imaging) depending on the drug administered and the patient's clinical situation. [5, D]

Monitoring.- Treatment should be followed up in cooperation with the primary care physician. [5, D]

Close and systematic follow-up has been shown to minimize the adverse effects of a drug. In fact, adverse events are less common in clinical trials precisely because patients are closely monitored. Any channel that facilitates communication between the primary care physician and the person responsible for treatment, or between the patient and health professionals, is expected to improve patient safety.

Monitoring.- During follow-up, special emphasis must be placed on monitoring adverse events, particularly infections, lung and heart involvement, and, in specific cases, laboratory abnormalities (dyscrasia, lipids, liver function). Patients should also be asked about contact with infected persons (including TBC or varicella). [5, D]

For more detailed information on management of risk during biologic therapy, see Table 26.

Monitoring.- Patients with active infection by HBV, HCV, or HIV should undergo an exhaustive follow-up if they initiate biologic therapy. [5, D]

Follow-up should include, at least, serology testing, determination of viral load, determination of CD4 count, and liver function tests. In the case of HBV infection, antiviral therapy should be considered; in the case of HIV infection, biologic therapy should also be combined with intense antiretroviral therapy (which should be started before biologic therapy). We recommend consulting a specialist in doubtful cases.

Approach to adverse events

Monitoring.- Infections during treatment should receive special attention. If the patient develops an infection, early diagnosis and treatment, as well as temporary suspension of biologic therapy, are essential. Biologic therapy can be restarted once the infection has resolved. [2b, B]

This possibility should be evaluated in patients with acute/subacute abdomen.

Monitoring.- During follow-up, patients should be questioned about any possible contact with persons infected with TBC. If the patient has had or could have had contact with an infected person, the tuberculosis skin test must be performed or treatment with isoniazid started. [5, D]

Even if the patient has been screened for TBC or pharmacological prophylaxis administered, the possibility of TBC remains. This eventuality must be borne in mind during follow-up. Appropriate action must be taken if necessary.

QuantiFERON is an in vitro immunological test based on rapid production of IFN-γ by circulating mononuclear cells in response to antigens that are more specific for detection of TBC than the PPD test. Use in patients with inflammatory diseases of immune origin is strongly correlated with risk factors for TBC and a low percentage of indeterminate results. However, further studies are necessary to evaluate its use in patients receiving TNF antagonists (Solovic 2010).

There is no evidence in favor of a minimum time necessary for treatment of TBC before initiating biologic therapy. Clinical experience advises as long a period as possible, while maintaining the activity of the patient's underlying disease at a reasonable level.

Monitoring.- If the patient develops cancer during biologic therapy, treatment must be suspended [2b, B].

The patient should also be advised to monitor him/herself and to report any skin changes.

Monitoring.- Special caution must be exercised with TNF antagonists and RTX in patients with heart failure, since this condition can worsen considerably. If heart failure does worsen, medication should be suspended. [4, C]

Medication should be suspended if clinical and/or ultrasound data indicate worsening of heart failure.

Monitoring.- Lung function should be closely monitored in patients with interstitial lung disease receiving biologic therapy. If symptoms deteriorate and lesions of lung disease spread, biologic therapy must be suspended. [4, C]

This area is poorly defined at present. The cause-effect relationship has not been clearly determined; therefore, the risk-benefit will be evaluated on an individual basis until further evidence becomes available.

Monitoring.- Biologic therapy should be suspended in cases of severe cytopenia. Other possible causes should be investigated before cytopenia can be attributed to biologic therapy. Once cytopenia is resolved, biologic therapy can be restarted. [4, C]

Given its mechanism of action, RTX can cause lymphopenia, which would not itself be a reason for suspension. With TCZ, cytopenia often results from a pharmacodynamic; both the literature and the Summary of Product Characteristics contain recommendations for management. Furthermore, anemia, leukopenia, lymphopenia, and thrombcytoopenia could be a consequence of disease activity. In any case, the origin should be investigated and decisions taken based on the risks and benefits.

Monitoring.- Biologic therapy should be suspended in the case of lupus-like syndromes or other severe autoimmune disorders. [2b, B]

The presence of lupus-type antibodies in the absence of other signs or symptoms is not a reason for suspending biologic therapy.

Monitoring.- TNF antagonists and TCZ should be suspended if symptoms of demyelinating disease or optic neuritis appear. [2b, B]

Monitoring.- Antiviral therapy should be added to biologic therapy in cases of activation or onset of infection by HBV, HCV, or HIV. [4, C]

Nevertheless, the option of temporarily suspending biologic therapy until initiation of effective antiviral therapy is able to control viral replication should not be ruled out.

Monitoring.- If psoriatic lesions appear in patients receiving biologic therapy, the lesions should be treated appropriately. Biologic therapy should be suspended if psoriasis medication fails or skin involvement is severe. [4, C]

Close monitoring is necessary in cases of psoriatic lesions.

VII. Other treatments

Intra-articular treatment

VII.1.1. Indications

Local therapies are indicated in joints with persistent active disease after systemic RA treatment.

During the course of RA, some joints not infrequently remain actively inflamed, characterized by pain, mainly at rest, swelling, and localized warmth, despite an acceptable clinical drug-response. In these circumstances, the background medication should be maintained and intra-articular treatment should be applied to control joint inflammation.

VII.1.2. Types of intra-articular treatment

The recommended local treatment of choice is intra-articular infiltration with slow-release steroids. When steroid infiltrations have failed (3 consecutive infiltrations 4 weeks apart), isotopic synovialitis or chemical synovialitis with osmic acid can be considered. Before starting local treatment, the presence of infection should be reasonably ruled out. [5, D]

VII.1.2.a. Intra-articular steroid infiltration

The administration of intra-articular corticoids is the procedure of choice in an RA patient with a swollen joint in whom infection has been ruled out. This guideline recommends the use of triamcinolone hexacetonide due to its prolonged action, lasting several months (Blyth, 1994). Since this product is not marketed in Spain, an alternative is triamcinolone acetonide. After administering the corticoid, the joint should be rested for 24 hours (Chakravarty, 1994).

VII.1.2.b. Radioisotopic synovectomy

Radioisotopic synovectomy consists of the intra-articular administration of a colloidal radioactive drug that emits high-energy beta particles. This drug is phagocytosed by synovial lining cells which die via apoptosis, causing atrophy and sclerosis of the synovial membrane, which improves inflammatory symptoms in the medium and long term. The most commonly used products are yttrium-90 for the knee, rhenium-186 for the hip, shoulder, elbow, carpal and ankle, and erbium-169 for the metacarpophalangeal and the metatarsophalangeal and interphalangeal joints (Schneider, 2005). The clinical trials and systematic reviews published to date have not shown that isotopic synovectomy offers better results than infiltration with corticoids (Heuft-Dorenbosch, 2000; Jahangier, 2005), thus its indication should be assessed individually only in case of failure of steroid infiltration and lack of availability of other techniques of local therapy. This treatment is not advised in patients with incomplete bone maturation.

VII.1.2.c. Chemical synovectomy

Chemical synovectomy consists of the intra-articular administration of a chemical agent capable of producing necrosis of the synovial tissue. The most commonly used agent is osmium tetroxide (Bessant, 2003).

Rehabilitation in rheumatoid arthritis

VII.1.3. Introduction

Rehabilitation includes the evaluation, prevention and treatment of disability, with the objective of facilitating, maintaining or returning the greatest possible degree of functional capacity and independence. Its main purpose in RA is to treat the consequences of the disease (pain, muscular weakness, limitations in the activities of daily living...) and to prevent functional decline.

The rehabilitation process consists of 5 phases: 1) identification of the patient's problems and needs; 2) relation of the problems with factors that can be modified (what aspects are subject to intervention?); 3) definition of objectives, selection of the most appropriate measures and their proposal to the patient, who should participate in the decisions (how to intervene?); 4) application of the selected measures; and 5) evaluation of their effect, introducing modifications if necessary.

Achieving the objectives of rehabilitation requires the participation of different professionals working as a team: physicians, occupational therapists (Hammond, 2004b), physiotherapists (Fransen, 2004b), orthopedic technicians and social workers. Rehabilitation focuses mainly on conservative non-pharmacological measures (Flórez García 2004; Vliet Vlieland, 2003).

VII.1.4. Non-pharmacological interventions

VII.1.4.a. Therapeutic exercise

From the time of diagnosis a program of aerobic physical exercise is recommended. It should initially be supervised to adapt it to the individual's level of physical preparation and the specific joint and extra-articular circumstances stemming from the disease and comorbidities. [1.a, A]

Aerobic exercises can be combined with muscle strengthening exercises (regional or general), and exercises to improve flexibility, coordination and manual dexterity.

Exercise programs should be an important part of RA treatment. From the time of diagnosis, a program of aerobic physical exercise should be recommended to all patients if there are no general contraindications and the patient is motivated. This should be supervised at first to adapt it to the individual's level of physical preparation and the specific joint and extra-articular circumstances stemming from the disease and other comorbidities. Aerobic exercises can be combined with exercises to strengthen the muscles (regional or general) and to improve flexibility. Hand exercise programs can be effective in improving muscular strength if the patients follows them independently after receiving instruction. In the subgroup of patients with the greatest functional repercussion (grades III and IV), more clinical trials analyzing the effect of exercise programs are needed.

Patients with RA often reduce their level of physical activity due to pain, limitations on mobility, and fatigue. There is loss of muscular strength (which according to some studies reaches 30-70% of that of a healthy person), of resistance (up to 50% of normal) and of physical conditioning (Ekblom, 1974; Ekdahl 1992). Different types of exercise have been proposed to reverse this situation (Vliet Vieland, 2003; Pedersen 2006b; Iversen, 2006):

- Aerobic exercises

Their objective is to improve physical conditioning. These exercises use large muscle groups involved in repeated movements, increasing the heart rate without exceeding the anaerobic threshold (up to 70-85% of the maximum heart rate for age). In RA they are usually performed with low to moderate intensity. These include weight bearing exercises (walking, dancing...) and non-weight bearing exercises (swimming, bicycling...). Exercises performed on a bicycle seem to be slightly better than other exercises for increasing aerobic capacity (Westby, 2001).

- Flexibility or stretching exercises

These are intended to lengthen the muscles and soft tissues in order to maintain or increase full range of motion in joints that tend to be stiff. There are many types of stretching exercises: static, dynamic (including Tai-Chi), active (like yoga), proprioceptive neuromuscular facilitation...

- Progressive resistance training exercises

These exercises are intended to improve muscular strength, resistance and power by contracting the muscles against certain types of resistance such as elastic bands, weights or the patient's own weight. They may be static (isometric) or dynamic (with joint movement).

- Exercises to improve coordination and manual dexterity

Coordination is fundamental for carrying out most activities, but especially for those that require manual dexterity. There are numerous exercises, but the important thing is to adapt them to the patient's specific limitations that need to be trained or improved.

Ideas about physical exercise in RA have changed a great deal in recent times (Bykerk, 2005; Kettunen, 2004). Years ago it was assumed that moderate or high intensity dynamic exercise programs and most sports activities could be harmful for these patients. Moreover, extreme caution was recommended when prescribing any other type of exercise to avoid increasing symptoms, disease activity or joint destruction. However, current evidence from various reviews (Westby, 2001; Stenstrom, 1994; Van den Ende, 1998; Munneke, 2000; Stenström, 2003; Ottawa Panel, 2004; Wessel, 2004; Van den Ende, 2006; Steultjens, 2006; Han, 2006; Hakkinen, 2004a) and from numerous high quality clinical trials emphasizes not only the effectiveness but also the safety of physical exercise (even done with high intensity and during prolonged periods of time) (Hakkinen, 2004a) from the early stages of the disease (Gossec, 2006).

The members of the Ottawa Panel (Ottawa Panel, 2004), after analyzing 16 clinical trials, recommend exercise programs in RA treatment. Different types of exercises (alone or in combination) were evaluated in these studies, including both overall exercises and those done for different anatomical regions. Clinical trials have been published, with varying results, on regional strengthening of the shoulder (Mannerkorpi, 1994), knee (McMeeken, 1999; Lynbgberg, 1994) and hand (O'Brien, 2006), but most studies include programs of general aerobic exercise or muscular strengthening. A review has recently been published

within the Cochrane Collaboration (van der Ende, 2006) that includes six trials of dynamic exercise in RA. The authors point out the positive effects of exercise in this disease. However, an important limitation is that most of the work has been done in patients who are in functional classes I and II, and very few studies include patients in classes III and IV (Bilberg, 2005).

Physical exercise has little influence on the RA patient's pain, and disease activity remains stable or decreases (de Jong, 2005). Physical exercise does not appear to significantly increase bone mineral density (Hakkinen, 1999; Hakkinen, 2004b). Nonetheless, some authors (Hakkinen, 2001; de Jong, 2004a) have found that dynamic exercise increases it in the long term, with a small but cumulative effect. When the disease is stable, programs that incorporate weight bearing exercises are well tolerated and do not generally lead to joint deterioration. Important structural damage of weight bearing joints (hips and knees) has only been observed in patients with radiologic progression after doing prolonged periods of high intensity exercises (including classic aerobic exercises, strengthening exercises and high-impact sports activities) (de Jong, 2003; Munneke, 2005). In contrast, these exercises are safe for the joints of the hands and feet (de Jong, 2004b). If there is considerable involvement of joints in the lower limbs, non-weight bearing exercises are preferable. Moderate or high intensity dynamic exercises are well tolerated in stable patients and have a better effect on muscular performance and function than low intensity or isometric exercises. To increase muscular strength, few repetitions with high resistance are recommended, and to improve resistance, many repetitions with a low load are recommended.

Muscle weakness in the hand may have an important effect on function. Wessel (Wessel, 2004) has published a systematic review of hand exercises in RA, which included 9 clinical trials of varying quality. He concludes that hand exercises done during various months can increase strength, but it is not clear that they have any effect on deformity or dexterity. In some studies, functional improvements were described. It has been suggested (Byers, 1985) that exercises done in the evening may help decrease morning stiffness. However, in a Cochrane review of occupational therapy in RA, Steuljens et al (Steultjens, 2006), did not find conclusive evidence of the effectiveness of isolated hand training exercises, based on seven studies, although only one of them was considered of high methodological quality (Hoenig, 1993). O'Brien (O'Brien, 2006), in a recent randomized controlled clinical trial, analyzed the efficacy of a home-based program of hand exercises in 67 patients followed for 6 months. They found significant improvement in both grip strength and upper limb function. There are no contraindications for doing hand strengthening exercises, even of the flexor muscles (Chadwick, 2004).

Not all types of exercises are beneficial in RA. A Cochrane review (Han, 2006) has analyzed the effect of Tai-Chi, an increasingly popular type of exercise. It was concluded that, although well tolerated, it lacks clinically relevant effects since the only parameter that improved was ankle plantar flexion.

Patients may need to adjust their exercise program as the disease evolves, according to their level of activity. In periods of acute disease, the level of physical activity should be reduced, but never completely eliminated to avoid the harmful effects of prolonged inactivity. Exercise is more cost-effective if performed in non-healthcare settings (Stenstrom, 2003). For the effects to persist, patients should incorporate exercise into their daily routine (van den Ende, 2000). The patient should receive specific recommendations about the exercise program, including frequency, intensity, type, duration, how to progress, materials needed, and time of day and place to perform the exercise (in the patient's own home or another place) (McDermott, 2006). Exercise instructions are often imprecise or inappropriate, and this leads

to lack of compliance (Hakkinen, 2004a). Both group and individual programs are equally effective (van den Ende, 2006), but exercising in groups benefits compliance and socialization.

VII.1.4.b. Physical treatments (passive modalities)

Low level laser therapy and transcutaneous electrical nerve stimulation (TENS), used alone and independently, are effective in reducing pain in the short term (TENS has the advantage of easy application with portable units that can be used at home). [1.a, A]

The combination of paraffin (thermotherapy) and active exercises also appears to be effective against pain. Data on ultrasound, muscular electrostimulation and magnetotherapy remain insufficient to recommend them for routine use, but they should be considered in selected cases that do not respond to other alternatives. The application of thermotherapy alone and the local application of cold do not appear to offer any clinical benefit. [2.b, B]

The main objective of applying physical agents in symptomatic regions is to reduce pain and the feeling of stiffness. A secondary objective could be to help improve joint mobility, muscular strength and functioning. Low level laser therapy and TENS, used alone and independently, seem to achieve a significant reduction in pain as compared to placebo in the short term (up to 3 months). More data are available on the laser, but TENS has the advantage of easy application with portable units that the patient can use at home after receiving instruction. The combination of paraffin and active exercises is another alternative that is probably useful. Although the few CTs on ultrasound, muscular electrostimulation and magnetotherapy suggest they may be efficacious, the data do not yet appear to be sufficient to recommend these treatments for routine use; however, they should be considered in selected cases that do not respond to other alternatives. The application of thermotherapy alone does not appear to offer any clinical benefit. It is quite doubtful that the local application of cold, at least as used in the CTs, will achieve clinically relevant effects on joint inflammation.

Numerous CTs and various systematic reviews and meta-analyses have been published. The most recent reviews with the highest methodological quality are those made by the Cochrane Collaboration (Robinson, 2002) and by a multidisciplinary group sponsored by the American Physical Therapy Association (the Ottawa Panel) (Ottawa Panel, 2004). The most relevant scientific evidence on the efficacy of physical agents is summarized below.

- Superficial Thermotherapy (including paraffin)

In a meta-analysis conducted by the Cochrane Collaboration (Robinson, 2002) 7 RCTs were found that compare different modalities of applying superficial heat (thermotherapy) or cold (cryotherapy) with a control group (without treatment) or with another alternative. Used alone, thermotherapy did not show significant effects on any clinically relevant parameter (joint swelling, pain, medication intake, range of motion, grip strength, hand function…) as compared with not applying any treatment or with another alternative. There was a trend in favor of cryotherapy in reducing swelling at 2 or 3 days. The combination of paraffin plus exercises was the only treatment that showed a significant improvement as compared with the control group in various parameters (pain intensity, flexion deficit, pain with movement, grip strength and pinch function). However, the application of paraffin alone did not produce any improvement. The Ottawa Panel concluded that there is good evidence that

thermotherapy, especially paraffin combined with exercises, improves mobility, pain and stiffness (Ottawa Panel, 2004).

One systematic review has been published on the application of paraffin, the most popular treatment (Ayling, 2000). Four RCTs were found, three of which suggested that the combination of paraffin with exercises produces significant improvement. Several studies (Abramson, 1964; Borell, 1980; Stimson, 1958) have looked at the physiological effects of paraffin. Paraffin baths increase skin temperature to 40-45ºC and this increase reaches the joint capsule, whose temperature increases by some 5ºC. This would contraindicate its use in highly inflammatory phases. The skin temperature decreases rapidly 15 minutes after finishing the application and by 60 minutes has returned to normal. Paraffin baths also produce a temporary sensation of decreased joint stiffness which may make it easier to begin active exercises.

- Transcutaneous Electrical Nerve Stimulation (TENS)

TENS refers to the application of an electrical current through electrodes placed on the skin with the objective of producing an analgesic effect. A Cochrane Collaboration review (Brosseau, 2003) has been published that analyzes the efficacy of TENS application at the wrist level in three CTs. One of these (Langley, 1984b) compared the effect of two types of TENS used in a single 20-minute session with placebo. There was significant reduction in joint tenderness but not in pain intensity. The other two CTs (Mannheimer, 1978; Abelson, 1983) used various treatment sessions (3 and 15, respectively) with similar parameters: two electrodes placed on the palm and back of the hand and a fixed frequency of 70 Hz of current. In both cases, a significant reduction in pain intensity was observed. The Cochrane Collaboration notes that the data suggest the clinical usefulness of this therapy, although more studies are needed. The Ottawa Panel (Ottawa Panel, 2004) considers that there is good evidence to recommend the use of TENS alone in the treatment of hand and wrist pain in RA. The Arthritis Society also recommends the use of TENS (Lineker, 1999).

- Low level laser therapy

Low level laser therapy generates an extremely pure beam of light of a single wavelength. It has no thermal effect. Its action at the cellular level is mediated by photochemical reactions. Experimental studies (Aimbire, 2006) suggest that it could have an anti-inflammatory and anti-nociceptive effect. It is one of the treatments that has been subject to the best analysis. A Cochrane Collaboration review published in 2003 (Brosseau, 2005) found 8 CTs. Five of them compared active laser with placebo laser, and 3 used the contralateral joint as a control. The placebo-controlled studies observed a significant reduction in pain in the areas where it was applied (MCF, IPF, knees and feet), and in morning stiffness, with increased flexibility in comparison with the control group. Only 2 trials (Gotas, 1996; Hall, 1994) had long-term follow-up of patients after completion of treatment, and they found no differences in any of the outcome measures beyond 3 months. The Cochrane review concluded that the laser is efficacious as short-term symptomatic treatment with a minimum of 2-3 sessions a week for 4 weeks. The Ottawa Panel (Ottawa Panel, 2004) also considered that the laser achieves a clinically important benefit on pain when applied at the level of the hand, knee or foot.

There are no conclusive data on the most effective laser modality, although there is a trend towards greater improvement in outcome with the 632 nm wavelength laser as compared with the 820 nm wavelength laser (Brosseau, 2005).

- Ultrasound

A Cochrane review has been published (Casimiro, 2002) which found only 2 RCTs (Hawkes, 1986 and Konrad 1994). A double-blind study (Konrad 1994) compared continuous subaquatic ultrasound to the palmar and dorsal aspects of the hand (10 sessions with a dose of 0.5 W/cm^2 applied during 10 minutes) with inactive ultrasound. A significant improvement in grip strength, wrist dorsal flexion, duration of morning stiffness, and pain intensity was observed. Another CT (Hawkes, 1986) compared combining exercises with three alternatives: paraffin, ultrasound or ultrasound plus faradic currents. All three groups improved, with no significant differences among them. Based on these studies the Ottawa Panel (Ottawa Panel 2004) recommends its use. The Cochrane Collaboration suggests it may be useful, but points out the limitations of basing conclusions on a single RCT.

- Muscular electrostimulation

Joint pain may make it difficult to contract muscles with sufficient intensity to increase strength and muscular resistance. Electrical stimulation of the muscles could be an alternative for these patients. A Cochrane review has been published (Pelland, 2002) which found only one CCT (Oldham, 1989) comparing electrostimulation of the first dorsal interosseous muscle with no treatment. Although significant improvement was seen in grip strength and fatigue resistance, the low quality of the study limits its validity.

- Magnetotherapy

Two double-blind RCTs observed a significant improvement in pain with respect to the control group. The active treatment used in one study was disks placed at the level of the knee which generated pulsed magnetic fields (Segal, 2001). In the other RCT, a device was applied that delivered pulsed magnetic fields (Shupak NM 2006), which appear to have the best biological effects.

VII.1.4.c. Occupational therapy

Occupational therapy (OT) includes a wide set of therapeutic and educational activities. Its objectives in RA are: 1) evaluation and re-education of the activities of daily living, both basic (personal hygiene, eating, dressing, bathing,…) and instrumental (domestic tasks, leisure activities…); 2) training of motor abilities, dexterity and manual coordination by doing exercises; 3) education about joint protection and strategies to conserve energy; 4) selection, counseling and instruction in the use of assistive devices; and 5) development of some upper-limb orthotics.

Different OT interventions can be carried out in a group or individually in patients with specific needs (Florez García, 2004; Hammond, 2004a). Strategies focusing on behavior modification seem to be more effective than interventions that are strictly educational (Superio-Cabuslay, 1996; Riemsma, 1997; Riemsma, 2002). Treatment can be administered in different healthcare settings (Li, 2006a) and with different cost-effectiveness (Li, 2006b).

- Integral occupational therapy

In patients with important functional limitations, usually those with advanced disease, a lasting improvement has been observed. [1.b, A]

The different OT interventions can be done alone or in combination (integral treatment). Current data suggest it would be appropriate for those with important functional limitations to receive integral OT since the improvement obtained has been seen to persist over time.

A Cochrane Collaboration systematic review (Steultjens, 2004) analyzed the effectiveness of different categories of OT interventions. No CTs were found for some modalities. Positive effects of OT were observed in patients with advanced RA. The review included four studies referring to integral OT; limited evidence was obtained that the treatment improved functional ability but not other outcome parameters measured. One of the studies (Helewa, 1991) was a RCCT comparing home OT with no treatment; this study found a clinically relevant improvement in function. Other recent reviews (Wilkins, 2003; Steultjens, 2002; Steultjens, 2005; Li, 2005) reached similar conclusions.

Much controversy exists about the utility of OT in the early stages of disease. Malcus-Johnson et al (Malcus-Johnson, 2005) conducted a 10-year follow-up study of 168 patients with early RA (less than 2 years' evolution) and with varying degrees of involvement, from mild to very serious cases. According to the authors, half of the follow-up visits in OT generated interventions (primarily prescription of assistive devices and orthotics and, less frequently, instructions about hand-training exercises, education and environmental modifications). Patients in this study, the same as in a previous one (Mowat, 1980), considered these types of interventions to be beneficial. In contrast, a high quality RCCT (Hammond, 2004a) conducted in 326 patients, also with early RA (less than two and a half years' evolution) and followed for 2 years observed that, although there was improvement in the ability to perform self-care activities, no changes were apparent in other functional or clinical parameters. In these patients with mild disability the possible effects were not easily quantifiable, nor did the patients perceive clear benefits.

In various longitudinal studies (Eberhardt, 1990; Eberhardt, 1995; Harrison, 2000; Uhlig, 2000; Young, 2000), it has been observed that functional abilities are reasonably well preserved in most RA patients during the first 5 years of evolution. OT would be especially indicated in more advanced phases of the disease or in cases with significant functional limitation. The reality is that, in Spain, only a very small percentage of RA patients receive OT treatments as the disease is evolving.

- Joint protection and energy conservation programs

In advanced phases of RA it is useful to instruct the patient about rules for joint protection. Teaching strategies to conserve energy is indicated only in patients in whom fatigue is an important symptom. [4, C]

Joint protection techniques consist of educational methods to teach the RA patient how to carry out different daily activities with the minimum amount of stress on the affected joints. In the Cochrane review of Steuljens et al (2006), 8 studies of these techniques were analyzed in 370 patients with established RA. It was concluded that there is strong evidence, based on two high quality RCCTs (Hammond, 1999a; Hammond, 2001), one of them with 1-year follow-up (Hammond, 2001), that joint protection interventions increase patients' knowledge and significantly improve their functional ability. In a previous review, the same author (Steultjens, 2002) had found only limited evidence. Another study (Hammond, 2001) subsequently supported the conclusions of the Cochrane Collaboration. Moreover, one study (Hammond, 2004a) with a 4-year follow-up of RA patients with less than 5 years' evolution since diagnosis, observed that an educational program focusing on behavior significantly improved patient compliance and maintained functional ability in the long term. The benefits appear to be more evident with time, therefore joint protection could help to slow down the effects of RA progression. In early RA, one review (Gossec, 2006) of 5 RCCTs did not find beneficial effects of group instruction on function. although it did find slight beneficial effects on pain.

Energy conservation techniques include instruction on how to alternate between activity and rest (including micro-naps) and ways to simplify tasks (Hammond, 2003). Their objective is to save energy while doing daily activities. This energy savings can be devoted to other activities that are important for the person and that help to maintain physical and emotional wellbeing and the social role. Their efficacy in RA has not been analyzed in CTs. Instructions based on cognitive-behavioral models appear to be much more effective than traditional teaching methods (Hammond, 2001; Hammond 2004; Freeman, 2002).

There are no studies investigating the impact on joint protection or energy conservation of counseling given during the medical consultation, but this could be a reasonable option in the absence of more structured programs (Philips, 1989).

- Assistive devices

The use of assistive devices for important tasks should be evaluated in RA patients who have difficulties carrying out basic or instrumental activities of daily living due to weakness or lack of manual dexterity (who do not improve with an exercise program), or due to pain (that is not controlled with other therapies). [5, D]

Assistive devices refer to products, instruments, equipment or technical systems designed and manufactured to compensate for the functional limitations of disabled persons. They are prescribed to try to reduce pain while performing tasks, compensate muscular weakness that makes it difficult to perform tasks adequately, or minimize functional repercussions (García Pérez, 2004). These devices can help to conserve independence in daily activities and increase the quality of life. About 80% of RA patients have at least one assistive device (Veehof, 2006). Although there are many varieties (Rogers, 1992), the ones most commonly used by RA patients are mobility aids such as canes, crutches or walkers (almost half of patients have one of these) (van der Esch, 2003), drinking and eating aids (Thyberg, 2004), such as specially adapted knives, and systems to facilitate opening faucets or using keys (Shigham, 2003). Home modifications are also frequently employed (elevated toilet seats, wall grab bars, shower seats…), special furniture, velcro closings (for clothes and shoes) and curved, lengthened and/or thickened handles to attach to different small utensils.

Interest in the therapeutic possibilities of assistive devices is increasing, but little research has yet to be done (Ivanoff, 2006). A recent Cochrane review on occupational therapy (Steultjens, 2006) analyzed two publications about instruction on the use of assistive devices in RA patients, one of which was a CCT (Hass, 1997), although of low quality. Sufficient data could not be found to determine their impact. In a multicenter study (Thyberg, 2004) of 284 patients with RA, it was observed that the use of assistive devices was related with disease severity and amount of disability. Moreover, the number of assistive devices used in practice is a function of other factors like longer RA duration (van der Heide, 1993) and the system of financing, which varies greatly among different countries (Veehof, 2006), and is almost non-existent in the Spanish public health system. Most patients who use them are generally satisfied. Possession of assistive devices is related with the patient's psychological wellbeing (Befo, 2006). However, some devices end up being discarded as time goes by, or are never used (Rogers, 1992). It has been observed that many RA patients have never received adequate information about assistive devices (Mann, 1995). Some case series support the use of assistive devices in RA to reduce pain during daily activities (Ivanoff, 2006) or to facilitate their performance (Nordenskiold, 1996).

If it is considered necessary to prescribe assistive devices, the most appropriate ones should be selected. Ideally, an occupational therapist will train the patient in their correct use and maintenance to avoid their being discarded and possible harmful effects. It is advisable to

periodically review their condition and level of use so that they can be changed if they are damaged, and to adapt them to each phase of the disease (Malcus-Johnson, 2005).

VII.1.4.d. Orthotics

- Splints or upper limb orthotics

In periods of active inflammation (with the main objective of avoiding pain and reducing inflammation), static orthotics can be used (at first during the whole day and later only at night). If the patient has functional problems these can be combined during the day (part time) with functional orthotics adapted to the specific problem and to the anatomical region interfering with function. [4, C]

Their efficacy should be evaluated periodically, and orthotics that do not meet expectations should be rejected. [5, D]

Most authors consider that wrist and hand orthotics can play an important role in the treatment of RA patients. However, there is no consensus on the most basic questions: For which patients are they indicated? When should they be prescribed? Which objectives can be achieved and which cannot? What is the most effective and cost-effective type and model? What guidelines for use should be recommended?... In periods of active inflammation, the main objective will be to avoid pain and reduce inflammation, for which purpose static orthotics can be used, initially almost all day long and later only at night. Their value in preventing or correcting deformities has not been demonstrated. If the patient has functional problems, they can be combined during the day (part time) with functional orthotics adapted to the specific problem and the anatomical region considered to interfere with function. An eclectic approach is always needed, with the proposal of specific objectives and using the trial-and-error method, discarding orthotics that do not meet expectations.

In RA orthotics are used mostly for the hand and/or wrist, and they can be prescribed with various objectives (Hammond, 2004a): 1) to reduce pain and joint inflammation; 2) to stabilize and provide rest for weakened and/or deformed joint structures in an attempt to prevent deformity from occurring and/or progressing; 3) to reduce joint contractures (especially in the proximal interphalangeal joints) and/or 4) to improve hand function by proper alignment of joints. A large variety of models is available (prefabricated or made to measure, with different characteristics and made of materials of different consistency). Rigid orthotics provide better support, but those that are flexible are tolerated better (Calinnan, 1996). The mechanisms used to hold them in place and to close them should be easy to put on and take off (preferably made of velcro). They should not exert pressure either on painful areas or directly on the cubital styloids. Orthotics can be classified by the anatomical region to which they are applied (wrist, wrist and hand, triphalangeal fingers, thumb…) and according to the mechanism of action (static or resting, functional, dynamic...) (Alcántara Bumbiedro, 2004).

Different types of orthotics are employed in RA (Street, 2004; Ewing, 2005). The most commonly used are static or resting splints and functional orthotics. Static splints immobilize the wrist and hand in a functional position during acute inflammation and are gradually withdrawn as the inflammation decreases. If there is bilateral involvement, they can be used simultaneously or alternately. To reduce joint inflammation and soft tissue edema, compression gloves and pneumatic orthotics have also been used. Functional splints include several types of orthotics, from those that stabilize a painful wrist to others than reduce cubital deviation of the metacarpophalangeal joints, which is useful in patients who need this

correction in order to be able to continue performing certain activities (Rennie, 1996). The use of orthotics in the form of a metal ring for triphalangeal fingers with swan neck or boutonniere deformities is not appropriate for pronounced or completely established deformities, but may be prescribed for flexible contractures that are corrected passively. In these cases dexterity and coordination can be improved by better joint placement (Palchick, 1990; Ziljstra, 2004). They should not be used during active inflammation. There are splints designed specifically for the thumb that can be used to rest the joints or to improve function. Finally, so-called dynamic splints are used to correct deformities. A stable correction is unlikely to be achieved in the case of long-standing deformities.

A Cochrane review specifically on orthotics in RA (Egan, 2006) analyzed various published studies which had important methodological limitations. These studies evaluated two types of upper limb orthotic (for the wrist to be used during activities and for resting the hand and wrist at night) versus placebo or versus other interventions. Studies comparing different orthotics were also included. The evidence was not sufficient to obtain firm conclusions on the effectiveness of either of the two orthotics, but there did not appear to be any adverse effects (reduced mobility, dexterity or strength) with long-term use; patients preferred using resting orthotics to not using them (Callinan, 1996) and tolerance was better if they were padded. These conclusions differ from those obtained in another Cochrane review (Steultjens, 2006) on occupational therapy which included a larger number of investigations, 16 studies with large variations in their design, only two of which were of high quality (Tijhuis, 1998, Ter Schegget, 2000). UP to six different types of orthotics were evaluated. The authors concluded that the use of orthotics was effective in reducing pain immediately and in the long term, and in increasing grip strength immediately, but no other beneficial effects were observed. The effects on deformity were not analyzed.

New studies have subsequently appeared (Zijlstra, 2004; Li-Tsang, 2002; Haskett, 2004, Pagnotta, 2005), with different designs and of sufficient quality, which have observed beneficial effects in different parameters in different types of orthotics.

RA deformities often develop slowly, allowing the gradual adaptation of the patient, who often maintains surprisingly good levels of functional capacity. When splints are used, it is important to consider that they can worsen function instead of improving it. If good compliance is to be achieved, the orthotic must provide manual functionality and not only achieve more aesthetic joint alignment. Functional orthotics may occasionally make some activities more difficult initially, but dexterity later improves with use after a phase of adaptation and training (Haskett, 2004).

When orthotics are prescribed, they should be reviewed periodically to assure optimal adjustment. The patient's compliance with treatment will depend on the perceived benefit. In long-standing RA of the hand, there may be multiple entrenched problems such as pain, joint instability, fixed deformities, skin fragility and/or reduced function. When choosing an orthotic in this situation, a logical order of therapeutic priorities must be established.

- Lower limb orthotics

Pain of the forefoot can be improved with hard and soft orthotics. Hard orthotics improve pain in the hindfoot in the initial phase of the disease. Use of a special model can prevent the development and progression of hallux valgus. Shoes with special widths improve the results. [1.a, A]

Studies of orthotics are highly heterogeneous, and it is not possible to establish which type of orthotic is the most appropriate for each type of involvement. [5, D]

There is little information about the most appropriate orthotics in advanced stages of the disease.

Lower limb orthotics are used most commonly for the foot and ankle. Current data suggest that pain in the forefoot can be improved with hard and soft orthotics, that hard orthotics improve pain in the hindfoot in early stages of the disease, and that use of a special model can prevent the development and progression of hallux valgus. Use of shoes with a special width improves the results. There is little information on the most appropriate orthotics in advanced stages of disease. Most of the patients analyzed in CTs find orthotics to be comfortable. Orthotics also appear to be cost-effective since, on average, they do not need to be replaced before 2 years. The problem for the clinician is that studies on orthotics are highly heterogeneous, and it is not possible to establish which type of orthotic is the most appropriate for each type of involvement.

At the time of diagnosis, about 16% of patients exhibit foot symptoms, but over the long term over 90% present symptoms (Shrader, 1999). Orthotics are generally prescribed to improve pain (in the forefoot, midfoot or hindfoot) and to permit normal walking. Another potential objective is to prevent the appearance or progression of deformities. They act by redistributing pressures and/or stabilizing particular segments of the foot. Depending on the type of material from which they are made, they are classified as soft, semi-rigid or rigid orthotics. There are a large number of models and varieties, but the most commonly used are total contact insoles, with accommodative orthotics to reduce the pressure on the forefoot (retrocapital bar or ball) and/or to stabilize the hindfoot. Orthotics can be combined with specially adapted shoes with special widths.

A Cochrane Collaboration review was published in 2001, which was updated in 2003 (Egan, 2003). It concluded that there is evidence that orthotics reduce pain during weight-bearing activities such as walking, standing and climbing stairs. The results improve if combined with shoes with a specially adapted width. In a 3-year randomized prospective study, a special type of orthotic was shown to prevent the progression of hallux valgus (10% progression in the treatment group versus 25% in the control group). Two systematic reviews were subsequently published, in 2005 and 2006 (Farrow, 2005, Clark, 2006), which reached similar conclusions. The most recent review (Clark, 2006) includes 11 CTs, 6 of them randomized, and asserts that there is strong evidence that orthotics improve pain and functional capacity.

VII.1.4.e. Balneotherapy

Balneotherapy can be recommended in cases of polyarticular involvement without active disease, where other more accessible therapies have been ineffective. [2.b, B]

Balneotherapy is a well-known treatment that has been applied in numerous diseases since antiquity (van Tubergen, 2002). It is used as symptomatic treatment in RA.

A Cochrane review (Verhagen, 2006) found six highly heterogeneous RCCTs on different types of balneotherapy in RA patients of varying severity. The studies compared its effects with other therapies or with no treatment. Only two were considered to be of high quality (Hall, 1996; Franke, 2000). Most found moderately beneficial effects that persisted in the long term (3-6 months). However, it was not possible to obtain conclusions based on solid scientific evidence due to the presence of a large number of methodological defects. Another, earlier review (Brosseau, 2002) also arrived at the same conclusion. The favorable results of balneotherapy can be attributed to a multitude of factors such as temporary change of surroundings, with a reduction in physical and emotional stress and everyday obligations, the

thermal effects of immersion in hot water, chemical or mineral properties of the water, or association with other therapies applied at the same time, such as exercises.

Despite its popularity and long tradition, balneotherapy suffers from problems of accessibility and high cost. It is difficult to give practical recommendations about its indications. In RA patients it is best tolerated at temperatures of 34-35º C, for short periods of time, not daily, to avoid fatigue (Hall, 1996).

VII.1.4.f. Combination treatments. Multidisciplinary approaches

It is important that all professionals who participate in the treatment of the RA patient have a coordinated approach focusing on specific problems, with appropriate assessment of the effects of interventions. [5, D]

Current evidence is insufficient to draw conclusions about the most effective and efficient model to use in the approach to complex cases and about the best way to combine different treatments. What does appear to be important is good coordination among all professionals who participate in treatment, focusing on specific problems and with appropriate assessment of the effects of interventions. The cost/benefit relation and the advantages of a "more" intensive and multidisciplinary approach are not clear.

Multidisciplinary approaches are difficult to evaluate and depend primarily on the types of interventions that are combined. A systematic review observed that intensive multidisciplinary treatments in hospitalized patients with RA showed a greater effect than conventional outpatient treatment (Vliet Vlieland, 2003). The comparison of intensive outpatient treatments and multidisciplinary programs of care in day hospitals showed contradictory results, but the treatments that included hospital admission had much higher costs (Lambert, 1998; Tijhuis, 2002).

Surgical treatment in RA*

Before performing surgical treatment, several factors should be considered: bone quality, the patient's preferences and level of motivation, estimation of the extent to which disease progression can be modified by surgery, and estimation of the degree to which surgical treatment can reconstruct joint function and improve the patient's independence. [5, D]

Appropriate medical treatment of each case will reduce the indications for surgery and improve the probability of successful surgery. Consultation with the orthopedic surgeon should not always mean that surgery is indicated, but the exchange of opinions and clinical assessment will help improve the patient's clinical and functional status.

The rheumatologist should consider surgical treatment when joint function either has not improved or is clearly reduced, when incapacitating pain persists, and when there are potentially serious or limiting neurological complications (Dreyer, 1999; Grob, 1999).

In making the decision to intervene surgically, evaluation of clinical and functional status will predominate over simple radiologic modification of the disease.

When visiting the orthopedic surgeon, the RA patient typically has several joints requiring surgical evaluation, therefore priorities need to be established. The joint that the patient finds most incapacitating is generally the first to be treated.

Patients who cannot walk due to lower limb pain or deformity need a functional upper limb to facilitate the post-surgical period. When the upper limbs are so affected (pain, deformity or stiffness) as to impede the use of walking aids, the upper limbs should be reconstructed first. If there are different levels of involvement, those with the best prognosis should be reconstructed first.

The joint prosthesis is the most effective surgical measure to halt the progressive loss of functional capacity. Joint replacement, in whatever joint, should be performed before irreversible deformities become established. [5, D]

Synovectomy appears to produce a slight improvement in the synovectomized joints, but this effect is not maintained at 3 years.

Arthrodesis is a good control measure, but is more limiting from the functional point of view. It is still a widely used technique in RA as a way to palliate deficiency from joint destruction, especially in the interphalangeal joints of the hand, the metacarpophalangeal joint of the thumb, the wrist, ankle and hindfoot (Bogoch, 1999). Arthrodesis of other joints is less acceptable.

Joint prosthesis is the most effective surgical method to halt the progressive loss of functional capacity. Whatever joint is involved, joint replacement, should be performed before irreversible deformities are established (e.g., axial contractures or deviations and instabilities) because these will limit the success of arthroplasty (Waldman, 1998; Creighton, 1998; Hargreaves, 1999).

Surgical success or complications in RA are associated with the surgeon's experience, the patient's previous status, and post-operative care, especially rehabilitation and occupational therapy. The latter two factors are an important aid in establishing optimal joint function, especially after arthroplasty of the knee or shoulder and hand surgery.

* This section has not been updated since GUIPCAR-2001.

The incidence of infection in orthopedic surgery may increase during the perioperative period, although this has not been conclusively confirmed. A reasonable course of action is to omit the weekly dose of MTX in the week before and after surgery, which reduces the small possibility of perisurgical complications, at the expense of the risk of reactivating the disease (Carpenter, 1996; Bridges, 1991).

VIII. MANAGEMENT

When a patient with a health problem seeks aid in the health system, a series of actions aimed at improving or solving the problems are set in motion.

The way in which the patient receives health care depends, in large measure, on the structural characteristics of the entire system, which include different aspects. The health system that receives the patient has a certain structure, which depends on: a) characteristics of the population from which the patients come (age, socioeconomic level, prevalence of RA, incidence of RA…); b) structural characteristics of Primary Care (health centers, patient/physician ratio, professional qualifications, patient/nurse ratio); and c) structural characteristics of the Rheumatology Service (existence of an RA unit, patient/physician ratio, teaching activity…)

The set of actions aimed at improving or solving the health problem (in this case, RA) constitute the so-called "process of care," for example, referral from Primary Care to Specialty Care, patient visits, clinical history or quality and number of treatments applied.

As a result of this process, an outcome is produced, which can be measured according to its effect on the patient's health status (improvement, no change, deterioration, or even death).

Current management systems focus above all on process indicators or measures (number of consultations, ratio of subsequent visits to first visit, number of times a particular drug is dispensed in the pharmacy, etc.) which are confusing for the clinician, affect only economic aspects and, in short, are not capable of detecting the final outcome achieved, which is the primary objective. As a result, it is impossible to make inferences about whether one or another organizational strategy or modification or patient-related intervention is efficient or not.

In this chapter a series of indicators for RA management are proposed which can be used to help analyze and compare different Units or Services in terms of quality, as well as to evaluate strategies or programs implemented to improve the detection, referral, and speed of diagnosis and treatment of RA patients. These indicators are based on the time elapsed between different stages of the process of care and on quality indicators based on the proportion of RA patients who are managed appropriately.

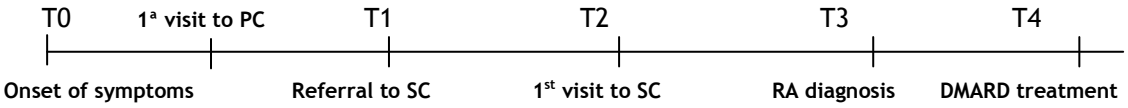
Many Rheumatology Services currently use software applications to store information relating to all or part of the process of care. Among other advantages, computerization makes it possible to have structured information, to make queries, to perform statistical analysis, or to use aids to clinical decision making and quality control programs. When clinical records are computerized, the indicators proposed in this guideline can be calculated by adding fields to the software application to calculate them automatically, thus facilitating periodic and systematic evaluation of the quality of RA management. In cases where the information is not computerized, it will be necessary to resort to manual review of the clinical records.

Indicators based on time

In the natural history of RA, the events that mark the points of contact between patient and health system can be useful in evaluating the quality of care (figure). The distribution of times between these events and the proportion of patients for whom the times are within the standards defined and accepted by rheumatology specialists constitute quality indicators.

We can define the following dates of interest, which are usually easy for the rheumatologist to obtain:

T0 = onset of symptoms
T1= date of referral to Specialty Care
T2= date of first visit to the specialist
T3= date of RA diagnosis
T4= date of first DMARD treatment



Based on the proposed dates, the following 10 time indicators are derived:

T10=T1-T0 is the time elapsed between symptom onset and the date of referral to the specialist. The time period has two components, the time between symptom onset and first visit to the Primary Care physician, and the time between the first visit to the Primary Care physician and referral to the specialist. It is a mixed indicator that combines access to Primary Care and Primary Care efficiency in referral to the specialist.

T20= T2-T0 is the time elapsed between symptom onset (T0) and first visit to the specialist (T2). For RA, this time should be less than 4 months.

T21=T2-T1 is the time elapsed between referral (T1) and first visit to the specialist (T2). This time should be less than 15 days.

T30=T3-T0 is the time from symptom onset (T0) to RA diagnosis (T3). This time should be less than 6 months.

T31=T3-T1 is the time elapsed between the date of referral to the Primary Care physician (T1) and establishment of a diagnosis of RA (T3).

T32=T3-T2 is the time elapsed between first visit to the specialist (T2) and establishment of the RA diagnosis (T3).

T40=T4–T0 is the time elapsed between symptom onset (T0) and establishment of DMARD treatment (T4).

T41=T4-T1 is the time elapsed between referral to the Primary care physician and establishment of DMARD treatment (T4).

T42=T4-T2 is the time elapsed between first visit to the specialist (T2) and establishment of DMARD treatment (T4).

T43=T4-T3 is the time elapsed between RA diagnosis (T3) and establishment of DMARD treatment (T4).

Indicators based on percentages

VIII.1.1. Early detection

Definition: Percentage of patients with recent-onset arthritis (arthritis with patient-reported symptom onset less than 6 months previously) divided by the total number of new patients with arthritis:

Calculation:

> *Denominator:* Number of new patients diagnosed with arthritis (patients for whom a clinical history was opened in the preceding calendar year).
>
> *Numerator:* This is the part of the denominator composed of those patients who have come to the Rheumatology Service in a period of less than 6 months from symptom onset.

Standard: This indicator could vary from one unit to another depending on the pattern of referral, geographic location, and age structure of the reference population. It could be of greatest value as a comparison within services over reference periods of time.

VIII.1.2. DMARD treatment in window of opportunity

Definition: Percentage of persons diagnosed with RA who begin DMARD treatment (of those included in the guideline) in the **first 6 months since onset** of disease symptoms, divided by the total number of patients with newly diagnosed RA during a natural year (other periods of time could also be used).

Calculation :

> *Numerator*: Number of patients with DMARD treatment who were diagnosed with RA in the last natural year and who began DMARD treatment in the first 6 months after diagnosis.
>
> *Denominator:* Number of new patients diagnosed with RA.

Standard: 100% (following the GUIPCAR recommendation that all patients with RA should be treated with a DMARD as soon as the diagnosis is established).

This indicator is currently around 46.5% (Fuente: emAR).

VIII.1.3. Patient visits for recent-onset RA

Definition: Average number of visits per patient during a one-year period.

Calculation:

Numerator: Number of visits (nursing staff, physician) of new RA cases diagnosed in one calendar year.

Denominator: Number of new RA cases diagnosed in one calendar year.

Standard: 6 (following the GUIPCAR recommendation that recent onset RA cases should be evaluated every 1-3 months).

VIII.1.4. Patient visits for established RA in complete remission

Definition: Average number of visits per patient during a one-year period.

Calculation:

Numerator: Number of visits (nursing staff, physician) of cases with established RA in complete remission in one calendar year.

Denominator: Number of cases of established RA in complete remission in one calendar year.

Standard: 1.5 (Following the GUIPCAR recommendation that patients with established RA in complete remission should be evaluated 1-2 times per year).

VIII.1.5. Percentage of patients with DMARD treatment

Definition: Percentage of patients diagnosed with RA who are receiving DMARD treatment divided by the total number of patients diagnosed with RA who are being monitored.

Calculation:

Denominator: Number of patients diagnosed with RA who are being monitored.

Numerator: Number of patients in the denominator who have received DMARD treatment.

This indicator is currently 93.4% (source: emAR)

VIII.1.6. Use of orthopedic surgery

Definition: Percentage of patients diagnosed with RA who have a surgical intervention divided by the total number of cases being monitored.

Calculation:

Denominator: Number of patients diagnosed with RA who are being monitored.

Numerator: Number of patients in the denominator who received orthopedic surgery.

This indicator is currently around 5.6% year.

VIII.1.7. Losses to follow-up

Definition: Percentage of persons diagnosed with RA and receiving DMARD treatment who have failed to appear for a consultation for 1 month or more after the first missed appointment.

Calculation:

> *Denominator:* Number of patients who have received a diagnosis of RA and a DMARD prescription who have been monitored for at least 12 months.
>
> *Numerator:* Number of persons in the denominator who have missed at least 2 consecutive visits in the last 12 months of follow-up.

VIII.1.8. Remission

Definition: Percentage of persons diagnosed with RA who are in remission at 12 months follow-up. Remission to be defined according to the EULAR criteria (see Guideline section on EULAR response criteria).

Calculation:

> *Denominator:* Number of patients diagnosed with RA.
>
> *Numerator:* Number of persons in the denominator who are in remission.

IX. Appendices

Data collection instruments for parameters used in initial evaluation and monitoring of RA patients

This appendix contains a model data collection sheet for the evaluation and monitoring of RA patients.

This model can be adapted to each specialist's needs in accordance with the way the particular hospital or clinical practice is run, and can be added to the patient's usual clinical record.

First, there are three scales that the patient should fill out with reference to the previous week: change with respect to the last visit, pain, and global assessment of disease. The bottom half is for the physician. It is useful to mark the swollen joints with a dot (•) and the painful joints with an X.

The usual procedure is to give this sheet to the patient at the end of the visit, and ask the patient to fill it out at home the day before returning for the next appointment. The physician should emphasize that this is not to be done any sooner, and that the patient should fill out the form thinking only of the previous 7 days. The bottom half is for the physician's assessment.

The HAQ, also included in this appendix, should be printed on the back of the same sheet.

Finally, this appendix also includes instructions on how to correct the HAQ, the most commonly used joint indices, and different ways of calculating the DAS.

Clinical history |___|___|___|___|___|___| Date: ___/___/___/

Please answer the following questions **one day before** your appointment with the rheumatologist.

Complete this section only

1) How has your arthritis been in comparison with your last visit?

☐ Much better ☐ Somewhat better ☐ The same ☐ Somewhat worse ☐ Much worse

2) How much pain have you had during the past week?

No pain — Worst pain

0 1 2 3 4 5 6 7 8 9 10

3) In general, how has your arthritis been during the past week?

Very good — Very bad

0 1 2 3 4 5 6 7 8 9 10

PaGA (0-100)

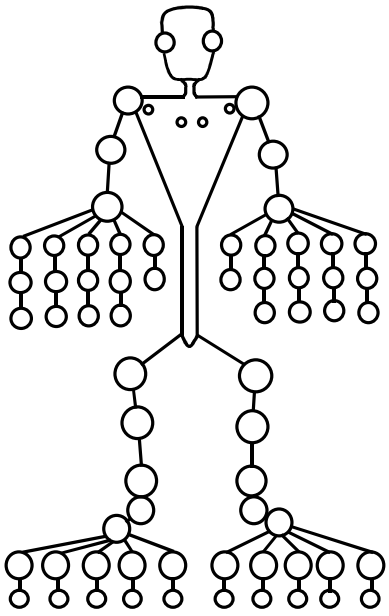
Physician

Physician's global assessment of disease

Very good — Very bad

0 1 2 3 4 5 6 7 8 9 10

- NSJ:
- NPJ:
- RI:
- ESR: / CRP:



DAS = 0.54 ($\sqrt{RI}$ + 0.065(NSJ) + 0.33 (ln ESR) + 0.0072(PaGA)

DAS28 = 0.56($\sqrt{NPJ28}$) + 0.28($\sqrt{NSJ28}$) + 0.70(ln ESR) + 0.014(PaGA)

During the <u>past week</u>, were you able to…

		↓	↓	↓	↓
Dressing	1) Dress yourself alone, including tying shoelaces and doing buttons?	☐	☐	☐	☐
	2) Shampoo your hair?	☐	☐	☐	☐
Arising	3) Stand up from a straight chair?	☐	☐	☐	☐
	4) Get in and out of bed?	☐	☐	☐	☐
Eating	5) Cut your meat?	☐	☐	☐	☐
	6) Open a new carton of milk?	☐	☐	☐	☐
walking	7) Drink by yourself?	☐	☐	☐	☐
	8) Walk outdoors on flat ground?	☐	☐	☐	☐
	9) Climb up five steps?	☐	☐	☐	☐
Hygiene	10) Wash and dry your entire body?	☐	☐	☐	☐
	11) Get on and off the toilet?	☐	☐	☐	☐
	12) Take a shower?	☐	☐	☐	☐
Reaching	13) Get a 1 Kg bag of sugar down from a shelf located above your head?	☐	☐	☐	☐
	14) Bend down to pick up clothing from the floor?	☐	☐	☐	☐
Gripping	15) Open a car door?	☐	☐	☐	☐
	16) Open jars which have been previously opened?	☐	☐	☐	☐
	17) Turn faucets on and off?	☐	☐	☐	☐
Other	18) Run errands and shop?	☐	☐	☐	☐
	19) Get in and out of a car?	☐	☐	☐	☐
	20) Do chores such as sweeping or washing dishes?	☐	☐	☐	☐

SCALE	
PD	HAQ
0	0.000
1	0.125
2	0.250
3	0.375
4	0.500
5	0.625
6	0.750
7	0.875
8	1.000
9	1.125
10	1.250
11	1.375
12	1.500
13	1.625
14	1.750
15	1.875
16	2.000
17	2.125
18	2.250
19	2.375
20	2.500
21	2.625
22	2.750
23	2.875
24	3.000

Check the activities for which you **need help from another person:**

Washing, grooming .☐ Standing up.☐ Eating ..... ☐ Walking ..... ☐

Personal hygiene .....☐ Reaching.....☐ Opening and closing things ..... ☐ Errands and chores ..... ☐

Check any of these aids or devices that you usually use:

Cane, crutches, walker or wheelchair .....☐ Cutlery with wide handles..... ☐

Seat or special bar for the bathtub .....☐ Raised toilet seat ..... ☐

Jar opener for jars previously opened ☐

Instructions for scoring the Spanish version of the Health Assessment Questionnaire (HAQ)

Description. The HAQ is a **20-item** self-administered questionnaire that evaluates the degree of difficulty of performing 20 activities of daily living, grouped into eight areas (the number of items per area is shown in parentheses): a) dressing and grooming (2); b) arising (2); c) eating (3); d) walking (2); e) personal hygiene (3); f) reaching (2); g) gripping (3); and h) other activities (3). Each item is rated from 0 to 3 on the following scale: 0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do. The questionnaire also includes several **corrective questions** asking about the need to use any type of AID OR DEVICE or HELP FROM ANOTHER PERSON to carry out the activities described in the 20 items. These questions are of interest because they can modify (correct) the score in the areas affected.

In the case of aids or devices, there are questions about the need to use:
- Cane or crutches, walker, wheelchair .....affect area d) walking
- Cutlery with wide handles.....affect area c) eating
- Special seat or bar for the bathtub,
  raised toilet seat.....affect area e) personal hygiene
- Opener for previously opened jars.....affect area g) gripping

The need for help from another person can affect all of the areas.

Evaluation.

a) First, **choose the highest score** of the 2 or 3 items that comprise each of the 8 areas of the questionnaire: a) dressing, b) arising, c) eating,... h) other activities.
For example, in the category "**c) eating**", if the patient answers the following:
¿Are you able to...
1. Cut your meat?.....[1] (with some difficulty)
2. Open a new carton of milk?.....[2] (with much difficulty)
3. Drink by yourself?.....[0] (without any difficulty)
Score [2], that is, the highest value of the three items that make up the category.

b) **Modify the score for each area in accordance with the corrective questions, as necessary.** If the score for an area is [2] or [3], there is no need to look at the corrective questions. But if the score is less than [2], the fact that the patients indicates a need for some AID OR DEVICE or the HELP OF ANOTHER PERSON for any activity related with that area, means that a score of [2] should be assigned to that area.
For example; if in the area "**d) walking**" the patient answers:
¿Are you able to...
1. Walk outdoors on flat ground? .....[0] (without any difficulty)
2. Climb five steps?.....[1] (with some difficulty)
But further down checks the box indicating that he/she uses crutches, the score for the area "walking" will be [2] instead of [1].

c) **Calculate the mean**. Find the mean of the 8 values corresponding to the 8 areas described: a) dressing, b) arising, c) eating,... h) other activities. This will be the direct score (DS) for the HAQ functional capacity questionnaire. The direct score, after being transformed according to the HAQ scale, can range between 0 (no disability) and 3 (maximum disability). Questions not answered will be assigned the highest value of the

remaining items making up that area. If one or two whole areas are not answered, the sum of the 7 or 6 other areas will be divided by 7 or 6, respectively, to obtain the mean value, which will be between zero and three (0-3). Questionnaires with answers for fewer than 6 areas are probably not valid.

Indices for the evaluation of swollen and painful joints

	ACR (66/68)	Ritchie (53)	NSJ (44)	Fuchs (28)
Cervical spine	-	+*m	-	-
Temporomandibular	+	+*	-	-
Sternoclavicular	+	+*	+	-
Acromioclavicular	+	+*	+	-
Shoulder	+	+	+	+
Elbow	+	+	+	+
Wrist	+	+	+	+
Metacarpophalangeal	+	+*	+	+
Proximal interphalangeal	+	+*	+	+
Distal interphalangeal	+	-	-	-
Hip	+	+ m	-	-
Knee	+	+	+	+
Ankle	+	+	+	-
Subtalar	+	+ m	-	-
Midtarsal	+	+ *m	-	-
Metatarsophalangeal	+	+*	+	-
Interphalangeal (foot)	+	-	-	-

- The joints marked with an asterisk (*) are counted as a single joint.
- The ARA/ACR index counts the subtalar and midtarsal joints as a single joint.
- The Ritchie index quantifies the presence of tenderness or pain on motion (m) on a scale of 0 to 3.

Disease Activity Score

Ranges between 0 (no disease activity) and 10 (maximum disease activity).

DAS28 with four variables:

$$\text{DAS28} = 0.56(\sqrt{NPJ28}) + 0.28(\sqrt{NSJ28}) + 0.70(\ln \text{ESR}) + 0.014(\text{PaGA})$$

DAS28 with three variables:

$$\text{DAS28} = 0.56(\sqrt{NPJ28} + 0.28(\sqrt{NSJ28}) + 0.70\ (\ln \text{ESR}) + 1.08 + 0.16$$

Formula to transform original DAS to DAS28:

$$\text{DAS28} = 1.072(\text{DAS}) + 0.938$$

Original DAS with four variables:

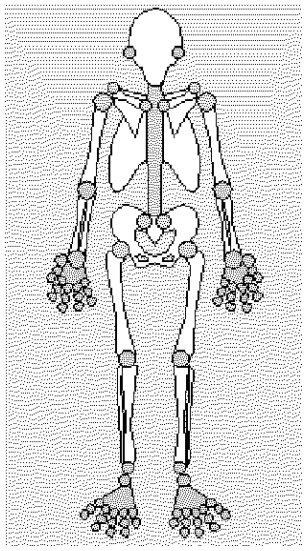
$$\text{DAS}=0.54(\sqrt{RI}) + 0.065(\text{NSJ44}) + 0.33(\ln \text{ESR}) + 0.0072(\text{PaGA})$$

Original DAS with three variables:

$$\text{DAS} = 0.54(\sqrt{RI}) + 0.065(\text{NSJ44}) + 0.33(\ln \text{ESR}) + 0.224$$

NPJ28: Number of painful joints based on a count of 28 joints
NSJ28: Number of swollen joints based on a count of 28 joints
ln: Natural logarithm
ESR: Erythrocyte sedimentation rate
PGA: Patient's global assessment of health or disease on a VAS from 0 (very good) to 100 (very poor). Either of the two scales produces the same results, although the latter one is preferable.
RI: Ritchie index
NSJ44: Number of swollen joints based on a count of 44 joints

Joint counts



ACR Count. The ACR (previously the ARA - American Rheumatism Association) count can be defined as the most complete index [Deandrade, 1965; Williams, 1983; Ward, 1983; Paulus, 1984]. It is the US standard. It includes evaluation of tenderness to pressure in 68 joints and of swelling in 66 joints (excluding both hips). The following joints are assessed: distal interphalangeal, proximal interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, acromioclavicular, sternoclavicular, temporomandibular, hip (only for pain), knee, ankle, subtalar-midtarsal, metatarsophalangeal, and proximal interphalangeal joints.

Ritchie Index. This is the European index most commonly used. It includes assessment of pain alone in 53 joints and is calculated based on 26 joints, since some joints are considered together [Ritchie, 1968]. The following joints or groups of joints are evaluated: right and left proximal interphalangeal (2), right and left metacarpophalangeal (2), wrist (2), elbow (2), shoulder (2), cervical spine (1), acromioclavicular (1), sternoclavicular (1), temporomandibular (1), hips (2), knee (2), ankle (2), subtalar (2), midtarsal (2), and right and left metatarsophalangeal (2) joints. This method quantifies joint tenderness or pain on motion only in the case of the cervical spine, hip, subtalar and midtarsal joints. Pain is scored on a 4-level scale: 0 = no pain; 1 = pain; 2 = pain and wincing; 3 = pain, wincing, and withdrawal (maximum score: 78). In the case of joint groups, the highest score assigned to any of the joints in the group is assigned to the whole group.

44-joint Index. Swelling is evaluated in the following 44 joints: proximal interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, acromioclavicular, sternoclavicular, knee, ankle, and metatarsophalangeal joints. The fact that swollen joints are included in this index makes it a complement to the Ritchie index.

28-Joint Index. Fuchs et al. [Fuchs, 1989] observed that a simple evaluation of tenderness and swelling in 28 joints provided the same sensitivity to change in clinical trials as more complex indices [Fuchs, 1994]. The index includes the following joints: proximal interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, and knee joints.

When counting joints, one can either make a simple count of the number of painful and swollen joints (present/absent) or semi-quantify the degree of pain and swelling in each joint using a 4-level ordinal scale (0-3). This guideline recommends counting painful and swollen joints without adding any type of quantification. The advantages obtained by quantifying are lost in the increased variability of the measurements.

The ACR recommended the use of complete counts on 68 joints, although it later accepted the use of counts based on 28 joints in clinical trials. The same committee emphasized, however, that indices based on 28 joints exclude those in the foot and ankle, which are affected in over 50% of patients, therefore they provide less information at the individual level in daily clinical practice [OMERACT, 1994]. The use of a reduced index does not mean that these joints should not be examined. Thus, this guideline recommends the use of the ACR index of 68 joints.

ACRONYMS

ABT	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
AEME	*Agencia Española del Medicamento* (Spanish Medicines Agency)
AHT	Arterial hypertension
AIMS	Arthritis Impact Measurement Scales
AMI	Acute myocardial infarction
ANK	Anakinra
Anti-CCP	Anti-cyclic citrullinated peptide antibodies
Anti-TNF	Anti-tumor necrosis factor
APR	Acute phase reactants
AUR	Oral gold
AZT	Azathioprine
BAL	Bronchoalveolar lavage
BOOP	Bronchiolitis obliterans organizing pneumonia
BP	Blood pressure
CCP	Cyclic citrullinated peptides
CCT	Controlled clinical trial
CDAI	Clinical Disease Activity Index
CI	Confidence interval
CLQ	Chloroquine
COBRA	*Combinatietherapie Bij Reumatoide Artritis* (Combination therapy in rheumatoid arthritis: corticosteroids + DMARD)
COMB	Combination
CRP	C-reactive protein
CSA	Cyclosporin
CT	Clinical trial
CTX	Cyclophosphamide
DAS	Disease Activity Score
DM	Difference between means
DMARD	Disease-modifying anti-rheumatic drug
DPC	D-penicillamine
EMEA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
EULAR	European Leagues Against Rheumatism
FDA	Food and Drug Administration
GUIPCAR	*Guía de práctica clínica de la Rheumatoid arthritis* (Rheumatoid Arthritis Clinical Practice Guideline)
GUIPCAR_2006	Update of GUIPCAR
GLM	Golimumab
HAQ	Health Assessment Questionnaire

HCQ	Hydroxychloroquine
IFX	Infliximab
IG	Injectable gold
ILAR	International Leagues Against Rheumatism
IME	*Índice Médico Español* (Spanish Medical Index)
LEF	Leflunomide
LPIA	Least possible inflammatory activity
LS	Likert scale
MHAQ	Modified Health Assessment Questionnaire
MR	Magnetic resonance
MTX	Methotrexate
NHP	Nottingham Health Profile
NPJ	Number of painful joints
NS	Numerical scale
NSAID	Nonsteroidal anti-inflammatory drugs
NSJ	Number of swollen joints
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
OT	Occupational therapy
PaGA	Patient's global assessment of health
PE	Patient education
PhGA	Physician's global assessment of health
RA	Rheumatoid arthritis
RAQol	Rheumatoid arthritis quality of life
RCCT	Randomized controlled clinical trial
RCT	Randomized clinical trial
RF	Rheumatoid factor
RI	Ritchie index
ROAD	Recent Onset Arthritis Disability index
ROAU	Recent-onset arthritis unit
RR	Risk ratio
RR	Relative risk
RTX	Rituximab
SDAI	Simplified Disease Activity Index
SER	*Sociedad Española de Reumatología* (Spanish Rheumatology Society)
SF	Short Form
SIP	Sickness Impact Profile
SR	Systematic review
SSS	Secondary Sjögren's syndrome
SSZ	Sulfasalazine
TAISS	*Técnicas Avanzadas de Investigación en Servicios de Salud* (Advanced Research Techniques in the Health Services)
TENS	Transcutaneous electrical nerve stimulation
TCZ	Tocilizumab
VAS	Visual analogue scale

VASn	Visual analogue scale with numerical descriptors
WHO	World Health Organization

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3. Articles that complement one of the articles on the clinical trials (tables 22 and 23)

Complement of 22

C1. Weinblatt ME, Polisson R, Blotner SD, Sosman JL, Aliabadi P, Baker N, et al. The effects of drug therapy on radiographic progression of rheumatoid arthritis: results of a 36-week randomized trial comparing methotrexate and auranofin. Arthritis Rheum 1993; 36(5): 613-9.

Complement of 23

C2. Lopez-Mendez A, Daniel WW, Reading JC, Ward JR, Alarcon GS. Radiographic assessment of disease progression in rheumatoid arthritis patients enrolled in the cooperative systematic studies of the rheumatic diseases program randomized clinical trial of methotrexate, auranofin, or a combination of the two. Arthritis Rheum 1993; 36(10): 1364-9.

Complement of 37

C3. Ward JR, Williams HJ, Boyce E, Egger MJ, Reading JC, Samuelson CO. Comparison of auranofin, gold sodium thiomalate, and placebo in the treatment of rheumatoid arthritis: subsets of responses. Am J Med 1983; 75(6A): 133-7.

Complement of 40

C4. Davis P, Menard H, Thompson J, Harth M, Beaudet F. One-year comparative study of gold sodium thiomalate and auranofin in the treatment of rheumatoid arthritis. J Rheumatol 1985; 12(1): 60-7.

Complement of 44

C5. Van Riel PLCM, Larsen A, Van de Putte LBA, Gribnau FWJ. Effects of aurothioglucose and auranofin on radiographic progression in rheumatoid arthritis. Clin Rheumatol 1986; 5(3): 359-64.

Complement of 46

C6. Schattenkirchner M, Kaik B, Muller-Fassbender H, Rau R, Zeidler H. Auranofin and sodium aurothiomalate in the treatment of rheumatoid arthritis: a double-blind, comparative multicenter study. J Rheumatol Suppl 1982; 8: 184-9.

Complement of 54

C7. Rau R, Herborn G, Menninger H, Sangha O. Progression in early erosive rheumatoid arthritis: 12 month results from a randomized controlled trial comparing methotrexate and gold sodium thiomalate. Br J Rheumatol 1998; 37(11): 1220-6.

C8. Rau R, Herborn G, Menninger H, Blechschmidt J. Comparison of intramuscular methotrexate and gold sodium thiomalate in the treatment of early erosive rheumatoid arthritis: 12 month data of a double-blind parallel study of 174 patients. Br J Rheumatol 1997; 36(3): 342-52.

Complement of 56

C9. Porter D, Madhok R, Hunter JA, Capell HA. Prospective trial comparing the use of sulphasalazine and auranofin as second line drugs in patients with rheumatoid arthritis. Ann Rheum Dis 1992; 51(4): 461-4.

Complement of 57

C10. Capell HA, Marabani M, Madhok R, Torley H, Hunter JA. Degree and extent of response to sulphasalazine or penicillamine therapy for rheumatoid arthritis: results from a routine clinical environment over a two-year period. Q J Med 1990; 75(276): 335-44.

Complement of 59

C.11. Heijde DM, Riel PL, Nuver-Zwart IH, Gribnau FW, Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989; 1(8646): 1036-8.

C12. Van der Heijde DM, Van Riel PLCM, Van de Putte LBA. Sensitivity of a Dutch Health Assessment Questionnaire in a trial comparing hydroxychloroquine vs sulphasalazine. Scand J Rheumatol 1990; 19(6): 407-12.

4. Articles that are redundant with one of the articles on clinical trials (tables 22 and 23)

Redundant with 1

R1. Woodland J, Mason RM, Harris J, Dixon AS, Currey HL, Brownjohn AM, et al. Trial of azathioprine, cyclophosphamide, and gold in rheumatoid arthritis. Ann Rheum Dis 1974; 33(4): 399-401.

Redundant with 7

R2. Berry H, Liyanage S, Durance R, Barnes CG, Berger L. Trial comparing azathioprine and penicillamine in treatment of rheumatoid arthritis. Ann Rheum Dis 1976; 35(6): 542-3.

Redundant with 19

R3. Strand V, Tugwell P, Bombardier C, Maetzel A, Crawford B, Dorrier C, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Arthritis Rheum 1999; 42(9): 1870-8.

Redundant with 25

R4. Jeurissen MEC, Boerbooms AMT, Van de Putte LBA, Doesburg WH, Lemmens AM. Influence of methotrexate and azathioprine on radiologic progression in rheumatoid arthritis: a randomized, double-blind study. Arch Intern Med 1991; 114: 999-1004.

R5. Kerstens PJSM, Boerbooms AMT, Jeurissen MEC, Westgeest TAA, Van Erp A, Mulder J, et al. Antiperinuclear factor and disease activity in rheumatoid arthritis: longitudinal evaluation during methotrexate and azathioprine therapy. J Rheumatol 1994; 21(12): 2190-4.

Redundant with 26

R6. Willkens RF, Stablein D. Combination treatment of rheumatoid arthritis using azathioprine and methotrexate: a 48-week controlled clinical trial. J Rheumatol 1996; 23(supl. 44): 64-8.

R7. Willkens RF, Urowitz MB, Stablein DM, McKendry RJR, Berger RG, Box JH, et al. Comparison of azathioprine, methotrexate, and the combination of both in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum 1992; 35(8): 849-56.

Redundant with 37

R8. Williams HJ, Ward JR, Egger MJ, Reading JC, Samuelson CO, Altz-Smith M, et al. Auranofin, gold sodium thiomalate, and placebo in the treatment of rheumatoid arthritis: cooperative systematic studies of rheumatic diseases. Clin Rheumatol 1984; 3(suppl.1): 39-50.

R9. Williams HJ, Ward JR. Comparison of oral and parenteral gold therapy and placebo in the treatment of rheumatoid arthritis. Scand J Rheumatol Suppl 1983; 51: 92-9.

Redundant with 46

R10. Schattenkirchner M, Bröll H, Kaik B, Müller-Fassbender H, Rau R, Zeidler H. Auranofin and gold sodium thiomalate in the treatment of rheumatoid arthritis: a one-year, double-blind, comparative multicenter study. Klin Wochenschr 1988; 66(4): 167-74.

Redundant with 48

R11. Huskisson EC, Gibson TJ, Wykeham Balme H, Berry H, Burry HC, Grahame R, Dudley Hart F, et al. Penicillamine or gold for rheumatoid arthritis?: multicentre trial using 'blind' observers: the first six months. Ann Rheum Dis 1974; 33(4): 399.

Redundant with 59

R12. Van der Heijde DMFM, Van Riel PLCM, Nuwer-Zwart IH, Van de Putte LBA. Alternative methods for analysis of radiographic damage in a randomized, double blind, parallel group clinical trial comparing hydroxychloroquine and sulfasalazine. J Rheumatol 2000; 27(2): 535-8.

Redundant with 71

R13. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999; 354(9194): 1932-9.

X. Participants

Expert panel

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Víctor Manuel Martínez Tabeada, rheumatologist, *Hospital Universitario Marqués de Valdecilla*, Santander. Licensed in Medicine and Surgery, *Universidad de Zaragoza* (1988), and Doctor of Medicine, *Universidad de Cantabria* (1998). Specialist in Rheumatology via MIR*, Hospital Universitario "Marqués de Valdecilla"* (1989-1992). Completed training at the Lupus Research Unit (The Rayne Institute, St. Thomas' Hospital, London, England; Clinical Fellow 1992) and in the Rheumatology Research Unit (Mayo Clinic, Rochester, Minnesota, US; Research Fellow 1993-1995). Currently Associate Physician (Area Specialist), Rheumatology Service, *Hospital Universitario "Marqués de Valdecilla*" and Associate Professor, Department of Medicine and Psychiatry, *Universidad de Cantabria*.

José María Salazar Vallinas, rheumatologist, *Hospital Regional Universitario Infanta Cristina*, Badajoz. Licensed in Medicine and Surgery (*Universidad Autónoma de Madrid*, 1977), Specialist in Rheumatology via MIR (*Hospital Ramón y Cajal*, Madrid 1980-83) and in Family and Community Medicine (Ministry of Education and Science, 1987), Master of Public Health (*Escuela Nacional de Sanidad*, Madrid 1986). Specialist in Rheumatology, *Hospital Regional Universitario Infanta Cristina de Badajoz* from 1987 to present. Associate Professor of Health Sciences, Department of Human Clinical Pathology, Area of Medicine/Rheumatology, *Universidad de Extremadura*, since 1989. Formerly President and Founding Member of the Extremadura Association of Rheumatology and board member of the Spanish Society of Rheumatology. Responsible for residency training in the Specialty of Family and Community Medicine and member of the Educational Committee (1988-95) and the Clinical History Committee (1990-96), *Hospital Regional Universitario Infanta Cristina de Badajoz*.

Alejandro Tejedor Varillas, Specialist in Family and Community Medicine, *Centro de Salud "Las Ciudades"* de Getafe, Madrid. Licensed in Medicine and Surgery. Specialist in Family and Community Medicine via MIR, 1991, in the *Hospital 12 de Octubre* and Area X of the *Insalud* (Madrid). Currently family physician, *Centro de Salud "Las Ciudades" de Getafe* (IMSALUD – MADRID). Responsible for MIR training in Family and Community Medicine and Coordinator of the National Group on Rheumatology of the SEMFYC since 1993. Associate physician in Emergency Medicine, *Hospital Universitario de Getafe,* in the areas of Traumatology and Internal Medicine since 1992.

Juana de la Torre Aboki, nurse, *Hospital General Universitario de Alicante*. Bachelor of Nursing, Dutch University *Hogeschool Zealand*. Co-manager of the Rheumatology Day Hospital, *Hospital General Universitario de Alicante*, responsible for programming, management and follow-up of biologic therapies. Associate professor of university course on Medical-Surgical Nursing III, *Universidad San Pablo-CEU* (Elche).

Coordinators

Pablo Lázaro de Mercado, Director, TAISS, Madrid. Founder and Director of the Health Services Research Unit (UISS in Spanish) of the *Instituto de Salud Carlos III* (1993-2000). Vice-director General of Health and Technology Evaluation, Ministry of Health and Consumer Affairs (1997-98). Licensed in Medicine (*Universidad Complutense de Madrid*, 1973). Doctor of Medicine (*Universidad Autónoma de Madrid*, 1989). Specialist in Internal Medicine and in Pulmonology (1977). Residency in Pulmonology, *Hospital 12 de Octubre de Madrid* (1974-77), and Associate Physician in Pulmonology, *Hospital Ramón y Cajal de Madrid* (1978-86). Master of Business Administration, *IESE* (1989). Post-doctoral studies in health policy analysis, RAND/UCLA Center for Health Policy Analysis, Santa Monica, California (US), where he helped develop clinical practice guidelines (1990-93). Experienced in health services research, socioeconomic evaluation, evaluation of medical technology, development of clinical practice guidelines and appropriateness criteria for clinical procedures.

Mª Dolores Aguilar Conesa, TAISS investigator, Madrid. Licensed in Medicine and Surgery (*Universidad de Murcia*, 1979). Specialist in Internal Medicine (1983). Master of Public Health, *Centro Universitario de Salud Pública* (1990). Doctor in Preventive Medicine and Public Health, *Universidad Autónoma de Madrid* (2005). Has worked since 1991 as investigator in various institutions (Center for Health Evaluation and Research, Health Services Research Unit, *Instituto de Salud Carlos III*, and Téc*nicas Avanzadas de Investigación en Servicios de Salud*). Experienced in clinical epidemiology, health services research, socioeconomic evaluation, evaluation of medical technology, development of clinical practice guidelines and appropriateness criteria for clinical procedures.

Loreto Carmona, rheumatologist, Director of the Research Unit of the *Fundación Española de Reumatología*. Licensed in Medicine and Surgery, Specialist in Rheumatology. Has carried out clinical and epidemiological research on rheumatic diseases over the last 10 years, after two years' training in the Arthritis Research Group of the University of California in San Francisco. Currently directs the Research Unit of the Spanish Society of Rheumatology, where she coordinates numerous studies and advises rheumatologists on clinical research projects. Contracted in 2001-2002 by the *Fundación del Hospital de la Princesa* for an Iberoamerican Cochrane Collaboration project, after which she produced various systematic reviews, and is a regular reviewer and professor of reviewers of the Spanish Society of Rheumatology. Has worked in the Spanish Medicines Agency as the technical person responsible for evaluation reports on products related with rheumatology.

Reviewers

Lydia Abásolo Alcázar, rheumatologist, *Hospital Clínico de San Carlos*, Madrid. Licensed in Medicine, *Universidad Complutense de Madrid* (1995). Specialist in Rheumatology (2001). Area Specialist, *Hospital Clínico de San Carlos* (2001-2005). Post-MIR research

contract since 2005, for training in clinical epidemiology. Completed course on "Evaluation of the Evidence" in the Spanish Society of Rheumatology (2005). Member of the SER panel of reviewers since 2005. Professor of continuing education course on conducting systematic reviews at the Spanish Foundation of Rheumatology in April 2006.

Cayetano Alegre de Miquel, rheumatologist, *Hospital Universitario Vall d'Hebron*, Barcelona. Doctor of Medicine and Surgery, *Universitat Autònoma de Barcelona*. Specialist in Rheumatology, *Hospital de les Malalties Reumàtiques*. Chief of Section of the Rheumatology Unit, *Hospital Universitario Vall d'Hebron,* and Chief of Service, *Instituto Universitario Dexeus*. Currently responsible for the Fibromyalgia Unit, *Hospital Vall d'Hebron*. Master in Psychology, *Universidad de Barcelona*. Reviewer of the evidence in Rheumatology for the SER since 2004.

Eugenio Chamizo Carmona, rheumatologist, General Hospital of Merida. Born in 1958, he is a rheumatologist at the General Hospital of Merida. Licensed in Medicine and Surgery at the Autonomous University of Madrid (1984). Specialist in Rheumatology via MIR (University Hospital Doce de Octubre, Madrid, 1986-89). Since 1990 he is Rheumatology associated at the Hospital of Merida, where he participates in representative bodies at the hospital (JTA Commission direction) and in the commission of medical records (since 1990), of which he is president since 1998. He has been a member of the SER, president of the AREX and treasurer of the FACME. Since 1996 he has participated as principal investigator in numerous clinical trials and epidemiological studies. Since 2005 is part of the panel of SER reviewers and since 2006 he is in the working group RBE of the SER.

Antonio Fernandez Nebro, rheumatologist, Carlos Haya Hospital, Malaga. Licensed in Medicine and Surgery at the University of Malaga (1984) and Doctor in Medicine, University of Malaga (1990). He did the specialty of rheumatology (via MIR) at the Regional Hospital Carlos Haya (1985-1989). He has worked as Associate Rheumatologist at the Hospital Universitario Virgen de la Victoria (1990-2004). He is currently Associate Professor of Health Sciences (since 1994) and Head of Department of Rheumatology of Carlos Haya Hospital in Malaga University (since 2004). He is a reviewer of the Spanish Society of Rheumatology (2004).

Maria Rosa Gonzalez Crespo, Rheumatology, Hospital Doce de Octubre, Madrid. Associate Physician Department of Rheumatology. Doctor in Medicine by the Complutense University, Madrid. Master of Analysis and Management of Science and Technology, Universidad Carlos III de Madrid. Specialist in Clinical Research Methodology of CUSP Autonomous University. She has published several articles in national and international journals of the specialty. She has written several chapters of books for the SER. She has participated in some systematic reviews for the SER.

Miguel Angel Hernandez Abad, rheumatologist, Hospital Virgen del Puerto, Caceres. Licensed in Medicine (Universidad Complutense de Madrid, 1991), specialist in Rheumatology via MIR (Hospital General Gregorio Marañon). He has worked as an associate specialist at the General Hospital Universitario de Guadalajara and at the Hospital Virgen del Carmen (Ciudad Real). Currently he is associate rheumatologist at Hospital Virgen del Puerto (Plasencia) since 2001. He belongs to the group of Rheumatology based on evidence from the SER. He is responsible for the clinical practice of pages of the web of the SER.

Blanca Hernandez Cruz, Rheumatology, Hospital Virgen Macarena, Seville. Licensed in Medicine, University of Veracruz, Mexico. Specialist in Internal Medicine, National Autonomous University of Mexico, Mexico. Specialist in Rheumatology, National Autonomous University of Mexico, Mexico. Master of Clinical Epidemiology, National Autonomous University of Mexico, Mexico. Doctor in Medicine, University of Seville, Spain. Researcher and Head of Research Unit in rheumatic diseases at the Rheumatology department, Hospital Universitario Virgen Macarena, Seville.

Jesús Maese, rheumatologist, Madrid. Licensed in Medicine and Surgery (*Universidad Complutense de Madrid,* 1977). Specialist in Rheumatology (School of Rheumatology, Faculty of Medicine, *Universidad Complutense de Madrid*, 1980). Master in Public Health (*Centro Universitario de Salud Pública*, 1998). Master in Health and the Environment (*Centro Universitario de Salud Pública*, 1997/1999). Accredited as Investigator with the Diploma for Advanced Studies (*Universidad Complutense*, Madrid, 2003). Monitored various projects in epidemiology (EMECAR, PROAR, SERAP) at the Research Unit of the Spanish Foundation of Rheumatology. Member of the working group on Evidence-Based Rheumatology.

Jose de la Mata Llord, rheumatologist, Hospital de la Zarzuela, Aravaca. Dr Jose de la Mata (1964), Licensed in Medicine at the Autonomous University of Madrid (1988), specialist in rheumatology at the hospital "12 de Octubre". Doctor in Medicine at the University of Alcala de Henares. Postdoctoral 18 month stay at the University of Texas Health Science Center (San Antonio, Texas). He currently directs rheumatology units of the Hospital de la Zarzuela clinic and Our Lady of the Valley in Madrid.

Esteban Mazzucchelli, rheumatologist, *Fundación Hospital Alcorcón*, Madrid. Licensed in Medicine and Surgery (*Universidad Autónoma de Madrid*, 1987). Specialist in Rheumatology (*Clínica Puerta de Hierro*). Since 1993, Associate Physician in Rheumatology in various Spanish hospitals, currently, the *Fundación Hospital Alcorcón*. Member of the SER group of reviewers since 2005.

Santiago Munoz, rheumatologist, Hospital La Paz, Madrid. Licensed in Medicine and Surgery in 1988 (Autonomous University of Madrid), specialist in Rheumatology (University Hospital La Paz 1989-1992), fellow of the FIS in the service of Immunology, same hospital during 1993. Degree of Doctor of Medicine at the Autonomous University of Madrid in 1997. Associate Specialist in La Paz University Hospital since 1993 where he is responsible for the area of Rheumatology Unit Uveitis since 1997. Technical Secretary of LIRE during the years 2002-03. Lead researcher and collaborator of several FIS projects associated with rheumatoid arthritis. Research lines: Events in rheumatological HIV infection; immunology of RA; uveitis and rheumatological diseases; early spondyloarthritis. Member of the groups of systematic review of evidence and of Uveitis of the SER.

M Betina Nishishinya, rheumatologist, *Hospital de la Santa Creu i Sant Pau*, Barcelona. Rheumatologist with 10 years' experience in clinical rheumatology and 7 years' experience in clinical and epidemiological research in rheumatic diseases. Two years' training in epidemiology in the master's program jointly directed by the *Hospital Italiano*, the *Universidad de Medicina de Buenos Aires* and the Harvard School of Public Health, in Argentina. Currently working in the Clinical Epidemiology and Public Health Service and in the Rheumatology Service of the *Hospital de la Santa Creu i Sant Pau*. Member of the Spanish Society of Rheumatology, collaborates with the Research Unit of the Spanish Society of Rheumatology (SER), SER working group on

Evidence-Based Rheumatology, as regular reviewer on different subjects related with the specialty. Also collaborates with the Iberoamerican Cochrane Center in conducting systematic reviews.

Ana Ortiz García, Rheumatology, Hospital de La Princesa, Madrid. Licensed in Medicine and Surgery (University of Alcala de Henares, 1991). Specialist in Rheumatology via MIR (Hospital Universitario de la Princesa, Madrid, 1994-1997). Ph.D. in Medicine with merits award (Autonomous University of Madrid, 2004). At present she works as Associate rheumatologist at Hospital Universitario de la Princesa since 1999 and collaborates on several projects funded by the FIS and related study of rheumatoid arthritis. She was trained in Systematic Literature Review in the course "Evaluating the evidence in Rheumatoid Arthritis" of the Spanish Society of Rheumatology (2003) and since then she is part of the SER reviewers.

Claudia A. Pereda Testa, rheumatologist, *Clínica Mediterráneo*, Almería. Specialist in Rheumatology (*Universidad de Buenos Aires*). Doctor in Medicine, University of Sheffield (United Kingdom). Rheumatologist at the *Clínica Mediterráneo – Almería*. Reviewer for the Spanish Society of Rheumatology (SER).

Conflicts of interest

• Mª Dolores Aguilar Conesa	Works in a company that conducts health services research, sometimes financed by the pharmaceutical industry, thus indirectly is receiving or has received income from the industry under investigation.
• Loreto Carmona	Coordinates research studies (not on efficacy) and gives courses in which there is or has been partial or complete financing from laboratories related with rheumatoid arthritis treatment (Wyeth, Schering, Abbott, BMS, MSD, Pfizer, Novartis and Aventis).
• Pablo Lázaro de Mercado	Works in a company that conducts health services research, sometimes financed by the pharmaceutical industry, thus indirectly is receiving or has received income from the industry under investigation.
• Alejandro Balsa Criado	Has received a *Fundación Española de Reumatología*-Abbott research grant and has been a speaker at events sponsored by Schering, Abbott, Wyeth, Roche, BMS and UCB-Pharma.
• Alejandro Tejedor Varillas	No conflicts of interest
• Ángel Elena Ibáñez	No conflicts of interest
• César Hernández García	No conflicts of interest
• Enrique Batlle Gualda	Has received income from Sanofi-Aventis, Shering-Plough, Abbott and Wyeth for research studies, talks, courses and continuing medical education activities.
• Federico Díaz González	Receives income for research from Schering, Abbott and Roche, and for consulting activities from Roche, BMS and UCB.
• Fernando García Pérez	No conflicts of interest
• Juana de la Torre	Has received economic compensation from Schering Plough, Abbott and Wyeth Laboratories for conducting research projects, talks, consulting, and continuing education activities. Does not possess any economic interests related with these laboratories.
• José Luis Andréu Sánchez	No conflicts of interest
• José Luis Marenco de la Fuente	Receives income for research from Schering, Abbott and Roche, and for consulting activities from Roche, BMS and UCB.

• José Mª Salazar Vallinas	No conflicts of interest
• Mª Victoria Irigoyen Oyarzábal	No conflicts of interest
• Mariano Tomás Flórez García	No conflicts of interest
• Nuria Guañabens Gay	Has been consultant for Novartis
• Víctor Martínez Taboada	Has received money for research from Schering-Plough and Wyeth-Pharma. Has given talks for Pharmacia-Pfizer, Schering-Plough, Lilly, Zambon, Wyeth-Pharma, Abbott, Almiral, Brystol-Myers Squibb, and Roche. Has organized and participated in Continuing Medical Education for Abbott and Brystol-Myers Squibb. Has performed consulting activities for UCB-Pharma. Has participated in clinical trials of Novartis, Schering-Plough, Wyeth-Pharma, Abbott, Brystol-Myers Squibb, Roche, Serono, and Amgem.
• Ana Ortiz García	No conflicts of interest
• Antonio Fernández Nebro	Has conducted conferences for Roche, Schering Plough, BMS, Abbott, Aventis and MSD. Has been consultant for Roche and Schering-Plough. Has received research grants from Roche and Schering-Plough. Has received educational material from Aventis, Pfizer and Novartis.
• Betina Nishishinya	Participated in a research project receiving money directly from Abbott.
Blanca Hernández Cruz	Receives, through the *Asociación Sanitaria Virgen Macarena,* a salary as investigator from Wyeth funds. Is investigator in multiple controlled clinical trials for Roche, Novartis, BMS, and Wyeth. Teacher for the Continuing Medical Education program of BMS and Roche. Has participated as consultant with Shering, BMS, Wyeth, and Roche.
• Cayetano Alegre de Miguel	Has received aids for continuing education from the Wyeth, Abbott and Schering Laboratories, in amounts of less than €3,000.
• Claudia Alejandra Pereda	No conflicts of interest
• Eugenio Chamizo Carmona	No conflicts of interest
• Jesús Maese	No conflicts of interest
• José de la Mata Llord	No conflicts of interest
• Lydia Abásolo Alcázar	No conflicts of interest
• Miguel Ángel Abad Hernández	No conflicts of interest
• Ramón Mazzuchelli	No conflicts of interest
Rafael Ariza Ariza	Has received income from Abbott for participating in teaching activities, and from Schering for consulting. No type of remuneration received from the Cochrane review of Adalimumab.
• Rosa González Crespo	No conflicts of interest
• Santiago Muñoz	Received an unrestricted research grant from Wyeth during 2006 and 2007. Is consultant for the Reumaconsult project of Schering-Plough. Is consultant for the "Go Ahead" spondyloarthropathies group of Abbot. Member of the Continuing Medical Education Group of Bristol-Myers.