CLINICAL PRACTICE GUIDELINES Management of Patients with Gout

SPANISH SOCIETY OF RHEUMATOLOGY



for the

CLINICAL PRACTICE GUIDELINES for the Management of Patients with Gout





These clinical practice guidelines serve to support decision making in healthcare. Adherence to these them is not obligatory and they are not a substitute for the clinical judgement of health professionals.

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Foreword

The Spanish Society of Rheumatology (SER) is a non-profit scientific association. Having recognised the need for developing this clinical practice guideline (CPG), SER has supported the process, deciding on the initial group of researchers to be involved in its development and the timetable for the work. It also signed agreements with the funding bodies safeguarding the editorial independence of the guideline developers regarding its contents.

The SER Research Unit selected the principal investigator (PI) and the panel members in accordance with current legislation, developed the methodology to be followed, and coordinated the meetings held and the drafting of the CPG, including the systematic reviews (SRs) of the evidence conducted as part of the process.

The main goal of this Clinical Practice Guideline for the Management of Patients with Gout is to provide practical recommendations for clinicians based on the best available scientific evidence on the most effective treatment and follow-up of this disease.

The content of this CPG brings the evidence available at the time of writing the previous GuipClinGot up to date, that is, including new evidence from the start of 2013 to the end of 2019. With advances in knowledge and the appearance of new evidence, it is anticipated that the guidelines should be updated again in 4 years' time.

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Collaborating organisations

Spanish Society of Rheumatology (SER) Spanish Society of Family and Community Medicine (semFYC) Spanish Society of Nephrology (SEN) Spanish Society of Skeletomuscular Radiology (SERME)

Members of these organisations have contributed to the authorship of the CPG.

Declaration of interests:

All members of the GuipClinGot working group have made declarations of interest and these are presented in Appendix 5.

Public scrutiny:

These guidelines were made available for public scrutiny. Information detailing this process is available from the Clinical Practice Guidelines section (under Research) on the SER website (www.ser.es).

Funding:

The development of this CPG, under the auspices of SER, has been funded by Grünenthal Pharma and Menarini. The printing of copies of the guide has been fully funded by Menarini. The Foundation of the Spanish Society of Rheumatology (FER), the body responsible for employing the staff of the SER Research Unit and coordinating payments to panellists and reviewers, acted completely independently. The funders had no direct or indirect influence on the selection of panellists, search for or interpretation of the evidence, or any part of the final draft of the



guidelines. In this way, it was ensured that the design of the process and analysis and interpretation of the results have been conducted completely independently of the industrial funders.

This guideline should be cited as follows:

GuipClinGot working group, Clinical Practice Guidelines for the Management of Patients with Gout, Madrid, Spanish Society of Rheumatology (SER), 2020.

Clinical questions of interest

Drugs as monotherapy

1. How effective and safe are urate-lowering drugs as monotherapy for the treatment of gout?

Combination therapy

2. How effective and safe is combination therapy for gout?

Imaging tests for monitoring treatment response

3. How useful are imaging tests for the follow-up of patients with gout?

Chronic kidney disease

4. How effective and safe is gout treatment in patients with chronic kidney disease?

Impact of gout treatment on cardiovascular disease

5. Are patients with gout treated with urate-lowering drugs at a higher risk of cardiovascular morbidity and mortality?

Solid organ transplantation

6. How effective and safe is gout treatment in solid organ transplant recipients?

CPG Recommendations*

Treatment targets

In patients with severe gout (tophaceous gout, frequent flares, arthropathy or a high crystal load), the suggested goal is to reduce serum urate levels to substantially below the saturation point, at least below 5 mg/dL, to accelerate the dissolution of urate crystals (Grade D recommendation).

Drugs as monotherapy

In patients with gout, the recommendation is to start urate-lowering therapy with xanthine oxidase inhibitors as monotherapy (Grade B recommendation).

Pharmacological urate-lowering therapy should be started at low doses, and if needed, gradually escalated to doses that are effective in reducing serum urate levels to the therapeutic target* (Grade D recommendation).

*The urate treatment target should be at least <6 mg/dL in general and at least <5 mg/dL in patients with severe gout.

On grounds of efficacy, the recommendation is to prescribe allopurinol initially and use this drug until treatment targets are achieved or maximum tolerated or approved doses reached (Grade B recommendation).

Prescribing febuxostat as a first-line treatment can be considered in patients with severe gout, who require a therapeutic target for urate that is particularly low, within the limitations stated in the SmPC (see sections on cardiovascular disease, chronic kidney disease and transplantation) (Grade $\sqrt{$ recommendation).

Lesinurad should only be prescribed in combination with xanthine oxidase inhibitors (Grade A recommendation).

Benzbromarone as monotherapy may be an option in patients with gout who have a poor response to treatment, adverse reactions to xanthine oxidase inhibitors or cardiovascular disease (Grade C recommendation).

In patients with refractory gout or no other treatment option, it is appropriate to consider prescribing pegloticase, which is a "foreign medication" but may be requested under special circumstances (Grade V recommendation).

^{*} The system used for grading the recommendations is set out in Appendix 1.



Combination therapy

In patients with gout, combination therapy of xanthine oxidase inhibitors with uricosuric agents should be used when serum urate targets are not achieved with monotherapy at appropriate doses or maximum tolerated doses (Grade V recommendation).

Given the stronger evidence in terms of safety, the addition of lesinurad to a xanthine oxidase inhibitor should be considered before the combination with benzbromarone (Grade A recommendation).

The GDG considers that there is currently no evidence supporting the use of two drugs with the same mechanism of action (i.e., two xanthine oxidase inhibitors or two uricosuric agents) (Grade V recommendation).

Treatment of acute episodes

The choice between nonsteroidal anti-inflammatory drugs and glucocorticoids for the treatment of gout flares depends on patient preferences and comorbidities (Grade $\sqrt{recommendation}$).

Imaging tests for monitoring treatment response

Plain radiography is recommended for assessing the extent of joint damage and monitoring bone erosions (Grade C recommendation).

Ultrasound is recommended for assessing the effect of urate-lowering therapy in terms of urate deposits, double-contour sign and size of tophi (Grade C recommendation).

There is no evidence on which to base a recommendation regarding the time between examinations (Grade V recommendation).

There is insufficient evidence to make a recommendation for or against the use of dualenergy computed tomography for follow-up (Grade v recommendation).

Chronic kidney disease

The same target serum urate levels should be used for the treatment of gout regardless of whether patients have chronic kidney disease (Grade V Recommendation).

In patients with gout and chronic kidney disease, the use of a xanthine oxidase inhibitor (allopurinol or febuxostat) as a first-line treatment should be considered, with the specific limitations stated in their summary of product characteristics (Grade V recommendation).

In patients with gout and chronic kidney disease, the dose of allopurinol should be adjusted downwards for the initial doses (50 to 100 mg daily for the lowest levels of renal function) and escalated gradually (monthly increases of 50 to 100 mg daily depending on renal function) to attempt to attain serum urate targets and reduce the risk of toxicity (Grade \vee recommendation).

Allopurinol should be avoided in patients who are known to have the HLA-B*58 allele (such as those who are transplant recipients or on a transplant programme)* (Grade C recommendation).

(*) The EMA does not recommend systematic genotyping before prescribing allopurinol in the white population; however, it seems that it is cost-effective in Asian ethnic groups.

In patients with gout and chronic kidney disease, benzbromarone should only be prescribed after a poor response or adverse effects related to a xanthine oxidase inhibitor (Grade $\sqrt{recommendation}$).

Lesinurad should be prescribed provided patients do not have severe kidney disease, always in combination with a xanthine oxidase inhibitor (allopurinol or febuxostat), and taking into account the warnings and precautions for use mentioned in the summary of product characteristics (Grade A recommendation).

In patients with severe kidney disease, the use of uricosuric agents (benzbromarone and lesinurad) is not recommended, as they are not effective (Grade A recommendation).

The use of pegloticase should be considered in patients with severe kidney disease, with refractory gout or who do not tolerate well other treatment options* (Grade $\sqrt{recommendation}$).

*As this drug is not currently marketed in the European Union, it is considered a "foreign medication" and authorization should be sought for prescribing it (Official State Bulletin [BOE] 19 June 2011).

The GDG considers that there is insufficient robust evidence to support specific recommendations on the use of urate-lowering drugs in patients on dialysis. Referral of these patients to units with greater clinical experience in their management should be considered (Grade V recommendation).

Cardiovascular disease

In patients with gout and a previous cardiovascular event, the recommendation is to use allopurinol as a first-line treatment (Grade A recommendation).

In patients with gout and a history of a cardiovascular event with a poor response to or intolerance of allopurinol, it is advisable to add lesinurad (if they have had no vascular event in the last year) or change to benzbromarone as monotherapy. Another option is pegloticase, specially requested as it is currently a foreign medication (Grade V recommendation).

In patients with high cardiovascular risk but no history of a cardiovascular event, the benefitrisk balance should be assessed carefully if treatment with febuxostat is considered (Grade V recommendation).

Solid organ transplantation

Given that there is insufficiently robust evidence, due to a lack of specifically designed studies, the GDG is unable to provide specific recommendations about the most effective and safest treatment for gout in solid organ transplant recipients (Grade V recommendation).

The GDG considers it reasonable for patients who are solid organ transplant recipients to be treated by specialist nephrology, hepatology, and rheumatology units with considerable specific experience in the treatment of gout in such patients (Grade V recommendation).

Role of nurses

Support by specially-trained nurses should be included in the regular follow-up of patients with gout, when the healthcare setting allows (Grade A recommendation).

1. Introduction

Gout is a type of arthritis produced by both acute and chronic anti-inflammatory phenomena that appear in response to the deposition of monosodium urate (MSU) monohydrate crystals¹. The inflammation generated in this way mostly affects musculotendinous structures lined by synovial membranes, such as joint cavities, tendon sheaths and bursae². Though deposits have been described in many types of tissue, the skin and bone are the most often affected after joint and periarticular structures and their involvement is indicative of extensive deposition or severe gout³.

Management of this type of arthritis is important for three main reasons: first, it is common; second, it is reversible; and third, there are highly effective treatments. Nonetheless, the results of treatment are suboptimal: treatment adherence tends to be low⁴ and treatment targets are often not attained⁵, this having been associated with higher mortality rates⁶.

From a physicochemical perspective, gout develops when urate levels in blood exceed the saturation point, a condition known as hyperuricemia. This condition is associated with genetic susceptibility conferred by variants of renal and gut uric acid transporters, congenital and other conditions that lead to hyperuricemia (e.g., obesity and kidney disease) or external factors (medications) that cause hyperuricemia. Any or a combination of these factors results in persistent hyperuricaemia may lead to uric acid deposition, and eventually, gout, with the nucleation, growth and aggregation of urate microcrystals.

Considering the aforementioned factors, and especially that hyperuricaemia is reversible, meaning that urate deposits formed may dissolve and the formation of new deposits may be avoided, it is very important that there are recommendations and guidelines for the clinical management of gout: from national bodies, such as those of the American College of Rheumatology (ACR)⁷, or multinational groups, such as those of the European League Against Rheumatism (EULAR)⁸ or the Treat to Target (T2T) recommendations for gout⁹, not to mention the wide range of recommendations from other national scientific societies, among them those of the SER. These documents overlap in certain aspects of clinical management, but given the different contexts in which they have been developed, both in terms of the methods used and the clinical practice setting, they may differ in the interpretation of the evidence, conclusions and even approach to therapeutic intervention, such as the recommendation of the American College of Physicians (ACP) against urate-lowering interventions¹⁰. In addition, different indications and medications have been approved in different care settings. Nonetheless, after

the publication of our previous Gout Guideline (GuipClinGot 2013, see Appendix 3), improvements have been observed in terms of the attainment of treat-to-target enpoints¹¹. For these reasons, the SER and the associated foundation (FER), having been concerned to ensure funding for audits of the management of patients with gout over the last decade, such as the Gout Evaluation and Management (GEMA and GEMA 2) studies and previous GuipClinGot guideline, have considered it appropriate to bring the 2013 guideline up to date in all respects. Particular attention has been paid to the key role of monitoring adherence to treatment protocols, which may be carried out by nursing staff; newly approved medications, especially those paid for by the national health system; and changes in their Summaries of Product Characteristics (SmPC), especially in patients with either a history of cardiovascular events or high cardiovascular risk.

With the material available and participation of a multidisciplinary group, including specialists in family and community medicine, radiologists, nephrologists, rheumatologists, and nurses, selected for their academic, research and clinical experience, as well as patients, the 2020 GuipClinGot seeks to provide more detail in the parts of the guide that had become the most out of date, using a new methodology and conducting new SRs. In addition, we have added diagnostic and treatment algorithms that we hope can be used in the clinical practice of any of the aforementioned groups.

The gout guideline is a tool that we hope will be useful for healthcare professionals in the range of specialities involved in the multidisciplinary assessment, diagnosis, treatment and follow-up of this condition.

William Shakespeare wrote that there is no cure for love or gout; the latter may now be considered curable.

1.1 Epidemiology: the scale of the problem in quantitative terms

Gout is the most common inflammatory joint disease. Estimates of its prevalence and incidence vary between studies with the method used, the prevalence in adults in France varying from 0.9% based on confirmed cases to 3.7% based on self-report¹². Globally, the reported values for prevalence range from 1% to 7% and for incidence from 0.6 to 3.0 per 1,000 person-years¹³. In Spain, the prevalence in over-20-year-olds has been estimated at 2.4% based on recent data from the EPISER study¹⁴. Here, we do not consider data from countries in which gout has a strong genetic component, such as those with Polynesian and Asian populations.



The prevalence is higher in older age groups¹³, as well as in frail individuals, such as patients with chronic kidney disease (CKD)¹⁵ and solid-organ transplant recipients¹⁶. Further, the prevalence of vascular risk factors is high among patients with gout¹⁷. The management of gout in these populations has been paid special attention in this new version of the guidelines

1.2 Clinical manifestations

Gout has the typical characteristics of acute arthritis: rapid onset, excruciating pain and major functional impairment. Nonetheless, the fact that some patients present with atypical clinical signs and symptoms, the course of the most severe polyarticular forms with symmetrical involvement and the high prevalence of hyperuricaemia in the adult population², above all in older age groups, make it necessary to update the recommendations concerning the utility, feasibility, and effectiveness of the various diagnostic methods available.

We should take into account the natural history of gout when left untreated, or poorly controlled, shows a tendency to structural joint damage, with irreversible functional impairment³, this, in turn, limiting perceived quality of life and being associated with a higher risk of premature death¹⁸. Both situations are, evidently, undesirable in the practice of healthcare in the 21st century, all the more so in the case of a disease considered "curable" ¹⁹.



2. Scope and objectives

Scope

This guideline focuses on the care of adults with gout. It seeks to offer users guidance concerning the ideal systematic approach to using the treatments available, as well as the general principles for diagnosing and monitoring this disease.

It addresses factors concerning the treatment of gout, including the range of treatment options, and also covers general matters related to diagnosis, assessment and collaboration between specialities (nephrologists, radiologists and general practitioners).

Objectives of the guideline

Primary objective:

To make recommendations to rheumatologists and other health professionals involved in the care of patients with gout, concerning treatment options available for the clinical management of adults with this condition, based on the best available evidence. If the evidence is insufficient or of poor quality, recommendations are based on the consensus reached by the members of the working group.

Specific objectives:

- To enhance the clinical skills of health professionals involved in the care of people with gout to improve the quality of care provided
- To reduce variability in clinical practice in the treatment of the disease
- To assess the efficacy, safety, efficiency and cost-effectiveness of the various pharmacological and non-pharmacological treatments proposed
- To summarise the scientific evidence to increase the knowledge of all professionals involved in the care process, hoping in this way to improve patient quality of life
- To improve the clinical approach to gout with recommendations focused on the early initiation of treatment to reduce the disability and morbidity associated with this condition
- To encourage collaboration between professionals from different specialities involved in the treatment of patients with gout
- To produce general informative materials for patients with gout and their families and caregivers, to help improve their understanding of the process and factors that have an impact on the course of the disease.



Target users of the guideline

Seeking to achieve comprehensive patient care, the guideline is aimed not only at rheumatologists but also at other health professionals who may contribute to the care of patients with gout working in primary or specialist care, namely, those from the specialities of cardiology, nephrology, urology, family medicine, and nursing, as well as other specialities potentially involved in the care of these patients. It is also aimed at patients and family members who have contact with these health professionals. In the case of patients and families, this is a tool that will help them learn about the potential strategies for and types of gout treatment, and thereby avoid the use of treatment regimens that are not backed by scientific evidence or by strong expert consensus.



3. Method of development

In the development of this Clinical Practice Guideline (CPG) on the Management of Patients with Gout, a series of steps were followed, as described below:

Establishment of the guideline development group (GDG)

A multidisciplinary working group was established, composed of professionals involved in care delivery, technical staff of the SER Research Unit and representatives of patients. All participants are listed in the authors and collaborations section. The composition of the group is outlined below:

• **Coordinators**: one specialist in rheumatology, as the principal investigator, and one methodological expert, a member of the technical staff of the SER Research Unit, were responsible for the coordination of the clinical and methodological aspects of the CPG and provision of support to the GDG.

• **Expert panel**: specialists in rheumatology, nephrology, radiology, family medicine, and specialised nursing were selected through a call for experts or contacting the corresponding scientific societies. As members of the expert panel, these people were responsible for drafting the recommendations in the CPG.

• **Reviewers of the scientific evidence**: several rheumatologists, members of the SER reviewer working group, were responsible for systematically reviewing the available scientific evidence and gathering the evidence on the basis of which the expert panel formulated the recommendations.

• **Patients**: as well as clinical professionals, two patients participated in the GDG itself, from the early stages of the project.

A work plan was established outlining the different stages in the development of the guideline and deadlines for their completion.

Definition of the scope and objectives

The time since the publication of the previous gout guideline (GuipClinGot2013, see Appendix 3) and the new evidence that has emerged during that time warrant updating of this document. The new scope and objectives were defined by consensus based on the clinical experience and knowledge of the participating health professionals.



Drafting of the clinical questions

After establishing the scope and objectives of the guideline, the members of the GDG set the clinical questions to be answered. First, a list of general clinical questions was drawn up. Then, having selected those potentially related to the objectives of the guideline, questions were redrafted using the Patient, Intervention, Comparison and Outcome (PICO) framework. The Setting, Perspective, Intervention, Comparison, Evaluation (SPICE) framework was also used, to identify qualitative evidence that might offer information from "the perspective of patients".

Literature search, evaluation and evidence synthesis

A literature search was carried out in the following databases: Medline (through PubMed), Embase (Elsevier), Cochrane Library (Wiley Online Library) and Cumulative Index to Nursing & Allied Health Literature (CINAHL on EBSCOhost). These databases were selected because they are the main sources of biomedical information to which we had access. Natural language terms were combined with controlled vocabulary from the thesaurus of each database (MeSH, Emtree and DeCS), seeking to balance the sensitivity and specificity of the searches. No time restriction was applied. The first searches were carried out up to October 2018. Subsequently, the search was updated to include records up to November 2019. Searches were restricted to studies in humans published in English, French or Spanish.

Initially, all the search strategies were designed to retrieve only primary studies from the aforementioned databases; however, when this approach yielded few or insignificant results, they were supplemented by a manual search of the reference lists in the key documents selected for the review. References proposed by researchers or reviewers consulted were also included. The references retrieved were managed using EndNote X7 Reference Manager. The search strategy used for each of the databases is set out in detail in a methodological appendix on the SER website. The number of publications identified and selected is also documented on the website.

Regarding the "Patients' perspective" chapter, an SR was conducted of scientific studies of the experience of patients with gout. For this, questions were formulated using the SPICE framework and, in addition to the aforementioned sources of information, the PsycInfo database was used. Searches were carried out up to April 2019.

Study inclusion criteria

Studies were included if they had the characteristics described below:

Study population: adults diagnosed with gout

Intervention: diagnostic imaging tests, urate-lowering therapies (ULTs) as monotherapy or combination therapy, imaging tests for patient follow-up, treatment in special circumstances such as in patients with CKD, solid-organ transplant recipients, and patients with a high risk of cardiovascular morbidity.

Outcome variables: sensitivity, specificity and likelihood ratios for diagnostic tests; reduction in tophi and flares; reduction in serum urate or uric acid levels; intolerance and/or toxicity; cardiovascular risk/events/morbidity and mortality; patient survival and graft survival, in the case of transplant recipients; improvement in renal function or changes in the rate of "renal death"; dialysis/transplant; improvement in disease activity, functional capacity, and patient-reported outcomes; drug levels; infection; rates of survival, mortality, recurrence, and adherence; satisfaction and self-care capacity.

Study design: meta-analyses and SRs of randomised controlled trials (RCTs), other types of observational studies if there are not RCTs (cohort, case-control studies), and observational and descriptive studies (case series and case reports).

Exclusion criteria

The following were excluded: studies in children, adolescents and pregnant women; studies not suited to the PICO framework, given the type of the patient sample, intervention, comparison group(s), outcome(s) or study design; and abstracts, posters, narrative reviews, letters and any type of unpublished study.

Assessment of study quality

Studies likely to be relevant were selected by applying the aforementioned inclusion and exclusion criteria. Critical reading was performed using the methodological checklists of the Scottish Intercollegiate Guidelines Network (SIGN) and the Osteba critical appraisal tools²⁰, and the internal and external validity of studies were assessed. From the studies selected, evidence tables were constructed with the key data, concerning the study methods, results and quality. The modified SIGN system was used to assess the level of evidence²¹.

Drafting of the recommendations

After the critical reading, the recommendations were drafted based on formal assessment or considered judgement, having summarised the evidence relevant to each of the clinical questions²¹. The following were also taken into account: the quality, quantity and consistency of the scientific evidence and the generalizability of results, as well as their applicability and clinical implications. The modified SIGN system was also used to grade the strength of the

recommendations²¹. Any recommendations that were controversial or lacked evidence were agreed by consensus in a meeting of the GDG.

Preparation of patient information

As well as updating the evidence on the treatment of gout, the goals set for this CPG included the incorporation of the patients' perspective.

First, we tackled the task of gathering information on how patients with gout view their own condition. Various individuals with gout participated voluntarily in qualitative research, using discussion group techniques, to recount their experience and describe their concerns.

Subsequently, following a structure developed by the guideline coordinators based on the recommendations in the complete guidelines and the qualitative information, agreement was reached on a template for the patient version. This information was written in language and formatted in a style tailored to the target audience and covers topics related to the disease which might be most useful for them. For developing this patient-focused material, a specific sub-working group was created, including some professionals and the patients who were members of the GDG.

External review and publication of the final document

Having completed the aforementioned tasks, an advanced draft of the CPG was produced and then reviewed by the working group. Each section was analysed and changes considered necessary, from a comprehensive perspective, were proposed.

After this, the guidelines were externally reviewed by professionals selected for their knowledge of gout and guideline development methods. The purpose of this step was to increase the external validity of the document and ensure the accuracy of the recommendations.

Public scrutiny

The draft of the complete version of the CPG passed through a process of public scrutiny by the members of the SER and other stakeholders (pharmaceutical industry, other scientific societies and patients' associations). It was made available on the SER website for 15 days, together with a questionnaire to collect comments, seeking to gather data on people's opinion and scientific assessment of the guidelines' methods and/or recommendations. Detailed information concerning this process is provided in an appendix in the Research and Clinical Practice Guidelines section of the SER website: www.ser.es.

🜀 GuipClinGol



Scientific societies

The scientific societies involved in the development of this guideline, represented by members of the GDG, were the Spanish Society of Family and Community Medicine (semFYC), the Spanish Society of Nephrology (SEN) and the Spanish Society of Skeletomuscular Radiology (SERME), as well as the SER itself.

How to use the CPG

This CPG is organised into chapters. The chapters concerning PICO format questions contain a statement of the question, a table containing a statement of the recommendations and their strength, a brief introduction to the question, the amount of evidence and its consistency across studies, and the applicability and relevance in our setting.

4. Burden of gout in Spain

Indicators of disease burden. Global Burden of Disease Study.

In countries with a long-life expectancy and an advanced demographic and epidemiological transition, like Spain, traditional measures of mortality are insufficient to adequately capture the health status of the population. A good part of increases in survival is achieved by exchanging avoidable deaths for a higher prevalence of disability and ill health. Since a longer life does not always go hand in hand with better quality of life and a lower prevalence of ill health, indicators that reflect both fatal and nonfatal outcomes are more suitable for describing the true impact of health problems at population level. This is particularly important in the case of diseases that, by nature, seldom cause death, but may have widespread nonfatal effects in the population and/or a very serious impact on a part of the population, as is the case of rheumatic diseases.

Burden of disease studies seek to gather and synthesise data on these two types of impact of disease and injury. Their goal is to estimate and summarise in a single indicator not only the impact in terms of death (as reflected in mortality rates) but also the role of illnesses and accidents as a cause of disability and ill health. This makes it possible to reconsider and properly assess the population impact of diseases and disorders that, as they do not appear in statistics as the main cause of death, are less visible in traditional health indicators based on mortality. Numerous studies explain in more depth the overall goal of burden of disease studies²²⁻²⁵.

The indicator typically used in burden of disease studies is called disability-adjusted life years (DALYs). This indicator combines a measure quantifying premature death (years of life lost, YLL) with one quantifying health losses (years lived with disability or poor health, YLD). Both are calculated for each age, sex and cause (of death or disease).

The information on burden of gout and all rheumatic diseases in Spain presented in this guideline has been taken from the latest available [at the time of writing], namely, the 2017 Global Burden of Disease Study (GBD 2017), published in The Lancet* (November 2018), together with a description of the methods used and full results²⁶⁻³¹.

This study also reports retrospective data dating back to 1990, and these have also been considered in this section of the guideline.

^{*} For estimating the global burden of gout in the world population, the GBD 2017 used more than 100 sources of information, including registries, surveys and the scientific literature. Lists of the sources used are available from: http://ghdx.healthdata.org/gbd-2017/data-input-sources?components=5&causes=632.

The full results of the GBD 2017 can be viewed and downloaded from the website of the *Institute of Health Metrics and Evaluation*: https://gbd2017.healthdata.org/gbd-compare/



To obtain its results, the Global Burden of Disease Study gathers all the demographic and epidemiological data available, for each country, seeking to build the best possible picture of the impact of each disease on the population. It uses the national death registers of all the countries that have one, even if not exhaustive, and other sources of information on mortality if such registers do not exist (for example, verbal autopsies). Regarding information on the nonfatal consequences of diseases and injuries, it uses data from registers (general ones from primary and hospital care, as well as both population and hospital registers of specific diseases) as well as information from national health and disability surveys and so-called demographic and health surveys carried out by countries with no reliable registers. It also processes evidence on incidence, prevalence, stage, severity and sequelae for each disease and injury type reported in the scientific literature. Thousands of health professionals and experts from all over the world participate in this enormous task.



The procedure for estimating the burden of gout is outlined in the following flow chart:

Burden of gout in Spain

Rheumatic diseases (International Classification of Diseases, 10th Revision [ICD-10] Chapter XIII) are a significant health problem across the world. According to GBD 2017^{28, 29}, they account for 5.5% of the total global burden of disease, resulting in 138 million DALYs worldwide. In Western Europe and Spain, they have even more weight, approximately two-fold more, in the former the 13.6 million DALYs estimated for the former corresponding to 11.5% of the total burden of disease and the 1.27 million DALYs for the latter to 10.9% of the total burden of disease in the Spanish population in 2017 and more than 20% of the total YLD. The rheumatic disease-specific DALYs rates (per 100,000 persons) are somewhat higher in Western Europe overall than in Spain and in both cases are markedly higher than in the global population (Table 1).

Table 1

Disability-adjusted life years (DALYs; number, percentage and rate) for all causes, musculoskeletal diseases and gout globally, in Western Europe and in Spain in 2017

DALYs	Globally	Western Europe	Spain
All causes	2,499,292,056	118,322,529	11,701,353
Musculoskeletal disorders	138,723,945	13,556,409	1,273,881
Gout	1,284,953	155,170	17,589
DALY %	Globally	Western Europe	Spain
All causes	100.00 %	100.00 %	100.00 %
Musculoskeletal disorders	5.55 %	11.46 %	10.89 %
Gout among all causes	0.05 %	0.13 %	0.15 %
Gout among musculoskeletal disorders	0.93 %	1.14 %	1.38 %
DALY rate (per 100,000 persons)	Globally	Western Europe	Spain
All causes	32,711.3	27,328.1	25,224.3
Musculoskeletal disorders	1,815.6	3,131.0	2,746.1
Gout	16.8	35.8	37.9

Source: Produced in-house based on GBD 2017 data.

Gout is a subcategory within diseases that affect the musculoskeletal and connective tissue systems (called "Musculoskeletal disorders" in GBD 2017), which in turn belong to the broader category of non-communicable disease. In the classification of disease in the GBD 2017, the subcategory gout includes the ICD-10 code M10 and ICD-9 code 274.

Gout very seldom appears in mortality statistics. Specifically, in Spain, it is cited as the underlying cause of death in extremely few cases (for example, in 6 deaths in 2016, the last year for which data are available from the Spanish National Statistics Institute, 3 men and 3 women, all between 70 and 89 years of age). For this reason, in the GBD 2017, the estimation of the impact of gout on population health is based on nonfatal consequences, and hence, the DALYs are equal to the YLD.

Gout is estimated to have somewhat more impact on the health of the Spanish population than it does on that of Western Europe overall and three-fold more than on the global population: 17,589 DALYs in 2017, representing 0.15% of the total burden of disease in Spain (compared to 0.13 in Europe and 0.05 globally) and 1.4% of the total burden of musculoskeletal disorders in Spain (compared to 1.1 in Western Europe and 0.9 globally) (Table 1). DALYs are usually quoted as absolute values, measured in years of life. Nonetheless, for comparisons between populations or over time, it is useful to standardise the indicator, weighting it by population size (crude rates) or, above all, adjusting it for age and sex, to avoid the confounding effect associated with differences in age distribution between populations, as it is known that ageing directly affects the mean impact of illnesses and causes of death. For this, standardised or adjusted rates are calculated.

Age- and sex-standardised rates of burden of gout are higher in Spain (21.8 per 100,000 persons in 2017) than in Western Europe (20.6) or globally (15.9). Over time, in Spain, the rate tended to increase until 2011 and has decreased slightly since then. Globally, the rates have grown continually over the 30 years for which data are available (Figure 1).

Figure 1 Disability-adjusted life years for gout globally, in Western Europe and in Spain. Period 1990-



2017. Age- and sex-standardised rates (per 100,000)

		Western	
	Globally	Europe	Spain
1990	14.8	18.7	20.0
1995	15.0	19.0	20.7
2000	15.3	19.6	21.1
2005	15.3	20.3	21.9
2010	15.7	20.7	22.1
2015	15.8	20.7	21.9
2017	15.9	20.6	21.8

Source: Produced in-house based on GBD 2017 data.

In Spain, the age-standardised DALYs for gout are between four- and five-fold higher in men throughout the period 1990 to 2017 (36.5 per 100,000 men vs. 8.1 per 100, women, in 2017). The trend is similar in both sexes, following the same pattern as that observed considering the two sexes combined (Figure 2).



Figure 2 Disability-adjusted life years for gout in Spain by sex. Period 1990-2017. Age-standardised rates (per 100,000)

Source: Produced in-house based on GBD 2017 data.

Musculoskeletal diseases have very different weights depending on the component of disease burden considered. On the one hand, only 0.2% of all YLL in Spain in 2017 are attributable to these diseases (0.4% in 1990), as they seldom cause death and, generally, develop at advanced ages, and hence, have relatively little weight in this indicator of premature death. On the other, more than 1 in 5 YLDs (20.8%) in 2017 were caused by musculoskeletal diseases, meaning that they have an enormous negative impact on population health in Spain.

In the case of gout, all its weight comes from the YLDs attributable to the disease, as it does not cause death (YLL). The number of DALYs due to gout has grown steadily from 1990 (13,353 DALYs) to 2017 (17,589 DALYs). Further, the relative weight of gout among musculoskeletal diseases has increased in Spain over this period (from 1.09% of all DALYs in 1990 to 1.38% in 2017) (Figure 3).



Figure 3 Disability-adjusted life years (DALYs) for gout in Spain by sex. Period 1990-2017. Number of DALYs and percentage of all DALYs attributed to musculoskeletal disorders

Source: Produced in-house based on GBD 2017 data.



The burden of gout is not evenly distributed by age or sex. At all ages, the number of DALYs is higher in men than women, being as much as 3.5-fold higher overall (for all ages). The male-to-female ratio reaches as high as 10:1 among 40- to 44-year-olds. The age group with the highest burden of gout (in DALYs) is 45- to 74-year-olds in men but 70- to 84-year-olds in women, with the modal age groups being 55 to 59 years and 80 to 84 years, respectively. Adjusting the figures for the population in each age group and sex, the age- and sex-specific values indicate a similar magnitude of burden in men, but the modal age group shifts to 80 to 84 years, the same as that in women.

Figure 4



Burden of gout. Disability-adjusted life years (DALYs) in Spain by sex and age group in 2017. Number, rate (per 100,000) and ratio between sexes

Source: Produced in-house based on GBD 2017 data.

In conclusion, the burden of gout is higher in Spain than across Europe or globally, and has tended to increase over recent decades both in terms of number and rate of DALYs. It is considerably more prevalent in men than in women. The impact of gout on the health of the Spanish population is almost exclusively related to its nonfatal effects, as there are hardly any cases in which gout is cited as the underlying cause of death.



5. Pathogenesis

5.1 Risk factors

Gout is defined as the local deposition of MSU crystals. The two factors that predispose individuals to the formation of these crystals are sustained hyperuricaemia and local tissue characteristics that may favour the nucleation and growth of crystals. Except in the case of rare monogenic disorders, gout is a multifactorial disease, caused by the coexistence of several risk factors ³². The majority of the risk factors identified for gout are associated with an elevated risk of hyperuricaemia, local factors, such as cell- or tissue-related factors, having been investigated in relatively few studies and currently none having been shown to be clinically relevant.

Both genetic and environmental risk factors are important in the development of gout. Twin studies suggest a heritability (percentage of phenotypic variation explained by inherited genetic variants) of serum urate of 45-73%, although no data are yet available for gout. Based on genome-wide association studies, the heritability of gout in the European population has been estimated at between 27% and 41%³³. Some cases are attributable to rare single gene disorders such as Lesh-Nyhan syndrome, caused by a hypoxanthine-guanine phosphoribosyltransferase deficiency, and familial juvenile hyperuricaemic nephropathy, caused by a mutation in UMOD (the gene coding for uromodulin). Nonetheless, the genetic risk is mostly associated with genes that code for transporters involved in renal or extra-renal (intestinal) clearance of uric acid (*SLC22A12* – URAT1, *SLC2A9* – GLUT9, *ABCG2*)³³.

Gout is more common in men and the prevalence increases with age. Nonetheless, in women, the prevalence increases rapidly after menopause. The difference is probably related to the uricosuric effect of oestrogens³⁴. Comorbidities such as a high body mass index, hypertension and heart failure have been associated with an increased risk of developing gout. On the other hand, studies have not clarified whether the relationship is causal or these conditions are confounding factors and the relationships are indirect. CKD is associated with hyperuricaemia and with gout; for each 30 ml/min/1.73 m² decrease in estimated glomerular filtration rate (GFR)³³, a 2- to 3-fold increase has been observed in the prevalence of gout³⁵. Other diseases such as psoriasis and sickle cell anaemia are also associated with a higher risk of developing gout, presumably due to faster cell turnover.

Diet and alcohol use are risk factors for the onset of gout ³². Nonetheless, the strength of the majority of the associations is limited, with relative risks of less than 3, or associations that are only apparent comparing extreme quintiles. A diet rich in purines, whether from red meat or seafood, slightly increases the risk of developing gout. Alcohol use has a dose-response relationship with the onset of gout³⁶, the increase being particularly marked with beer, which

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contains guanosine, a purine, as well as alcohol. Sweetened soft drinks and fructose have also been associated with the risk of incident gout ³⁷. In contrast, coffee, dairy products, cherries and vitamin C seem to be protective, reducing the risk of gout³⁸.

Some medications have also been associated with the development of gout: diuretics, other antihypertensive drugs (beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers except losartan), ciclosporin, and tacrolimus. In contrast, calcium antagonists and losartan have a slight uricosuric effect.

Risk factors	
Genetic	<i>SLC22A12</i> (URAT1)
	<i>SLC2A9</i> (GLUT9)
	ABCG2
Sociodemographic	
Age	Older
Sex	Men
Place of residence	Urban areas
Lifestyle-related	
Diet	Purine-rich diet
	Alcohol (beer in particular)
Environmental	Lead exposure
Medication-related	Diuretics
	Ciclosporin, tacrolimus (transplant recipients)

Table 2: Risk factors for gout

5.2 Pathogenic classification of hyperuricaemia and gout

The deposition of MSU crystals requires serum urate levels to remain high over time. Under physiological conditions, urate levels of over 6.8 mg/dL provide a supersaturated concentration and enable the production of MSU crystals. Hyperuricaemia results from an imbalance between the production and elimination of uric acid, and therefore, may occur by two mechanisms, namely, urate overproduction or underexcretion (Table 3).

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Uric acid is the end product of purine catabolism. The mechanisms involved in controlling urate overproduction have not been identified, except in the case of some single-gene conditions associated with hypoxanthine-guanine phosphoribosyltransferase deficiency or accelerated degradation of purine nucleotides or adenosine triphosphate (ATP).

Unlike other mammals, humans and other primates do not have uricase to eliminate urate, and hence, uric acid is not converted to allantoin, a molecule that is more water-soluble and easier to eliminate. Two-thirds of uric acid is excreted by the kidney as uric acid and the rest by other routes, mainly in the faeces.

In the kidney, uric acid undergoes reabsorption and is secreted in the proximal tubule, with a net excretion of less than 10% of the uric acid filtered by the glomeruli. Numerous uric acid transporters have been reported in the proximal tubule. Among these, URAT1 (*SLC22A12*) and GLUT9 (*SLC2A9*) play an essential role in the reabsorption of uric acid, while *ABCG2* and *OAT1*, *OAT2* and *OAT3*, found in the apical and basolateral membrane, respectively, are key for its excretion³³. Part of the interindividual variation in serum urate levels is attributable to variants in uric acid transporters.

Regarding extra-renal elimination, uric acid elimination in the faeces occurs mainly through its secretion to the intestinal lumen. The ABCG2 transporter plays a key role in the intestinal secretion of uric acid³⁹. Dysfunction of this transporter reduces intestinal secretion, increasing the risk of renal urate overload⁴⁰. Some variants of the ABCG2 transporter gene have been associated with a poor response to allopurinol in various independent cohorts⁴¹.

Although the causes of gout are not detected in the majority of patients with this condition (idiopathic gout), numerous medications and comorbidities may alter urate levels and trigger the onset of the disease (secondary gout, Table 4). Enzyme deficiency, though extremely uncommon, may cause early gout with additional systemic manifestations. The identification of reversible causes -such as medications- is key as it may modify patient management.

Table 3: Pathogenic mechanisms of hyperuricaemia

Urate overproduction

Urate underexcretion

Reduction in renal excretion

Reduction in extra-renal excretion (mainly intestinal)



Urate overproduction	Purine-rich diet
	Accelerated adenosine triphosphate degradation (ethanol, intense exercise, tissue ischaemia, glucose metabolism disorders)
	Psoriasis
	Paget's disease of bone
	Blood disorders and cancer associated with high cell turnover
	Cytotoxic chemotherapy (including tumour lysis syndrome)
	Inborn errors in purine metabolism
	(phosphoribosylpyrophosphate synthetase superactivity,
	Lesch-Nyhan and Kelley-Seegmiller syndromes)
	Glucose-6-phosphate dehydrogenase deficiency (glycogen storage disease I)
Urate underexcretion	Chronic kidney disease
	Extracellular fluid volume contraction, dehydration
	Acidosis
	Medications (for example, thiazide diuretics, loop diuretics, niacin, pyrazinamide, ciclosporin)
	Lead poisoning (saturnine gout)
	Analgesic nephropathy
	Polycystic kidney disease
	Medullary cystic kidney disease
	Other hereditary interstitial kidney diseases
	Endocrine disease (hyperparathyroidism, hypothyroidism)

Table 4: Secondary causes of hyperuricaemia and gout

5.3 Natural history of the disease

Before developing gout, individuals tend to have had high serum urate levels for some time. Nonetheless, not everyone with hyperuricaemia will develop gout, and there is a direct relationship between serum urate levels and incident gout. Recent research based on nearly 19,000 patients, suggests that 9% of individuals with serum urate levels between 7-8 mg/dL will develop gout within 15 years, compared to 49% of those with serum urate levels above 10



mg/dL⁴². Although it remains unclear, there are likely to be local factors that favour or hinder the local deposition of crystals in patients with hyperuricaemia.

Studies using ultrasound or dual-energy computed tomography (DECT) suggest that 15 to 35% of patients with persistent hyperuricaemia have urate crystals despite not having experienced an acute gout flare⁴³. Currently, there are no data regarding the natural history of these clinically asymptomatic patients with urate crystal deposits, but it is likely that most experience inflammatory episodes at some point (Figure 5).

Typically, gout presents clinically as recurrent acute monoarthritis, with a short duration (days or weeks), with variable asymptomatic intercritical periods between inflammatory episodes. As the disease advances, the intercritical periods tend to become shorter, increasing the frequency of flares. MSU crystals may cluster to form crystal conglomerates surrounded by a local inflammatory response⁴⁴ known as tophi. Occasionally, tophi are the first sign of the disease, but more often they appear in patients with a history of gout. Tophi may lead to the onset of pain in joints and surrounding areas, through the development of bone erosions ⁴⁵.

ASYMPTOMATIC PHASE SYMPTOMATIC PHASE Stage A Stage B Stage C Stage D Hyperuricaemia Deposition of Deposition of urate crystals deposition of without with episodes polyarticular (past or present) monosodium urate crystals of gout of gout attacks

Figure 5: Natural history of gout (adapted from Dalbeth N et al.)46
6. Diagnosis/classification

6.1 Gold standard and classification criteria

Historically and as upheld in the most recent ACR/EULAR criteria, the gold standard for diagnosing gout is the identification of MSU crystals in synovial fluid or tophi. In cases in which this is not possible, clinical criteria may be used, including those based on imaging findings, to better identify and classify patients with gout^{47, 48}. Nonetheless, in recent years, a debate has emerged about the accuracy of imaging techniques for the diagnosis of gout. In relation to this, a recent study analysed the accuracy of DECT and synovial fluid aspiration in identifying urate crystals in patients with suspected gouty arthritis; it found that the diagnostic performance of synovial fluid aspiration and DECT were similar in patients with a clinical suspicion of gout, with a sensitivity of 58% in both cases and a specificity of 100% and 94%, respectively. The combination of the modalities (at least one of them being positive), provided a higher sensitivity of 85% and the same specificity (94%)⁴⁹. That is, the high specificity of the identification of urate crystals by optical microscopy remains the gold standard for the diagnosis; nonetheless, in clinical practice, we can and should take advantage of all the techniques available to us.

Safety of arthrocentesis

The Study for Updated Gout Classification Criteria (SUGAR) study assessed the safety of the techniques used for the diagnosis of gout, and observed no adverse events (AEs) using ultrasound and only a small number of AEs using arthrocentesis; in the only case of septic arthritis associated with arthrocentesis, the infection was concomitant rather than secondary⁵⁰.

Limitations of the classification criteria as a diagnostic tool

Although classification criteria are often used in clinical practice as diagnostic criteria, we must be aware of the limitations inherent to their use for that purpose. The classification criteria have been established for selecting patients to be included in clinical trials or epidemiological studies and hence, seek to offer certainty and homogeneity, identifying population samples that can be compared across studies. In contrast, diagnostic criteria seek to allow us to establish an accurate diagnosis in individual patients, and for this purpose, they use all the data available that could contribute to the diagnosis of the patient, not only those included in the classification criteria but rather all the potential factors that could guide us towards a diagnosis or that help distinguish between diseases. In general, patients who meet the classification criteria can be diagnosed with this disease with high specificity, and hence, these criteria are often used for confirming a suspected diagnosis. The opposite is not always true, however, that is, some patients who do not meet the criteria may also be diagnosed using data beyond those included in the classification criteria.

Numerous classification criteria for gout have been developed in recent decades (see Table 6). Currently, the recommendation is to use the ACR/EULAR 2015 gout classification criteria⁴⁷ which employed data from the SUGAR study that was specifically designed and undertaken for developing new classification criteria. This recommendation is based on the multiple approaches that contribute to the robustness of these criteria: a) they have the highest sensitivity and specificity among all the approaches listed in Table 6; b) they are recommended by ACR and EULAR meaning that they are based on consensus and representative of standardised procedures that are commonly are used; c) the population on which these criteria are based spans the full clinical spectrum of the disease in terms of clinical manifestations and disease duration, unlike other studies which had population selection biases; d) the diagnosis was made using the case definition as the gold standard; e) they include both clinical manifestations and laboratory results, and for the first time, imaging techniques such as ultrasound and DECT, and finally, f) as can be observed in Table 7, each of the signs, symptoms, laboratory results or imaging findings have been assigned different values to weight the extent to which any issue impacts on the final score to ensure that this reflects the classification criteria. As a limitation, we should note that these are classification criteria, rather than diagnostic criteria, although they show high sensitivity and specificity with respect to the firm diagnosis.

Criteria	Area under the receiver operating characteristic curve	Sensitivity	Specificity
ACR/EULAR 2015 ⁵¹	0.95	0.92	0.89
ACR/EULAR 2015 (clinical) ⁵¹	0.89	0.85	0.78
ACR 1977 ⁵²	0.83	1.00*	0.51*
Rome ⁵³	0.95	0.97	0.78*

Table 6. Validity of different classification criteria for gout

Rome (clinical) ⁵³		0.77*	0.78*
New York ⁵⁴	0.83	1.00*	0.78*
New York (clinical) ⁵⁴		0.79*	0.78*
Mexico ⁵⁵	0.84	1.00*	0.44*
Mexico (clinical) ⁵⁵		0.95	0.44*
The Netherlands 56	0.87	0.95	0.59*

Note: Studies are based on different reference populations and may not be directly comparable.

Clinical (without synovial fluid, microscopy or imaging parameters) *p<0.05 vs. ACR/EULAR criteria

Table 7. 2015 ACR/EULAR Classification criteria (≥8 points)^{47, 51}

Criteria	Categories	Score
Step 1: Entry criterion (necessary)	At least one episode of swelling, pain or tenderness in a peripheral joint or bursa	
Step 2: Sufficient criterion (if it is met, can classify as gout without the need to continue to step 3)	Presence of monosodium urate crystals in a symptomatic joint or bursa or tophus	
Step 3: Criterion (to be used if the sufficient criterion, Step 2, not met)		
Clinical features		
Pattern of joint or bursa involvement during symptomatic episodes	Ankle or midfoot (as part of monoarticular or oligoarticular episode, without involvement of the first metatarsophalangeal joint)	1
	Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episodes		
 Erythema overlying the affected joint 	1 characteristic	1
(patient-reported or physician-observed)	2 characteristics	2
 Inability to bear touch or pressure to affected joint 	3 characteristics	3
 Great difficulty walking or inability to use the joint involved 		



Tir	ne course of the episode(s), ever	1 typical episode	1
Presence (ever) of ≥2, irrespective of anti- inflammatory treatment:		Recurrent typical episodes	2
► Time to maximal pain <24 h			-
Þ	Resolution of symptoms in ≤14 days		
► syi	Complete resolution between mptomatic episodes		
Cli	nical evidence of tophus	Present	4
Dr no ov sit pa	aining or chalk-like subcutaneous dule under transparent skin, often with erlying vascularity, located in typical es: joints, ears, olecranon bursae, finger ds, tendons (e.g., Achilles)		
La	boratory features		
	Serum urate: measured by the uricase	➢ <4 mg/dL (<0.24 mmol/L)	-4
	patient is not receiving urate-lowering	➢ 6 - <8 mg/dL (0.36 - <0.48 mmol/L)	2
	therapy and >4 weeks from the start of	➢ 8 - <10 mg/dL (0.48 - <0.60 mmol/L)	3
	period). The highest value should be scored irrespective of timing.	➢ ≥10 mg/dL (≥0.60 mmol/L)	4
	Synovial fluid analysis of a symptomatic (ever) joint or bursa by a	Monosodium urate crystal negative	
	trained observer		-2
	Imaging features		
A	Evidence of urate deposition in a symptomatic (ever) joint or bursa: ultrasound (double-contour sign) or DECT	Present (any of the two modalities)	4
>	Evidence of at least one site of erosion typical of gout in hands and/or feet: conventional radiography	Present	4

The 2018 updated EULAR recommendations for the diagnosis of gout have been published⁴⁸. These recommendations put forward a three-step approach to the diagnosis of gout. The first step is based on the identification of urate crystals in the synovial fluid or tophus aspirates; if not feasible, the second step relies on a clinical diagnosis (based on the presence of hyperuricaemia and clinical features associated with gout); and finally, the last step

recommends the use of imaging, in particular, ultrasound and DECT, to search for evidence of deposition of MSU crystals. As a limitation, we should note that this update of the diagnostic recommendations is based on the opinion of experts and does not differ substantially from those proposed in the ACR/EULAR 2015 gout classification criteria; basically, their contribution is to specify the order in which various steps should be taken to implement the diagnostic classification.

EULAR recommendations on comorbidity

The updated EULAR recommendations for the diagnosis and treatment of gout underline the importance of investigating comorbidities associated with gout including obesity, CKD, kidney failure, high blood pressure, ischaemic heart disease, heart failure, diabetes and dyslipidaemia. They also emphasize, given their importance in treatment, that as well as screening for comorbidities, we should seek to identify risk factors such as medications that reduce serum urate levels (diuretics, low-dose aspirin, ciclosporin, tacrolimus, etc.) or consumption of alcohol (especially beer or spirits), purine-rich foods and/or sugary drinks.

Microscopy vs. Ultrasound

The study by Ogdie A *et al.*⁵⁷ is particularly relevant because they conducted a disaggregated analysis of elementary lesions found using ultrasound in patients with a firm diagnosis of gout (microscopy). The sensitivity, specificity, positive predictive value and negative predictive value for the presence of any of the elementary lesions observed were respectively 76.9%, 84.3%, 83.3% and 78.2%, considering the double-contour sign, tophi, and hyperechoic foci in synovial fluid producing a "snowstorm appearance". That is, ultrasound is a valid technique for the diagnosis of gout with sensitivity, specificity and predictive values that are sufficiently good for its use in clinical practice.

In Ogdie's study, the sensitivity was higher in patients with a disease duration ≥ 2 years and those with subcutaneous nodules on clinical examination (suspected tophi). Analysing patient data as by disease duration, defining a less-than-2-year history as early gout, MSU crystal deposition identified by ultrasound had a high specificity and PPV regardless of disease duration, but the sensitivity was somewhat lower for patients with early gout⁵⁷.

Further, DECT demonstrated sufficient validity to support the diagnosis of gout without evidence of MSU crystals, as commented earlier, but this technique is not currently available in hospitals in Spain.

6.2 Diagnosis of associated comorbidities

Gout is associated with multiple comorbidities and independently associated with an elevated risk of premature death. It has been demonstrated that patients with gout have a higher than normal prevalence of obesity, CKD, hypertension, type 2 diabetes, dyslipidaemia, heart disease (including coronary heart disease, heart failure and atrial fibrillation), stroke and peripheral artery disease. Given this, the screening and care for these comorbidities and cardiovascular risk factors are particularly important in patients with gout. Further, these comorbidities, in particular, CKD and drugs used for its treatment, influence the management of gout.

The strength of the relationship between chronic renal impairment and gout has been estimated using a measure of association, namely, the odds ratio (OR), finding a value of 2.48, with a 95% confidence interval (CI) of 2.19 to 2.81³⁶. Metabolic syndrome and its components (hyperglycaemia/diabetes, abdominal diabetes, hypertriglyceridaemia, low high-density lipoprotein cholesterol, hypertension and risk of atherosclerotic events) are independently associated with hyperuricaemia and gout⁵⁸⁻⁶⁰. A study on the temporal relationship between gout and metabolic syndrome demonstrated that a first flare may precede the diagnosis of metabolic alterations and associated health problems in as many as 90% of cases⁵⁹. Gout is more common among obese people⁶¹⁻⁶³, and over half (54%) of patients with gout are obese⁵⁹. Various studies have assessed the relationship between hypertension and hyperuricemia, these observing that around half of patients with untreated hypertension have hyperuricaemia⁶²⁻⁶⁷. Similarly, numerous studies have provided evidence of associations of gout with cardiovascular disease, and even with cardiovascular mortality⁶⁸⁻⁷⁴. Additionally, some 15% of patients with gout have diabetes and as many as 37% have hyperglycaemia at some point⁵⁹. Finally, hypertriglyceridemia is observed in as many as 63% of patients with gout and high-density lipoprotein cholesterol is found to be below normal levels in 17% of cases.

7. Gout assessment

The assessment of patients with gout includes an exhaustive clinical evaluation of disease activity and burden and investigation of the underlying cause(s) of the hyperuricaemia, which may be modifiable, associated with comorbidities and specific medications that increase serum urate levels⁷.

7.1 Clinical history

Current CPGs on gout recommend screening for cardiovascular risk factors and hyperuricaemia, given their involvement in the course of the disease⁴⁸. Their detection and subsequent modification may improve the course of the disease. These factors have been discussed earlier in these guidelines (see Sections 5.1 and 6.2).

The specific assessment of patients with gout is based on taking a clinical history, gathering data on symptoms that characterise the acute episode. Research has shown that a patient score above 7 on the visual analogue scale (VAS) for pain and the presence of acute joint inflammation are valid clinical criteria for defining a gout flare⁷⁵. Other features of flares such as rapid onset, in less than 24 hours, often at night, resolution in less than 15 days and with the use of certain medications such as colchicine or ULT, have also shown to be valid in research into gout in epidemiological studies¹².

The clinical interview for patients with gout gathers data on:

Time since onset of first acute flare. At the start, gout flares are sporadic, occurring once or twice a year, but as the disease advances, they are more frequent and last for longer. It has been estimated that the mean time between the first flare and the development of signs of chronic gout, such as tophi, may be as much as 10 years⁷⁶.

Number of flares per year. Over time, the flares increase in intensity and frequency, eventually progressing to chronic arthritis. The number of episodes of arthritis per year is directly associated with the severity and extent of urate deposition and this is one of the main outcome variables used in clinical trials.

Number of joints involved in each flare. That is, it is important to identify whether there is involvement of a single, few or several joints, as this reflects the severity of the disease.

Site of joint involvement. This may be key to the diagnosis as initial flares are episodes of podagra, acute gout in the first metatarsophalangeal joint, in 50% of cases, this being the most

specific symptom of gout. Over time, this joint is involved in as many as 90% of patients with gout.

The sites of involvement are typically the joints of the feet and ankles early on, with knees, hands and elbows becoming involved at later stages of the disease. Nonetheless, we should recall that gout can attack any joint, especially if already damaged by trauma, arthritis or other conditions that cause deterioration of joint tissue.

7.2 Examination

At the time of the general physical examination, data are gathered on cardiovascular risk factors: body mass index, blood pressure, and peripheral vascular disease status, by routine methods. During the assessment of the musculoskeletal system, the most specific finding is the presence of tophi, which are generally firm nodules around joints or subcutaneously, in particular, at the first metatarsophalangeal joint, Achilles tendon, peroneal tendon, helix of the ear and/or olecranon bursa, but they may be found anywhere there is connective tissue. The number and size of tophi are an indicator of severity. It is important to quantify this feature. Various methods for measuring tophi have been described that are sensitive to change. In daily clinical practice, a simple tophus count or digital photography, repeated during follow-up, are straightforward to implement⁷⁷.

Chronic arthritis with synovitis and deformities develops in patients with severe advanced gout. In advanced stages, the disease tends to affect both higher and lower limbs, but deformity of the first metatarsophalangeal joints and tarsal bones is particularly characteristic. It is especially interesting to investigate the possibility of gout in women, which most commonly affects the hands in association with a degenerative process, and this sometimes leads to the tophi being mistaken for Heberden's or Bouchard's nodes⁷⁸.

The joint destruction underlying these deformities is performed using imaging techniques discussed elsewhere in this guide (see Section 8.10).

7.3 Laboratory testing

Laboratory tests, yielding blood counts, blood and urine biochemical parameters and acute phase reactant levels, help to identify comorbidities and risk factors as well as assess treatment response.

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The measurement of serum urate levels is recommended before starting ULT and not during an acute flare, as levels often drop to normal during inflammation. The main goal of therapy is to lower serum urate levels to below 6 mg/dL. The target should be changed to less than 5 mg in patients with severe gout, and it is essential to monitor serum urate levels in the follow-up of all patients with gout. After starting ULT, patients should be followed up initially monthly and subsequently every 6 months, seeking to keep urate levels at the therapeutic target until they stabilise. Regular check-ups help patients become more aware of the need to adhere to the ULT⁷.

Renal function. As many as 71% of patients with gout may have stage 2 CKD⁷⁹. Renal function is assessed at baseline, as part of the analysis of the risk factors for gout and for selecting and adjusting the treatment. During follow-up, it is measured to monitor for potential toxicity and even to detect improvement in terms of renal function due to the ULT⁸⁰.

Liver function. Many drugs used for treating gout are metabolised in the liver and could interfere with its function. Special care is needed in patients with fatty liver, a disease closely associated with the comorbidities of gout. An initial assessment of liver function is key for decision making regarding the choice of medications both for use during the acute episodes, nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine potentially increasing transaminase levels, and for ULT, in particular, benzbromarone, the use of which is questioned due to the cases of fulminant liver failure that have been described.

Patient-reported outcomes

Gout has a major impact on patient musculoskeletal function and quality of life, particularly in those with frequent acute flares and tophaceous disease. When the disease is not under control, it leads to absence from work, reduced social participation and increased resource use⁷⁶. These factors can be evaluated using self-report questionnaires, some of which are generic and others specifically designed for gout. Not all of them have met validation criteria in research studies, the physical functioning subscale of the 36-item Short Form Health Survey, version 2⁸¹ being the one that best passes the filter for validity. Nonetheless, other questionnaires specific to gout (Gout Assessment Questionnaire and Gout Impact Scale) have been used in various clinical trials.

Clinical evaluation of treatment response:

OMERACT has defined various outcome domains that meet the criteria for evaluating response to ULT⁸². From the point of view of clinical response, the most widely used and those which are included in measures of activity and remission criteria include patient-reported number of acute



flares, tophus burden, serum urate, patient's global assessment of global disease activity and pain VAS scores, and patient-reported health-related quality of life (HRQoL).

Some studies have validated the Gout Activity Score (GAS), a formula based on the number of flares in the previous year, serum urate, global VAS and tophus burden.⁸³ Remission criteria have also been validated, namely, serum urate <6 mg/dL, a lack of gout flares, resolution of tophi and global and pain score <2 on a VAS from 0 to 10⁸⁴.



8. Treatment

8.1 Treatment strategy

The main aim of gout treatment is to dissolve the MSU crystals deposited in and around joint structures. This is achieved by reducing serum urate levels and seems to occur most rapidly if serum urate levels are significantly lower than the MSU saturation point (estimated at 6.8 mg/dL)⁸⁵. The elimination of the microcrystal deposits would lead to the disappearance of the inflammation they trigger, evident during acute flares and present, subclinically, between them. Such a condition, that is, an absence of MSU crystals and related inflammation, has been considered to indicate that gout is cured⁸⁶.

8.2 Reduction of serum urate levels

The reduction and normalisation of serum urate levels can be achieved by both pharmacological and non-pharmacological approaches. While non-pharmacological measures are widely supported by experts (weight loss, dietary control, abstinence or reduced alcohol consumption, and dose adjustment of concomitant hyperuricaemia-inducing medications), there is no consensus on when pharmacological treatments should be started. Since the publication of the 2013 GuipClinGot Guideline for the Management of Gout, there have been updates of two of the main sets of recommendations worldwide, namely, the European recommendations⁸ and the British Society for Rheumatology guideline⁸⁷. For the first time, both sets of recommendations suggest considering, in collaboration with the patient, initiating pharmacological treatment as soon as after the first flare of gout. They continue to recommend starting treatment in the case of patients with repeat flares, secondary structural damage, tophaceous gout, renal involvement or cardiovascular morbidity.

An approach not yet considered is the option of starting pharmacological treatment when there is evidence of MSU crystals but there are no clinical signs or symptoms of gout, even atypical manifestations. Nearly 25% of patients with asymptomatic hyperuricaemia have subclinical deposits of MSU crystals, as has been shown in several imaging studies (ultrasound⁴³ and DECT⁸⁸) and by synovial fluid analysis⁸⁹. Though subclinical, such deposits are associated with inflammation^{90,91} and probably with a poorer atherosclerotic profile⁹². In this phase, especially in the case of significant renal and/or cardiovascular comorbidity, the guideline development group considers that we could propose to the patient that urate-lowering pharmacological treatment is started early.



8.3 Non-pharmacological measures

Diet contributes to the development of hyperuricaemia and gout, and in society, gout is widely linked to certain foods, though they are usually related not to a change in serum urate levels (and therefore the formation of MSU crystals) but rather to an increase in the risk of an exaggerated immune response, given their ability to activate the NLRP3 inflammasome pathway. Hyperuricaemia and gout are most strongly associated with purine-rich animal products (red meat, seafood), alcohol (in particular, beer), and fructose-rich drinks, and it is the intake of precisely these products that European experts recommend avoiding or reducing, together with encouraging a heart-healthy diet and weight control⁸.

Various studies in patients with gout have assessed the usefulness of dietary supplements, such as milk-derived products (glycomacropeptides) or vitamin C, results so far being controversial or negative⁹⁴.

Adherence to treatment is key in attaining treatment targets but tends to be notably poor in chronic diseases and/or long-term treatments, as is the case of gout⁹⁵. Some researchers concluded that providing patients with information on the origin of gout, treatment targets, and expected benefits and potential adverse effects, as well as the importance of their involvement in the approach to managing the disease, helps to improve adherence and attain target serum urate levels⁹⁶.

8.4 Treatment targets and long-term prevention

The reduction of serum urate to subsaturation levels makes it possible to achieve major improvements in terms of outcome measures of gout, such as the disappearance of MSU crystals in the synovial fluid and reductions in tophus size and gout flare frequency. Nonetheless, there is still no consensus on optimal target serum urate levels. Table 8 lists the serum urate targets recommended in various CPGs and recommendations published internationally.

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Table 8. Management of gout according to clinical practice guidelines and recommendations fromvarious scientific societies

Clinical practice guidelines or recommendations	Author and year	Serum urate targets	Level of evidence/grade/strength of recommendation for target serum urate levels	Comments and special situations
Dutch College of General Practitioners	Romeijnders, 2002 ⁹⁷	<6.38 mg/dL	NA	<7.06 mg/dL if poor renal function
South African Medical Association	Meyers, 2003 ⁹⁸	<5 mg/dL	NA	Especially if tophaceous gout
American College of Rheumatology	Khanna, 2012 ⁷	<6 mg/dL	-/A/-	<5 mg/dL may be necessary to improve signs and symptoms of gout
3e Initiative	Sivera, 2014 ⁹⁹	<6 mg/dL	2b/C/9.0	<5 mg/dL if tophaceous gout
European League Against Rheumatism	Richette, 2016 ⁸	<6 mg/dL	3/C/8.8	<5 mg/dL if severe gout (tophaceous, chronic arthropathy, frequent flares) <3 mg/dL not recommended in the long term
British Society for Rheumatology	Hui, 2017 ⁸⁷	<5 mg/dL	4/-/9.7	The lower the serum urate levels, the faster the elimination of urate crystals
Treat-to-target	Kiltz, 2017 ⁹	<6 mg/dL	1a/A/9.5	<5 mg/dL if severe gout (tophi, frequent flares) until clinical remission
American College of Physicians	Qaseem, 2017 ¹⁰⁰	No targets regarding serum urate levels	Inconclusive	Evidence was insufficient to conclude whether the benefits of escalating urate- lowering therapy to reach a serum urate target ("treat to target") outweigh the harms associated with repeated monitoring and medication escalation
Taiwan Rheumatologist Association	Yu, 2018 ¹⁰¹	<6 mg/dL	3/B/9.30±0.56	<5 mg/dL if tophaceous gout

As can be seen, 6 mg/dL is the most widely recommended target level and it the most commonly used both in clinical trials and daily clinical practice, although it has never been formally compared with stricter targets.

In patients with severe gout (tophaceous gout, frequent flares, arthropathy or a high crystal load), the suggested goal is to reduce serum urate levels to substantially below the saturation point, at least below 5 mg/dL, to accelerate the dissolution of urate crystals (Grade D recommendation).

8.5 Dose escalation

Various studies have demonstrated that ULT should be started at low doses and then gradually escalated until the target serum urate levels for each patient are attained. This strategy seems to, on the one hand, reduce the onset of gout flares triggered by an initial reduction in serum urate levels,¹⁰² and on the other, reduce hypersensitivity reactions, in particular, those associated with allopurinol¹⁰³. It has yet to be established what is the most appropriate interval between increments in the dose, though it may depend on factors such as patients' crystal load and renal function as well as the combined use of colchicine.

One study concluded that more than one target level can be set: an initial target with the goal of promoting the dissolution of existing urate crystals (therapeutic target) and once this has been achieved, a target to prevent new crystals from forming (preventative target) ¹⁰⁴. Both EULAR⁸ and the BSR⁸⁷ included this concept of variable treatment targets for serum urate levels in the latest updates of their guidelines.

8.6 Drugs as monotherapy

Clinical question 1

How effective and safe are urate-lowering drugs as monotherapy for the treatment of gout?

Recommendations

In patients with gout, the recommendation is to start urate-lowering therapy with xanthine oxidase inhibitors as monotherapy (Grade B recommendation).

Pharmacological urate-lowering therapy should be started at low doses, and if needed, gradually escalated to doses that are effective in reducing serum urate levels to the therapeutic target * (Grade D recommendation).

*The urate treatment target should be at least <6 mg/dL in general and at least <5 mg/dL in patients with severe gout.

On grounds of efficacy, the recommendation is to prescribe allopurinol initially and use this drug until treatment targets are achieved or maximum tolerated or approved doses reached (Grade B recommendation).

Prescribing febuxostat as a first-line treatment can be considered in patients with severe gout, who require a therapeutic target for urate that is particularly low, within the limitations stated in the SmPC (see sections on cardiovascular disease, chronic kidney disease and transplantation) (Grade $\sqrt{$ recommendation).

Lesinurad should only be prescribed in combination with xanthine oxidase inhibitors (Grade A recommendation).

Benzbromarone as monotherapy may be an option in patients with gout who have a poor response to treatment, adverse reactions to xanthine oxidase inhibitors or cardiovascular disease (Grade C recommendation).

In patients with refractory gout or no other treatment option, it is appropriate to consider prescribing pegloticase, which is a foreign medication but may be requested under special circumstances (Grade V recommendation).

Gout is characterised by the deposition of MSU crystals in and around joints. This deposition is preceded by a long period of hyperuricaemia⁴². The final goal of treatment in patients with gout is to completely dissolve these crystals. To achieve this, we need to reduce serum urate levels below the saturation point, using ULT.

Quality of the evidence

The evidence identified comes both from the results of an SR conducted by the Agency for Healthcare Research and Quality (AHRQ) for the drafting of the ACP Clinical Practice Guideline on the management of gout¹⁰⁵, and the updating of this with studies published between 2015 and the time of writing. The following articles have been identified: three on allopurinol, six on febuxostat and one on lesinurad, and lastly, two on pegloticase compared to placebo.

The AHRQ review identified two RCTs that investigated the use of allopurinol vs. placebo. The first RCT¹⁰⁶ compared the use of allopurinol, febuxostat and placebo over 28 weeks in patients with gout with normal renal function or renal impairment. A total of 134 patients were assigned to receiving placebo and 268 to receiving allopurinol (300 mg/day in patients with normal renal function and 100 mg/day in patients with renal impairment). A higher percentage of patients achieved serum urate < 6 mg/dL in the allopurinol than the placebo group (41% vs. 1%); additionally, the percent decrease in serum urate levels from baseline was larger (34% vs. 4%). There were no differences in rate of gout flares, number or size of tophi or rate of AEs. The study limitations include a high risk of bias related to concealment of the randomisation sequence and a high rate of loss to follow-up (over 20%) (Level of evidence 1-). The second RCT¹⁰⁷ compares the safety of allopurinol 300 mg/dL (n=31) to placebo (n=26) over 10 days in patients with gout experiencing an acute flare. No differences were observed in the rate of AEs or new flares, or in the level of joint pain. In this study, the risk of bias is low, but its short duration, the relatively small number of patients included, their low levels of comorbidity, and the combined use of indomethacin and colchicine for prophylaxis, suggest that the results should be interpreted with caution (Level of evidence 1+). In these studies, only one death was reported and no increase was observed in the development of cutaneous reactions.

Additionally, updating the literature search, we found two further studies. An RCT¹⁰⁸ that sought to compare the effect of delayed initiation of allopurinol with that of starting the treatment during acute flares in terms of the symptoms of acute gout. The study included 35 patients followed up for 28 days. Treatment with colchicine was started in all patients recruited (within 72-hours of initiation of a gout flare), and patients were randomly allocated to concomitant treatment with allopurinol (100 mg daily for the first 2 weeks and then 200 mg daily until the end of the study) or placebo. Serum urate levels at day 28 were observed to be lower with allopurinol than with placebo (6.42 mg/dL vs. 8.25 mg/dL), with no differences in the rate of AEs. This study has certain limitations, however, related to its objective being to assess the effect of starting allopurinol during an acute gout flare, the short follow-up, the small number of patients included, and it being conceived as a non-inferiority trial but using methods for superiority trials (Level of evidence 1-).

A non-blinded RCT^{109,110} evaluated the efficacy and safety of **different doses of allopurinol** escalating the dose until the therapeutic target was achieved, compared to allopurinol at a fixed dose in patients with gout over 12 months. Patients included had serum urate levels \geq 6 mg/dL despite treatment with at least a creatinine clearance (CrCl)-based dose of allopurinol for \geq 1 month. Patients were randomised to continue with the allopurinol dose taken at inclusion or

gradual escalation until urate levels fell to below 6 mg/dL (increasing the daily dose by 50 mg if CrCl <60 ml/min and 100 mg if ClCr≥60 ml/min at each visit at which serum urate levels exceeded 6 mg/ml). The mean doses of allopurinol at the end of the study were 413 mg/day and 288 mg/day in the escalating- and fixed-dose groups, respectively. In the escalating-dose group, serum urate levels decreased more (-1.5 mg/dL vs. -0.3 mg/dL, p<0.001) and fell to below 6 mg/dL at 12 months in a higher percentage of patients (69 % vs. 32 %, p<0.0001) than in the fixed-dose group. Nonetheless, no differences were observed in the percentage of patients experiencing an acute gout flare, reductions in number or size of tophi or functional activity as measured using the Health Assessment Questionnaire (HAQ). Further, there were no differences in the volume of urate estimated using DECT, erosions measured using plain radiography or CT imaging, or the reduction in joint space on plain radiography. The rate of AEs was similar in both groups. The same results were obtained in *post hoc* analysis¹¹¹ of the subgroup of patients with mild-to-moderate renal impairment (Level of evidence 1+).

With regards to febuxostat, the AHRQ review identified two RCTs that assessed the efficacy and safety of febuxostat vs. placebo. The first RCT¹¹² compared different doses of febuxostat with placebo in patients with gout over a 28-day period. The frequency of gout flares was not significantly different with febuxostat 40 mg but was higher with febuxostat at doses of 80 mg or 120 mg (43% and 55% respectively vs. 37% with placebo and 35% with the lower dose of 40 mg). No differences were found in the rate of AEs. All the doses of febuxostat were associated with a higher probability of attaining the therapeutic target (serum urate <6 mg/dL), with a dosedependent behaviour (the target being achieved in 56%, 76% and 94% of cases with the increasing doses of febuxostat, respectively, vs. 0% with placebo). The risk of bias in this study was low, although data were not provided to assess allocation sequence concealment (Level of evidence 1+). The second RCT¹⁰⁶, also lasting for 28 weeks, analysed 134 patients in the placebo group and 267, 269 and 134 patients in the 80-, 120- and 240-mg dose groups, respectively. This study included patients with gout who had normal renal function or renal impairment. Patients on higher doses of febuxostat were more likely to need treatment for gout flares during the first 8 weeks on the prophylaxis (28%, 36% and 46% with increasing doses of febuxostat vs. 20% in the group on placebo), while results were similar from week 9 to 28. No substantial differences were observed in the number or size of tophi. All the doses of febuxostat were associated with a higher percentage of patients achieving serum urate <6 mg/dL by week 28, the highest dose (240 mg) being the most effective (76%, 87% and 94% with increasing doses vs. 1% with placebo). No differences were found in the rate of AEs. The risk of bias of this RCT was

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considered high, as no data were provided for assessing allocation sequence concealment and the rate of loss to follow-up was over 20% (Level of evidence 1-).

The most widely reported AEs in these RCTs are abdominal pain, diarrhoea and musculoskeletal pain, but the risk of these events was not significantly different to that observed with placebo. No AE-related deaths were reported. Nonetheless, the authors conclude by making reference to the message of the drug manufacturer, namely, that patients on febuxostat in RCTs have experienced a higher rate of cardiovascular thromboembolic events (cardiovascular death, acute myocardial infarction or stroke), the rate being higher with febuxostat (0.74 per 100 patient-years) than with allopurinol (0.5 per 100 patient-years). In this way, they add a note of caution and indicate the need for careful monitoring, despite no causal relationship having been established.

In a literature search to update the evidence, four other RCTs were identified. The first study¹¹³ evaluated the effect of febuxostat at doses of 40-80 mg daily vs. placebo in 314 patients with early gout (one or two previous flares) over 24 months. In the febuxostat group, serum urate levels at the end of the follow-up were lower (5.7 mg/dL vs. 8.2 mg/dL), a higher percentage of patients had serum urate levels below 6 mg/dL (63% vs. 6%), and a lower percentage of patients had had at least one flare (29% vs. 41%). The rates of all AEs, serious AEs and AEs leading to treatment discontinuation were similar in the two groups. This study is considered to have a low risk of bias, though methods of blinding, randomisation or allocation sequence concealment were not described. The rate of loss to follow-up was high, but losses were well balanced (Level of evidence 1+).

The second RCT¹¹⁴ assessed the impact of febuxostat vs. placebo on renal function in 96 patients with gout and moderate-to-severe renal impairment over 1 year. As secondary objectives, this study provides data on the efficacy of febuxostat in lowering urate levels and its safety in this population (patients with CKD). It considered two groups on febuxostat: the first given 30 mg twice daily and the second 40 mg once daily, increasing to 80 mg once daily if serum urate levels were \geq 6 mg/dL. In both febuxostat groups, the reduction in serum urate levels after 12 months was larger (-5.0 mg/dL with 30 mg twice daily and -4.2 mg/dL with 40/80 mg once daily vs. - 0.2 mg/dL with placebo, p<0.05), and the percentage of patients with serum urate levels \leq 6 mg/dL was higher (69% and 45% in the febuxostat groups, compared to 0% with placebo, p<0.05). The rates of all AEs, serious AEs and AEs leading to treatment discontinuation were similar (Level of evidence 1+).

The last two RCT^{115, 116} both evaluated two doses (40 mg and 80 mg daily) and two formulations (immediate and extended release) of febuxostat compared to placebo over 3 months, the first in 189 patients and the second in 1790 patients. In the first, Gunawardhana et al.¹¹⁵ observed that the percentages of patients who achieved serum urate below 6 mg/dL and 5 mg/dL at 3 months were higher in all of the febuxostat groups than in the placebo group (32% and 54% with 40 mg doses of immediate- and extended-release febuxostat, and 60% and 55% with 80 mg doses of immediate- and extended-release febuxostat, respectively, vs. 0% with placebo). Nonetheless, despite colchicine prophylaxis, the percentage of patients who experienced at least one gout flare was significantly higher in all febuxostat groups than in the placebo group, except the extended-release febuxostat 40 mg group. The rate of AEs was similar across all the groups, with a slightly higher rate of serious AEs in the extended-release febuxostat 80 mg group (11%) than the others (0-3%) (Level of evidence 1++). In the second study, Saag et al.¹¹⁶ confirmed that the percentage of patients achieving serum urate below 6 mg/dL was higher in all the febuxostat groups than in the placebo group (40% and 48% with 40 mg doses of immediate- and extended-release febuxostat, respectively; 58% and 61% with 80 mg doses of immediate- and extended-release febuxostat, respectively; vs. 1% with placebo). No significant differences were observed in the percentage of patients experiencing at least one gout flare. The rates of AEs, serious AEs and AEs leading to treatment discontinuation were similar across all the groups (Level of evidence 1+). The applicability of these studies is limited since the extended-release formulation is not available commercially and the doses of febuxostat used are lower than those approved in the European Union. Nonetheless, the interval validity of these studies is high.

Just one RCT¹⁰² has assessed the incidence of acute gout flares during the initiation of treatment with **different febuxostat protocols** with or without colchicine in patients with gout. A total of 255 patients were randomly allocated to one of three groups: febuxostat 40 mg daily in combination with colchicine 0.5 mg daily, febuxostat 40 mg daily without colchicine, or slowly escalating doses of febuxostat (10 mg daily for 4 weeks, followed by 20 mg daily for 4 weeks and then 40 mg daily until the end of the 12-week study). At 3 months, the percentage of patients who had had at least one gout flare was higher in the group on a 40-mg fixed dose of febuxostat as monotherapy (36% vs. 19% in those on febuxostat 40 mg daily with colchicine and 21% in those on escalating febuxostat doses), with no significant differences between the stepwise increase in febuxostat and administering it in combination with colchicine. No differences were observed between the three groups in terms of the number of gout flares (per patient and in a given time) or the percentage of patients who achieved the therapeutic target of serum urate <

6 mg/dL. Further, no differences were detected between groups in the rates of all AEs or serious AEs. The limitations of this study include the lack of blinding and the difficulty of generalizing the conclusions as they were based on a Japanese population (Level of evidence 1+).

Regarding the comparison between allopurinol and febuxostat, the AHRQ review included four RCTs. One RCT¹¹⁷ compared 760 patients who received febuxostat (80 or 120 mg) or allopurinol (300 mg/d) once daily for 52 weeks. There were no significant differences in clinical outcomes, namely, incidence of gout flares (64%, 70% and 64%, respectively) or reduction in tophus area (83%, 66% and 50%, respectively). More patients discontinued the study in the group on 120 mg of febuxostat than in the groups receiving 80 mg of febuxostat or allopurinol. Four patients treated with febuxostat died. A higher percentage of patients treated with febuxostat achieved the therapeutic target of serum urate <6 mg/dL than with allopurinol (53%, 62% and 21%, respectively, p<0.001).

A second RCT¹⁰⁶ compared 1072 patients who received febuxostat (80, 120 or 240 mg once daily), allopurinol (100 or 300 mg once daily as a function of renal function) or placebo for 28 weeks. There were no differences between groups in the percentage of patients who required treatment for gout flares in weeks 9-28. During the first 8 weeks, while receiving prophylaxis for gout flares, the percentage requiring treatment was higher among patients on 120 or 240 mg of febuxostat than among those on 80 mg of febuxostat or allopurinol. No differences were observed between groups in the number or size of tophi, except for fewer tophi being observed with febuxostat 120 mg than with placebo. The rate of AEs was similar across the groups, except for dizziness and diarrhoea, which was more common with febuxostat 240 mg. The percentage of patients who achieved the target of serum urate <6 mg/dL after 3 months of febuxostat treatment was 48%, 65% and 69% with doses of 80, 120 and 240 mg, respectively; in contrast, only 22% of patients given allopurinol attained this target (p<0.05). Among the subset of patients with renal impairment, similar differences were found between the febuxostat and allopurinol groups in the percentage of patients reaching this target (Level of evidence 1-).

Third, the CONFIRMS study¹¹⁸ analysed 2268 patients who received febuxostat 40 mg or 80 mg daily or allopurinol (200 mg or 300 mg daily depending on renal function). The only clinical outcomes reported were gout flares and safety. The rates of flares were 10-15% in all the groups during the first 2 months and then decreased over the study period. No differences were observed between groups. AEs were reported by 56% of participants, the rate being similar across groups, and most of the AEs were mild or moderate. The target serum urate level of <6 mg/dL was achieved in 45% of patients on febuxostat 40 mg, 67% of those on febuxostat 80

mg and 42% of those on allopurinol (p<0.05 for febuxostat 80 mg vs. allopurinol). Outcomes were also better with febuxostat 80 mg or 40 mg than with allopurinol in the subgroup of patients with renal impairment.

Finally, the EXCEL¹¹⁹ study is an extension study of two pivotal trials in which randomly assigned treatment with febuxostat 80 or 120 mg or allopurinol 300 mg was continued for 40 months. The rate of gout flares increased after prophylaxis withdrawal at week 8, but then steadily decreased over the study period, less than 4% of participants reporting a flare beyond month 18. Complete resolution of baseline tophi was observed in 46%, 36% and 29% of participants on febuxostat 80 mg, febuxostat 120 mg and allopurinol, respectively. The overall rate of AEs was similar across groups. After 1 month of treatment, serum urate levels fell to <6 mg/dL in 81% and 87% of patients on febuxostat 80 mg and 120 mg, respectively, while these levels were only achieved by 46% of patients on allopurinol.

In a literature search to update the evidence, four RCTs have been identified that provide new results comparing febuxostat and allopurinol. One of these focused only on the safety of these drugs in relation to the cardiovascular system, while the other three provide data on efficacy as well as safety; however, these studies were performed in China, which constrains their external validity given the genetic and environmental differences between the populations studied and patients in our setting.

First, a trial by Wang et al.¹²⁰ randomised 160 patients to allopurinol 300 mg daily or febuxostat 80 mg daily over 6 months to assess the efficacy and safety of these treatments. Serum urate levels were lower in the febuxostat group at all the study time points (1, 3 and 6 months); in line with this, all patients in the febuxostat group attained serum urate <6 mg/dL at 6 months vs. 88% of those on allopurinol (p<0.05). At the same time, the patients on febuxostat had a higher rate of flares, but a lower rate of AEs (4% with febuxostat vs. 14% with allopurinol). Nonetheless, the quality of this study can be considered poor, as authors did not describe the methods of randomization or blinding, inclusion criteria or rates of loss to follow-up (Level of evidence 1-).

Second, in another RCT ¹²¹, a total of 504 patients with gout and normal renal function were randomised to allopurinol (300 mg daily) or one of two doses of febuxostat (40 mg or 80 mg daily) for 6 months. Patients on febuxostat 80 mg were more likely to achieve serum urate levels <6 mg/dL (59% vs. 45% with febuxostat 40 mg and 35% with allopurinol, p<0.05) and experienced greater reductions in serum urate levels than those on allopurinol, no significant differences being found between febuxostat 40 mg and placebo. The rates of gout flares, all AEs, serious AEs and AEs leading to treatment discontinuation were similar across the groups. The

external validity of this study is limited as, given the origin of the study population, the febuxostat doses used are lower than those approved in Europe, but the risk of bias of the study is low (Level of evidence 1++).

The third RCT¹²² compared the efficacy and safety of febuxostat (80 mg daily) and allopurinol (300 mg) in 109 patients. At week 12, the group on febuxostat showed both a larger reduction in serum urate levels and a higher percentage achieving serum urate < 6 mg/dL (59% vs. 11% with allopurinol). The rates of all AEs, serious AEs and AEs leading to treatment discontinuation were similar across groups. Nonetheless, the quality of this open-label study was also considered low, as the methods of randomization and blinding were not described, and the target sample size was not reached (Level of evidence 1-).

Finally, a trial by White et al.¹²³ evaluated whether febuxostat was similar to allopurinol in terms of rates of cardiovascular events. The study included 6190 patients with gout and a history of cardiovascular disease and had a non-inferiority design, patients being randomized to febuxostat (40 mg daily, increased to 80 mg daily if serum urate levels did not fall to < 6 mg/dL), or allopurinol (200 mg or 300 mg daily as the initial dose depending on renal function, increased to 400 mg or 600 mg daily if the serum urate target was not achieved). The data on cardiovascular safety are discussed in the corresponding section of this guideline. A higher percentage of participants achieved serum urate < 6 mg/dL in the febuxostat group than in the allopurinol group at 2 weeks (61% vs. 50%), 3 months (73% vs. 69%), 6 months (72% vs. 66%), 12 months (72% vs. 66%), 18 months (72% vs. 68%), 24 months (73% vs. 68%), 36 months (73% vs. 70%) and 60 months (76% vs. 72%). Similarly, a higher percentage of patients achieved serum urate <5 mg/dL in the febuxostat group than the allopurinol group at 2 weeks (34% vs. 19%), 3 months (43% vs. 27%), 6 months (44% vs. 28%), 12 months (46% vs. 31%), 18 months (47% vs. 33%), 24 months (46% vs. 32%), 36 months (50% vs. 34%), 48 months (49% vs. 34%), 60 months (54% vs. 40%) and 72 months (58% vs. 44%). The rate of flares was similar in the two groups (0.68 per patient-year with febuxostat and 0.63 per patient-year with allopurinol) (Level of evidence 1+).

We identified two RCTs comparing **allopurinol with benzbromarone**. In the first¹²⁴, conducted at a Spanish hospital, 37 patients with gout and renal impairment (creatinine clearance 20-80 ml/min) and candidates for ULT were randomized to benzbromarone (increased in steps of 50 mg from 50 mg/d to a maximum of 200 mg daily if needed) or allopurinol (100-150 mg daily initially, increased in steps of 50-150 mg depending on estimated renal function and to a maximum dose (100-300 mg/d) also based on estimated CrCl dosing). There was a greater



reduction in serum urate levels in the benzbromarone than in the allopurinol group (5.4 mg/dL vs. 3.1 mg/dL; p<0.05). No differences were observed in the number of gout flares or rate of AEs, with only one case of a cutaneous reaction in the allopurinol group. Seven patients switched from allopurinol to benzbromarone. As limitations, we should note that the trial was open-label and the sample size was small (Level of evidence 1-).

The second RCT¹²⁵ randomised 65 patients with gout and renal impairment in whom ULT was indicated to benzbromarone (100 mg daily) or allopurinol (100 mg daily, increased in steps of 100 mg intervals to a maximum of 300 mg daily). After 2 months, the doses of benzbromarone and allopurinol were increased to 200 mg and 600 mg daily, respectively, in patients with serum urate levels above 0.3 mmol/l (5 mg/dL). The percentage of patients who attained serum urate <0. 3 mmol/l at any time during the study was similar in the two groups (78%); however, the percentage of patients with serum urate levels <0.3 mmol/L in the second month was higher in the benzbromarone group. The rate of AEs was also higher in the benzbromarone group (20% vs. 7% with allopurinol). Among the limitations of the trial, it should be noted that it was open-label, had a small sample size and the analysis of the efficacy was per protocol (Level of evidence 1-).

Thirdly, we identified an RCT comparing benzbromarone with febuxostat¹²⁶. A total of 214 patients were randomised to low doses of febuxostat (20 mg daily) or benzbromarone (25 mg daily) for 12 weeks. There were no significant differences between groups in the percentage of patients who achieved serum urate <0.360 mmol/l (6 mg/dL) (38% in both groups) or who had a gout flare (23% with febuxostat and 34% with benzbromarone). Further, no differences were found in the rates of AEs or withdrawal from the study due to AEs (0.8% in both groups). Limitations of this trial include it having been open-label and the per protocol analysis of the efficacy (Level of evidence 1-).

Finally, we identified one paper reporting the results of two RCTs comparing pegloticase with placebo¹²⁷. The RCTs, one including 109 patients and the other 116, had an identical design, patients being randomised to placebo or one of two groups treated with pegloticase: 8 mg biweekly or every 4 weeks for 6 months. In the pooled analysis, the authors observed a higher percentage of responders (those who attained the therapeutic target) at 3 and 6 months in patients in both of the pegloticase groups (35% and 42% vs. 0% with placebo). Further, with both of the pegloticase doses, the percentage of patients that experienced resolution of at least one tophus was higher (40% and 21% vs. 7% with placebo) as was the improvement reported in terms of pain and quality of life (change in 36-item Short Form Health Survey score of 4.4 and

4.9 points vs. -0.3 with placebo). On the other hand, the rate and frequency of gout flares were higher with both pegloticase doses than with placebo in the first 3 months, though rates were similar from 3 to 6 months. The rate of AEs was similar overall across groups, but there were higher rates of serious AEs (23% and 24% vs. 12% with placebo) and AEs leading to treatment discontinuation in the pegloticase groups (18% and 19% vs. 2% with placebo). The quality of this study can be considered high, with a low risk of bias, although the methods of randomization and blinding were not reported (Level of evidence 1++).

Just one recent RCT¹²⁸ was found **on lesinurad**, comparing the use of this drug (400 mg daily as monotherapy) with **placebo** in 214 patients with gout and intolerance or contraindications to XO inhibitors, over 6 months. The percentage of patients achieving serum urate <6 mg/dL was higher in the group on lesinurad at the end of the study and all follow-ups after the first month. Similarly, more of the patients on lesinurad achieved the stricter targets of 5 or 4 mg/dL. The percentage of patients with at least one gout flare was similar. The lesinurad group had higher rates of serious AEs (8% vs. 4%) and AEs leading to treatment discontinuation (8% vs. 3%). The study found a notably high rate of renal AEs, 18% of patients on lesinurad experiencing a renal AE and 5% a major renal event. The quality of the study was high, although it has limited external validity, since lesinurad has been approved by the European Medicines Agency (EMA) in combination with XO inhibitors at doses of 200 mg daily (Level of evidence 1+).

The GDG considers that the results of the studies identified are compatible, providing similar results regarding the efficacy of the intervention of interest in terms of the percentage of patients achieving therapeutic targets and reductions in serum urate levels, with all ULTs compared to placebo. In contrast, the data on health-related outcomes (rates of flares, reduction in tophi) are similar in the active treatment and placebo groups, probably due to limited follow-up in the majority of studies. In comparisons between febuxostat and allopurinol, the efficacy of febuxostat was consistently higher, especially in the case of patients with some degree of renal impairment, although the doses of allopurinol tested are lower than the defined daily dose (DDD)¹²⁹. We should highlight that some of the studies report differences in the rates of AEs, in particular concerning mortality and cardiovascular events, while in others these rates were similar.

The results of most of the studies identified are directly applicable to our healthcare setting. Nonetheless, the GDG underlines that pegloticase, though recommended for market authorisation in the European Union in 2012, was suspended for commercial reasons. This drug can be obtained on request, if considered appropriate. Further, the findings of other studies may



not be strictly applicable as they were based on populations with a different ethnic background (mainly oriental) to that of patients in our setting and hence are difficult to generalise.

Before formulating the recommendations, the GDG has thoroughly discussed the use of ULT at the outset in patients with gout, as it is an issue with major clinical implications. Regarding which medication to use, there is no clear general answer, but given the contraindication of lesinurad as monotherapy and the restrictions on the use of benzbromarone, in most cases, the choice is between allopurinol and febuxostat. At the doses studied, there are differences in terms of efficacy, but the doses of allopurinol studied are lower than those recommended. Results are also mixed concerning safety, in particular, regarding risks to the cardiovascular system. Further, the costs differ between these options, and there are no clear data on differential costeffectiveness.

8.7 Combination therapy

Clinical question 2

How effective and safe is combination therapy for gout?

Recommendations

In patients with gout, combination therapy of xanthine oxidase inhibitors with uricosuric agents should be used when serum urate targets are not achieved with monotherapy at appropriate doses or maximum tolerated doses (Grade v recommendation).

Given the stronger evidence in terms of safety, the addition of lesinurad to a xanthine oxidase inhibitor should be considered before the combination with benzbromarone (Grade A recommendation).

The GDG considers that there is currently no evidence supporting the use of two drugs with the same mechanism of action (i.e., two xanthine oxidase inhibitors or two uricosuric agents) (Grade $\sqrt{$ recommendation).

Combination therapy with two medications is commonplace in medicine, especially in the treatment of highly prevalent conditions, such as hypertension, diabetes and hyperlipidaemia. Regarding gout, the first cases were reported in the nineteen-sixties, and then several cases series were published, but it was not until the first decade of the 21st century that clinical trials were carried out and these only tested new drugs.

For this reason, it is important to assess how much evidence can be gathered on efficacy and safety to support the use of combination therapies.

Quality of the evidence

Most of the evidence found is summarised in the SR by Wu *et al.*¹³⁰, although some other small studies/series¹³¹⁻¹³⁶ also show that adding benzbromarone to allopurinol^{131,133,134} or lesinurad to febuxostat^{132,135} or allopurinol¹³⁶ improves the effectiveness in terms of the rate of achieving target serum urate levels.

The combination of lesinurad with an XO inhibitor vs. lesinurad as monotherapy and the use of lesinurad 200 mg daily rather than 400 mg daily in this combination was associated with a lower rate of renal AEs, particularly in terms of the increase in creatinine levels and reduction in renal function¹³⁰ (Level of evidence 1+). The long-term open-label extension study of the CRYSTAL trial combining lesinurad and febuxostat produced results consistent with the core study in terms of efficacy and safety¹³² (Level of evidence 3).

The combination of benzbromarone and allopurinol is based on three studies with a lower level of evidence^{131, 133, 134} (Level of evidence 1-, 3, 3) that show that low daily doses of these drugs (allopurinol <300 mg daily and benzbromarone <100 mg daily) combined were not superior to either of them as monotherapy using the standard doses for allopurinol (300 mg daily) or benzbromarone (100 mg daily). Analysing by serum urate level and not treatment arm, a benefit was only observed in terms of velocity of tophus reduction when the combination of benzbromarone and allopurinol led to the achievement of lower levels of serum urate than those achieved with a standard dose of allopurinol¹³³ (Level of evidence 1-). None of the aforementioned studies provides high-quality evidence in terms of the long-term safety of this combination therapy. The SR did not find any studies assessing the combinations of benzbromarone and febuxostat, two xanthine oxidase (XO) inhibitors or two uricosuric agents. The GDG considers that the research available shows that adding a uricosuric agent to a fixed dose of XO inhibitor improves efficacy in terms of reducing serum urate levels, with an acceptable increase in AEs.

Our level of knowledge on the safety of treatments combining lesinurad and allopurinol or febuxostat is based on their clinical use in high-quality clinical trials and associated open-label extension studies. The evidence on the safety of the combination of benzbromarone and allopurinol is limited to the short term and of lower quality, and there is no evidence regarding the combination of benzbromarone and febuxostat.



The combinations of lesinurad with either allopurinol or febuxostat were both approved by the European Commission, and regulated in terms of indications and safety procedures in the EMA SmPC¹³⁷ and funding conditions in the Therapeutic Positioning Report (IPT in Spanish)¹³⁸ of the Spanish Agency of Medicines and Medical Devices (AEMPS). There is no combo pill available for any lesinurad combination with XO inhibitors.

For these reasons, such combination therapies should only be considered after the failure of other treatment options and by health professionals with extensive experience in the management of these medications.

The GDG considers that the combination of medications is an alternative to monotherapy when the maximum doses of a drug are not well tolerated, it is not reasonable for patients to assume the risks associated with such high doses or the therapy is not indicated (for example, benzbromarone as monotherapy is only approved for patients with severe gout or kidney disease or who are kidney transplant recipients).

Combinations with a higher level of evidence, especially in terms of the management of their safety, would be preferable to those backed by lower evidence.

8.8 Prevention of gout flares

The prevention of episodes of acute inflammation refers to the measures (pharmacological or non-pharmacological) required to avoid the onset of gout flares during the initiation of ULT. Despite the lack of clinical trials designed to study the various medications used for this purpose, some relevant information can be obtained from studies conducted with urate-lowering agents. These studies have demonstrated that colchicine or low-dose NSAIDs are effective in the prevention of gout flares, this being reported in the ACR and EULAR recommendations on gout management. The ACR guidelines recommend prophylaxis in patients starting ULT for whichever of the following periods is the longest: a) 6 months; b) 3 months after achieving target serum urate levels, in patients without tophi; and c) 6 months after achieving target serum urate levels, in patients with tophi⁷. The updated 2016 EULAR recommendations are more straightforward and recommend doses of 0.5-1 mg daily of colchicine for 6 months after starting ULT⁸. Further, colchicine is the only medication indicated (on its SmPC) for prophylaxis of gout flares in patients initiating ULT¹³⁹. Recently, a retrospective study with variable low doses of glucocorticoids has demonstrated the efficacy of these drugs in this scenario¹⁴⁰.

Various studies have shown that ULT should be initiated using low doses and then gradually escalated, especially in the case of XO inhibitors^{103, 141}. This would make it possible to, on the one hand, avoid AEs associated with the drugs, particularly in patients with renal impairment, and on the other, reduce the likelihood of developing flares¹⁰²; hence, the motto "Start low and go slow"⁸⁶.

Finally, the panel members consider that the best way to prevent acute episodes of inflammation is to eliminate the deposits of MSU crystals. If there are no deposits, there cannot be flares.

8.9 Treatment of acute episodes

Several SRs and meta-analyses have concluded that there are no differences in efficacy between the various NSAIDs approved or between NSAIDs and glucocorticoids in the treatment of episodes of acute inflammation in gout. On the other hand, glucocorticoids and Cox-2 inhibitors have a better short-term safety profile than classical NSAIDs¹⁴³⁻¹⁴⁷.

The choice between nonsteroidal anti-inflammatory drugs and glucocorticoids for the treatment of gout flares depends on patient preferences and comorbidities (Grade $\sqrt{recommendation}$).

International experts continue to recommend low-dose colchicine for acute flares⁸.

The adrenocorticotropic hormone, a synthetic derivative of which (cosyntrophin) is marketed in Spain, and IL-1 inhibitors (anakinra and canakinumab) have shown to be effective in patients with contraindications for NSAIDs, colchicine or glucocorticoids, or when their use is not considered clinically appropriate^{148, 149}. Anakinra is used off-label and the use of canakinumab in this context is approved but not funded by the Spanish Health System¹⁵⁰.

On the other hand, some studies have shown that local cold therapy partially alleviates the symptoms of gout flares¹⁵¹.

8.10 Imaging tests for monitoring treatment response

Clinical question 3

How useful are imaging tests for the follow-up of patients with gout?

Recommendations

Plain radiography is recommended for assessing the extent of joint damage and monitoring bone erosions (Grade C recommendation).

Ultrasound is recommended for assessing the effect of urate-lowering therapy in terms of urate deposits, double-contour sign and size of tophi (Grade C recommendation).

There is no evidence on which to base a recommendation regarding the time between examinations (Grade v recommendation).

There is insufficient evidence to make a recommendation for or against the use of dualenergy computed tomography for follow-up (Grade $\sqrt{recommendation}$).

As the recently proposed serum urate targets for reducing urate deposits through proper control of uricaemia could be assessed using imaging techniques, we should consider whether these techniques may be useful for the initial assessment and/or follow-up of the treatment of patients with gout.

Quality of the evidence

There is a paucity of evidence for addressing this question. We found two studies assessing the usefulness of plain radiography in the follow-up of patients with gout; further, we have identified three studies evaluating DECT and two exploring the role of ultrasound.

Conventional radiography

One retrospective observational study assessed changes in the size of tophi around the first metatarsophalangeal joint after ULT. The researchers evaluated serial radiographs showing tophi in 60 out of 350 patients who had received ULT for more than 6 months. Tophi were measured as an increase in soft tissue or calcifications and graded on a semiquantitative scale from 0 to 3. They concluded that plain radiography is useful to assess treatment response in patients with gout. The study has some serious methodological limitations, however: the

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treatment duration was very long, the outcome measure has not been validated in terms of accuracy and the radiography technique used varied¹⁵² (Level of evidence III).

An SR¹⁵³ provides information on the use of conventional radiography for assessing bone erosions and joint space narrowing based on four studies. Dalbeth et al.¹⁵⁴ reported a decrease in erosion score from 69.25 to 57.25 in patients treated with pegloticase, and another study by the same research group¹⁵⁵ did not find changes with zoledronate or placebo after 2 years. McCarthy et al.¹⁵⁶, following up 39 patients over 10 years, observed radiographic progression of erosions in 9 and evidence of improvement in 8, while in a study by Bloch et al.¹⁵⁷, radiographic improvement was observed in 21 out of 80 patients. Regarding joint space narrowing in patients treated with pegloticase¹⁵⁵, no changes were observed after 1 year; similarly, no differences were observed in patients on zoledronate or placebo after 2 years of follow-up¹⁵⁵.

Dual-energy computed tomography

An SR¹⁵⁸ identified four studies assessing whether DECT shows sensitivity to change¹⁵⁹⁻¹⁶², defined as the ability to detect changes in the volume of tophi. A coefficient of >0.8 was considered to indicate the effect size was large; 0.5 to 0.8 medium; 0.2 to 0.5 small and <0.2 negligible. The sensitivity to change for a reduction in the volume of tophi varied across studies, with an effect size ranging from 0.05 to 1.24, and the studies yielded contradictory results. The study by Rajan et al.¹⁶¹, a prospective observational study and the one that included the largest number of patients, did not find a correlation between a reduction in the volume of urate deposits based on DECT and a decrease in urate levels in patients on ULT, although the mean serum urate levels were above the saturation point. Only the study of Sun et al.¹⁶² described a significant correlation between serum urate levels and volume of urate deposits. The authors of the review concluded that the role of DECT for following up patients with gout on ULT remains uncertain. The review did not assess the quality of the studies included, and they were small scale and clinically heterogeneous (Level of evidence III).

One other study¹⁶³ sought to use DECT to assess changes in urate deposits in 46 patients treated on ULT. This study is based on secondary data from a phase 3 multicentre RCT comparing allopurinol and febuxostat. The follow-up period was 6 months (n=46), and in a subgroup of 16 patients, the follow-up was extended to 12 months. At 6 months, urate deposits around joints had disappeared in 67% of patients; however, in 28% of patients, while urate deposits had disappeared around some joints, they had appeared around others. The mean volume decreased from 1.3±3.8 cm³ at baseline to 0.6±2.1 cm³ after 6 months (mean change: -0.7±1.8 cm³). At 12 months, the mean volume of urate deposits was 0.05 ± 0.09 cm³. The authors concluded that the study confirmed the value of DECT for the diagnosis and monitoring of treatment in patients with gouty arthritis (Level of evidence II).

Finally, the SR by Durcan et al.¹⁵³ identified only one study¹⁶¹ that reported a minimum detectable change of 0.91 cm³ for urate deposits.

Ultrasound

We found an SR¹⁶⁴ that identified three prospective studies on the use of ultrasound to assess treatment response in patients with gout¹⁶⁵⁻¹⁶⁷. The studies of Thiele et al.¹⁶⁶ and Peiteado et al.¹⁶⁷ reported a decrease or disappearance of the double-contour sign in patients with serum urate levels <6 mg/dL. The study by Perez-Ruiz et al.¹⁶⁵ described a reduction in the longest diameter and volume of tophi. In patients with serum urate levels <6 mg/dL, there was a reduction greater than the minimum detectable difference in 68% of tophi. In contrast, in patients with serum urate levels >6 mg/dL, significant reductions were observed in only 10% of tophi. The authors of the review concluded that the use of ultrasound seems to be useful for the assessment of response to ULT in patients with gouty arthritis but that more well-designed studies are required to confirm these results (Level of evidence III).

The aforementioned SR by Durcan et al.¹⁵³ also included the studies by Thiele et al.¹⁶⁶ and Perez-Ruiz et al.¹⁶⁵ and identified one other study¹⁶⁸. The authors of the SR concluded that the imaging tests are able to detect urate deposits, structural damage and inflammation associated with gout, but well-designed prospective longitudinal studies are required and there is no single valid imaging test (Level of evidence III).

Lastly, we identified a follow-up study of a cohort of 23 patients who met the inclusion criteria of having recurrent flares or symptomatic gout over more than 4 months despite the treatment received¹⁶⁹. In all cases, the diagnosis was made based on the identification of MSU crystals. The double-contour sign was observed in 73.9% of patients at baseline and this percentage fell to 28.6% at 2 years of follow-up. Tophi were detected by ultrasound in 91.3% of patients at baseline and 81% after 2 years. The results indicate that the disappearance of the double-contour sign is more rapid than that of tophi. The study found clinical parameters to be significantly correlated with the double-contour sign (r=0.49; p=0.038), though not with ultrasound-detected tophi. The authors concluded that ultrasound findings are sensitive to change in patients with gout and correlated with decreases in urate levels after treatment, and hence, that ultrasound may be a useful tool for monitoring tophi (Level of evidence III).

The GDG consider it appropriate to mention at this stage that most of the studies found were not specifically designed to achieve changes in the measures of deposits that would be evaluable

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by imaging techniques, decreasing serum urate levels often being insufficient for obtaining notable differences in urate deposition. While ultrasound does show detectable changes in tophi and double-contour signs, in the case of plain radiography, there are only methodologically acceptable studies for the assessment of erosions, and for DECT, there are no sufficiently highquality studies to draw any conclusions.

The GDG recommends the use of plain radiography in clinical practice to assess the extent of irreversible (joint impingement) and reversible (erosions) structural damage. DECT is an expensive radiation-based technique that has yet to show clinically useful results. On the other hand, ultrasound, an inexpensive non-radiation-based technique, has shown a relationship between ULT and findings in terms of crystal deposits around the joints (tophi and double-contour sign) making it potentially useful in clinical practice.

9. Treatment of gout in special situations

9.1 Chronic kidney disease

Clinical question 4

How effective and safe is gout treatment in patients with kidney disease?

Recommendations

The same target serum urate levels should be used for the treatment of gout regardless of whether patients have chronic kidney disease (Grade V Recommendation).

In patients with gout and chronic kidney disease, the use of a xanthine oxidase inhibitor (allopurinol or febuxostat) as a first-line treatment should be considered, with the specific limitations stated in their summary of product characteristics (Grade V recommendation).

In patients with gout and chronic kidney disease, the dose of allopurinol should be adjusted downwards for the initial doses (50 to 100 mg daily for the lowest levels of renal function) and escalated gradually (monthly increases of 50 to 100 mg daily depending on renal function) to attempt to attain serum urate targets and reduce the risk of toxicity (Grade $\sqrt{recommendation}$).

Allopurinol should be avoided in patients who are known to have the HLA-B*58 allele (such as those who are transplant recipients or on a transplant programme)* (Grade C recommendation).

(*) The EMA does not recommend systematic genotyping before prescribing allopurinol in the white population; however, it seems that it is cost-effective in Asian ethnic groups.

In patients with gout and chronic kidney disease, benzbromarone should only be prescribed after a poor response or adverse effects related to a xanthine oxidase inhibitor (Grade $\sqrt{recommendation}$).

Lesinurad should be prescribed provided patients do not have severe kidney disease, always in combination with a xanthine oxidase inhibitor (allopurinol or febuxostat), and taking into account the warnings and precautions for use mentioned in the summary of product characteristics (Grade A recommendation).

In patients with severe kidney disease, the use of uricosuric agents (benzbromarone and lesinurad) is not recommended, as they are not effective (Grade A recommendation).



The use of pegloticase should be considered in patients with severe kidney disease, with refractory gout or who do not tolerate well other treatment options* (Grade $\sqrt{recommendation}$).

*As this drug is not currently marketed in the European Union, it is considered a "foreign medication" and authorization should be sought for prescribing it (Official State Bulletin [BOE] 19 June 2011).

The GDG considers that there is insufficient robust evidence to support specific recommendations on the use of urate-lowering drugs in patients on dialysis. Referral of these patients to units with greater clinical experience in their management should be considered (Grade v recommendation).

Among various conditions associated with gout, CKD is the one that has the greatest implications for treatment and the most prevalent, 40-50% of patients with gout having some degree of renal dysfunction. Hardly any of the medications used as a first-line treatment for gout are free from significant limitations in their use by patients with kidney failure. Given this, urate-lowering drugs have been used less or at lower doses in these patients, this having an impact on outcomes. Specifically, the use of uricosuric agents has been restricted due to their theoretical effect promoting the development of urolithiasis and their toxicity (in the case of benzbromarone) as has the use of uricostatic agents (the recommended doses of allopurinol in patients with CKD rarely attaining serum urate targets and febuxostat not having been tested until recently in patients with advanced CKD) and uricases, which have been very little studied in this population. Despite the association between gout and CKD, appreciably fewer patients with gout and normal renal function have been included in clinical trials. For this reason, health professionals have had to make treatment decisions based on data from studies with small sample sizes or short follow-ups¹⁷⁰.

Quality of the evidence

First, we present the evidence found concerning the treatment of patients with gout and stage 1-4 CKD, with respect to both the efficacy or effectiveness and the safety of each drug, compared to placebo or other drugs. Secondly, we present the evidence found regarding the treatment of patients with gout and advanced CKD on haemodialysis, given the specific characteristics of this population.

Treatment of patients with stage 1-4 chronic kidney disease

<u>Allopurinol</u>

We have identified only one post hoc analysis stratified by level of renal function, this being based on data from an open-labelled clinical trial of allopurinol dose escalation in 183 patients, assessing the efficacy of different doses. This study showed that similar percentages of patients achieved the serum urate target (<6 mg/dL) across the different levels of renal function (Kidney Disease: Improving Global Outcomes [KDIGO] Definition for CKD), with rates of 64.3%, 76.4%, and 75.0% in the patients with CrCl <30 ml/min, \geq 30 but <60 ml/min, and \geq 60ml/min, respectively (p=0.65). At the start of the study, patients with lower CrCL were on significantly lower doses of allopurinol: 146 (18) mg daily, 243 (10) mg daily and 323 (9) mg daily (p <0.001) being given to patients with CrCl <30ml/min, \geq 30 but <60 ml/min, and \geq 60 ml/min, respectively. Similarly, at the end of the study, patients with lower CrCl were on significantly lower doses of 250 (43) mg daily, 365 (22) mg daily and 460 (19) mg daily (p <0.001) being given to patients with CrCl of <30 ml/min, \geq 30 but <60 ml/min, and CrCl \geq 60 ml/min, respectively. These data are consistent with the pharmacokinetics of allopurinol¹¹¹ (Level of evidence 1+).

Data on the safety of allopurinol come from some other studies as well as those mentioned above. Given the little evidence available, we also include the most important results from studies that include patients not diagnosed with gout.

There are three relevant observational studies included in an SR by Thurston *et al.*¹⁷¹. The first suggestion for adjusting the dose of allopurinol in patients with CKD was based on a series of 6 cases of allopurinol-related toxicity and the review of another 72 patients from the scientific literature¹⁷². The authors related the risk of toxicity to the loss of renal function, suggesting adjusting the dose based on CrCl. In contrast, the second study did not show differences in AEs related to allopurinol in patients who received doses of allopurinol higher than those recommended based on CrCl, in accordance with the proposal in the previous study. Specifically, adverse reactions were observed in 2 out of 68 patients receiving non-adjusted doses and 3 out of 52 receiving CrCl-adjusted doses, with just one case of allopurinol hypersensitivity syndrome in the adjusted-dose group¹⁷³. The third study was a retrospective case-control study with negative results regarding the association between CKD and allopurinol-related toxicity, although this study included patients without gout and children with hyperuricaemia and therefore the findings are not applicable to the target population of this guideline¹⁷⁴ (Level of evidence 2-).

We found a case-control study that sought to assess the relationship between allopurinol dose, renal function, plasma levels of oxypurinol and granulysin, and prognosis (in terms of severity and mortality) in allopurinol-related severe cutaneous adverse reactions (SCARs). The HLA-B*58: 01 allele was found to be strongly associated with severe reactions to allopurinol (OR: 10; 95 % CI: 24.8- 481; p <0.001). In patients with SCARs, the estimated GFR was significantly lower; and the percentage of patients with severe kidney disease (estimated GFR < 30 ml/min) and the initial dose-to-estimated GFR ratio were higher than in allopurinol-tolerant controls. The multivariate logistic regression analysis identified poor renal function as an independent risk factor for SCARs due to allopurinol. The authors concluded that high plasma levels of oxypurinol and granulysin and impaired renal function were correlated with poor prognosis of allopurinol-related SCARs¹⁷⁵ (Level of evidence 2+).

A cohort study found that Blacks, Asians and Native Hawaiians/South Pacific Islanders had a 3to 6-fold higher risk of hospitalization due to allopurinol-associated SCARs than White or Hispanic populations, even after adjusting for age, sex, presence of CKD and initial dose of allopurinol, these factors having been found to be independently associated with hospitalization risk¹⁷⁶ (Level of evidence 2-).

Finally, other studies have found that gradual titration of allopurinol is safe even reaching doses up to 1.5-times higher than suggested previously for patients with CKD^{109, 111, 177-179} (Level of evidence 2-).

Febuxostat

We have identified three RCTs that show that febuxostat at 40-80 mg daily, compared to placebo, achieves target serum urate levels (<6 mg/dL) in a significantly higher percentage of patients with both moderate-to-severe (estimated GFR 15-50 ml/min)¹¹⁴ and moderate (estimated GFR >30 but <60 ml/min, stage 3) CKD, although data on the latter were from short studies (3 months)^{115, 180}. Compared to placebo, febuxostat was associated with a higher percentage of patients experiencing \geq 1 gout flare¹¹⁵ (Level of evidence 1+).

Only two out of these three RCTs provide data on safety and they are based on only 3 months of follow-up. Between 5.8% and 7.2% of patients had some type of treatment-related AEs and they were mild or moderate in most cases in all treatment groups, although the general incidence of AEs was higher in the subgroup with severe kidney failure than in groups with other levels of renal function. None of the serious AEs was considered to be related to the drug or its dose^{115, 116} (Level of evidence 1+).

We also found a retrospective study based on 1332 patients, most of whom received febuxostat at 40 to 80 mg/d; and of the total, 1222 (91.7%) had CKD with an estimated mean GFR of 20.8
ml/min/1.73m². In this study, 3.2% of patients had febuxostat-associated myopathy and all of these patients had CKD. The myopathy was not found to be associated with febuxostat dose but was significantly associated with estimated GFR in febuxostat users. The authors concluded that patients with a severely reduced estimated GFR had a higher risk of developing myopathy with febuxostat treatment¹⁸⁰(Level of evidence 2-).

Febuxostat vs. allopurinol

We identified two SRs and a cohort study comparing these drugs. The SR by van Etcheld¹⁸² included two RCTs assessing serum urate levels and adverse effects in patients with gout and mild-to-moderate renal impairment. In the 28-week RCT conducted by Schumacher et al., mentioned above, out of the 40 patients with impaired renal function (serum creatinine: 1.5-2 mg/dL), the percentage who achieved serum urate <6 mg/ml was higher among those on febuxostat 80 mg than allopurinol 100 mg (44% vs. 0%). One of the limitations of this study was the high rate of loss to follow-up¹⁰⁶ (Level of evidence 1-). In the CONFIRMS trial, 2269 patients (1483 with CKD) were randomized 1:1:1 to receive a daily dose of febuxostat 40 mg or 80 mg or allopurinol 300 mg if renal function was normal (estimated CrCl >90 ml/min) or mildly impaired (estimated CrCl >60 to 90 mg/min) or 200 mg in the case of moderate renal impairment (estimated CrCl >30 and <60 ml/min). Febuxostat 80 mg was more effective in achieving serum urate <6.0 mg/dL than 40 mg doses (72% vs. 52% in mild renal impairment and 71% vs. 43% in moderate renal impairment; p<0.001). Further, febuxostat 40 mg was more effective than allopurinol 100-300 mg daily (52% vs. 46% in mild renal impairment and 43% vs. 31% in moderate renal impairment; p=0.021) ¹¹⁸ (Level of evidence 1+).

In the second SR identified, the authors performed a meta-analysis to assess the efficacy and safety of febuxostat for reducing urate levels in kidney transplant recipients and patients with stage 3 or 4 CKD. The control group was composed of patients treated with allopurinol, mostly for between 3 and 6 months, 52% of patients in this group being on allopurinol in the analysis at 1 month and just 12% at 12 months. The results of this meta-analysis indicated that febuxostat was associated with significantly lower serum urate levels than the control agents after 1, 3 and 6 months of treatment; however, there were no significant differences in serum urate levels between febuxostat and control treatments after 12 months of follow-up. Nonetheless, these results should be interpreted with caution due to the low quality of the studies included and variations in the design of the studies included, comparison groups and patient inclusion criteria¹⁸¹ (Level of evidence 1-).

Data for comparing febuxostat and allopurinol in terms of AEs come from the results of two RCTs (one already mentioned above) and an observational study. In the CONFIRMS trial, 56% of participants reported at least one AE, most of which were mild or moderate. Further, 19 (2.5%), 28 (3.7%) and 31 (4.1%) of patients had more than one serious AE in the febuxostat 40 mg, febuxostat 80 mg and allopurinol groups, respectively. The rate and type of AEs were similar in patients with mild-to-moderate renal impairment and those with normal renal function (Level of evidence 1-). Several secondary analyses have been performed of data from the CONFIRMS trial considering subgroups by age, CKD stage and ethnicity¹⁸³⁻¹⁸⁵, and results were similar to those in the general group; there were some additional findings, though, such as the efficacy in reducing serum urate levels not being greater with febuxostat 80 mg than febuxostat 40 mg in \geq 65-year-olds with mild renal impairment, and among all those with mild renal impairment, the percentage of patients who achieved serum urate <6 mg/ml being significantly higher in \geq 65-year-olds than younger patients¹⁸³ (Level of evidence 1+).

One retrospective study assessed the impact of starting treatment with allopurinol at doses 100-250 mg (n=2076) or febuxostat at 40-60 mg (n=2426) on major cardiovascular events in patients with gout and a history of cardiovascular disease or heart failure diagnosed with stage 3 or 4 CKD in routine clinical practice with a mean follow-up of 9 months. The baseline characteristics differed between treatment groups, in that patients started on allopurinol had significantly higher rates of heart failure (51.8% vs. 44.3%, respectively, p=0.009), chronic obstructive pulmonary disease (21.7% vs. 16.2%, respectively; p=0.016) and use of angiotensin-converting enzyme inhibitors (42.9% vs. 37.6%, respectively; P = 0.054). The authors concluded that patients with moderate-to-severe CKD and cardiovascular disease or heart failure who initiated febuxostat had a significantly lower rate of major cardiovascular events than patients who initiated allopurinol¹⁸⁶ (Level of evidence 2-).

In contrast, no such pattern was observed in the CARES study on the safety of febuxostat vs. allopurinol in patients with gout and cardiovascular disease, in 6190 patients randomized to allopurinol or febuxostat and stratified by renal function. A non-inferiority margin of 1.3 was established for the relative risk of the final primary event (a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or unstable angina with urgent revascularization) and the median follow-up was 32 months. Both in intention-to-treat analysis and analysis of events, while patients were receiving the treatment, febuxostat was not inferior in terms of rates of adverse cardiovascular events; however, all-cause mortality was higher in the febuxostat group (relative risk 1.22; 95 % CI: 1.01-1.47) as was cardiovascular mortality (relative risk 1.34; 95% CI: 1.03-1.73)¹²³ (level of evidence 1+).

Benzbromarone

We have not found any studies that compared benzbromarone as monotherapy with placebo; in all studies found, either the control group was treated with allopurinol or benzbromarone was used in association with allopurinol.

An open-label RCT included 17 patients who received benzbromarone (increased from a starting dose of 50 mg, in steps of 50 mg, to a maximum of 200 mg daily) and 19 who received allopurinol (increased from a starting dose of 100-150 mg daily, in steps of 50-150 mg, to a maximum of the estimated CrCl-based dose). Patients had gout and moderate CKD (mean GFR 54 ml/min; 20-80 ml/min), and benzbromarone up titrated was more effective in attaining the target serum urate levels than allopurinol at a dose adjusted for CrCl: 94% vs. 63% of patients achieved serum urate <6.0 mg/dL; p=0.042¹²⁴ (Level of evidence 1-).

In another RCT, 65 patients with gout and impaired renal function who were eligible for ULT were randomised to benzbromarone (100 mg daily) or allopurinol (100 mg daily, increased in steps of 100 mg to a maximum of 300 mg daily). After 2 months, the doses were increased to benzbromarone 200 mg daily or allopurinol 600 mg daily in patients with serum urate levels above 0.3 mmol/l. The percentage of patients who achieved serum urate <0.3 mmol/l at any time in the study was similar in the two groups (78%); however, in the second month, the percentage was higher in the benzbromarone group. The rate of AEs was higher in the benzbromarone group (20% vs. 7%)¹²⁵ (Level of evidence 1-).

In another study on patients with moderate renal impairment (mean CrCl 47 ml/min), allopurinol in combination with benzbromarone was effective in reducing serum urate levels in those with moderate CKD (levels dropping from 7.8 to 5.7 mg/dL), but not in those with severe CKD, with a CrCl <30 ml/min (levels only changing from 9.8 to 8.2 mg/dL)¹⁸⁷ (Level of evidence 3).

Finally, a case series has been reported of six patients with unspecified CKD and severe tophaceous gout refractory to dietary interventions and allopurinol. Patients received benzbromarone 50 mg daily for the first month and subsequently 100 mg daily for a year, added to their pre-existing regular treatment. The results indicate that all patients tolerated benzbromarone well, and there were no significant AEs or changes in liver or renal function. Serum urate levels decreased to a mean of 0.46 mmol/L (range 0.25-0.73) after 1 year. The frequency of acute gout flares decreased in all patients, the mean decreasing from 16 (8-20) to 7.3 (1-16); p=0.01. Some patients reported reductions in tophus size, and in one case, that their tophi had disappeared¹⁸⁸ (Level of evidence 3).

Lesinurad

We identified one RCT comparing lesinurad with placebo, three RCTs assessing the combination of lesinurad and allopurinol, and one RCT assessing the combination of lesinurad and febuxostat. Registry-based clinical trials excluded patients with GFR <30 ml/min, and hence, in this population, no data are available on efficacy and safety and therefore their use is not recommended.

An RCT was conducted in 214 patients randomized to lesinurad 400 mg daily or placebo with a follow-up of 6 months and an extension study. Lesinurad 400 mg daily as monotherapy was superior in terms of reducing serum urate levels, but given the high incidence of creatinine elevation and renal-related adverse effects, the authors recommended against its use¹²⁸.

Two RCTs assessed the combination of lesinurad 200 mg or 400 mg with allopurinol (300-900 mg, or at least 200 mg daily in moderate CKD) vs. placebo and allopurinol in patients with severe gout and high rates of comorbidities. One of them, the CLEAR 2 study¹⁸⁹ is the international validation of the other, the CLEAR 1 study¹⁹⁰. Both included patients with mild-to-moderate CKD (GFR >30 ml/min). The percentage of patients who achieved serum urate <6 mg/dL at 6 months was 30-35% higher in the lesinurad 200 mg group and 40-45% higher in the lesinurad 400 mg for all stages of CKD. Regarding safety, there were no differences in the rates of kidney stones, but differences were found in the rates of serum creatinine elevation, these being 1-3% in the placebo group, 5-6% in the lesinurad 200 mg group and 15-16% in the lesinurad 400 mg group. These increases were transient and reversible in the majority of cases, during the study, and had resolved by the time of the next check-up in almost all cases (Level of evidence 1+).

Another multicentre double-blind RCT was a phase 2 study in 97 patients, in whom no reduction in serum urate levels was observed in the group on allopurinol as monotherapy after 4 weeks of treatment, while in the groups on allopurinol plus lesinurad 200 mg, allopurinol plus lesinurad 400 mg and allopurinol plus lesinurad 600 mg, urate levels decreased by 15.03%, 24.6% and 32.32%, respectively. No data are provided on AEs in the subgroup of patients with CKD, although the authors concluded that treatment was well tolerated¹⁹¹ (Level of evidence 1-).

In a 12-month RCT in 324 patients with tophaceous gout (serum urate levels \geq 8 mg/dL and \geq 1 tophus), all the groups received febuxostat 80 mg/d. The percentage of patients who achieved serum urate < 5 mg/dL after 6 months was significantly higher in the groups receiving lesinurad 400 mg (76.1%) or lesinurad 200 mg (56.6%) than in the placebo group (46.8%); however, rates of complete resolution of tophi did not differ between groups. While results were not presented



for patients with CKD, 80% of patients had a GFR of 30-90 ml/min (stage 2 or 3 CKD) ¹⁹² (Level of evidence 1+).

A meta-analysis concluded that lesinurad 200 mg or 400 mg daily was more effective in reducing serum urate levels than XO inhibitor, but differences were not found in the outcomes related to gout (including mean rates of gout flares that required treatment from month 6 to 12 and the rate of complete resolution of at least one target tophus by 12 months). For this reason, the authors concluded there was a need for long-term studies on lesinurad. The rates of overall and renal-related AEs were lower in the group on XO inhibitors as monotherapy than in either of the groups on lesinurad, but the difference only reached significance comparing with the lesinurad 400 mg group. Creatinine elevation was more common among patients with low GFRs¹³⁰ (Level of evidence 1+).

Recently, Perez-Ruiz *et al.* reassessed the safety of lesinurad, indicating that creatinine elevation was only statistically significant with the highest dose of lesinurad (400 mg daily in phase 3 clinical trials) tested. On the other hand, though the rate of AEs increased with decreasing renal function, this did not translate to a higher relative risk compared to placebo, as the rate of adverse effects increased more in the placebo group than in the lesinurad 200 mg daily group¹⁹³.

Pegloticase

A post hoc analysis of the subgroup of patients with stage 3 or 4 CKD was performed using data from two phase 3 double-blind RCTs^{127, 194}. Patients were randomised 2:2:1 to intravenous infusions of pegloticase 8 mg every 2 weeks (n=42), pegloticase 8 mg every 4 weeks (n=41) or placebo (n=20) for 24 weeks. The primary objective of this study was to assess the impact after 6 months on renal function as assessed by GFR. Patients who achieved serum urate < 6 mg/dL for 80% of the time during the 3-6 month period were classified as responders. Overall, 32%, 23%, 35% and 39% of patients were responders in stage 1, 2, 3 and 4 CKD subgroups, respectively, the differences not being significant (p=0.3). No changes in GFR were observed in patients with CKD. The rate of AEs was higher in patients on pegloticase (23-24%) than those on placebo (12%). Infusion-related reactions (26-42% of patients treated with pegloticase) resolved a few minutes after slowing down or stopping the infusion. No safety data were provided for the group of patients with CKD, but there were no differences in the safety of pegloticase as a function of CKD stage (Level of evidence 1+).

Treatment of patients with chronic kidney disease on haemodialysis

The available scientific evidence for this is very scarce. There is only one relevant case series on allopurinol¹⁹⁵. One prospective open-label pilot study was found based on 12 patients with a diagnosis of gout who were on haemodialysis. Treatment was initiated with allopurinol 300 mg daily for 3 months, and serum urate levels fell significantly from baseline levels of 10.13 (9-12.9) mg/dL to 6.60 (3.8-11) mg/dL (p <0.01) (Level of significant 3). There are two other studies reporting cases of single patients in whom serum urate levels decreased in haemodialysis patients concomitantly treated with allopurinol^{181, 182}; however, we should take into account that haemodialysis considerably reduces both serum levels and tissue deposits of urates by itself, and hence, it is not possible to determine the value of allopurinol in these cases.

An open-label RCT in which 53 haemodialysis patients with serum urate levels \geq 7 mg/dL not receiving ULT were randomised (1:1) to febuxostat 10 mg or placebo for 4 weeks. Serum urate levels were 8.2 ± 0.8 mg/dL at baseline and 4.9 ±1.3 mg/dL after 4 weeks in the febuxostat group (p<0.0001) and 8.3±0.9 mg/dL and 7.9 ±1.4 mg/dL respectively in the control group (p= 0.12), the between-group difference not being significant at baseline but reaching significance after treatment (p=0.0046). Nonetheless, this was an open-label study of few patients with a short follow-up¹⁹⁶ (Level of evidence 1-).

There have been no studies specifically evaluating the safety of treatments in this group of patients. We have only found one case report that described the onset of neutropenia in a woman with gout on haemodialysis and treated with febuxostat for 2.5 months; she recovered gradually after stopping febuxostat¹⁹⁷ (level of evidence 3).

The GDG considers that there are no studies that are high quality or specifically designed for patients with gout and clinically significant CKD. The evidence available comes from the post hoc analysis of registry-based clinical trials and poor quality small prospective series or retrospective studies. Further, there is high variability in terms of the design and quality of studies, though this has improved in the case of the most recent studies, especially those assessing drugs such as febuxostat and lesinurad.

The GDG considers that it is appropriate to mention that in most studies the goal has been to bring serum urate levels down to certain target values rather than reduce/eliminate joint pain associated with inflammatory flares and tissue urate deposition. In relation to this, there is a need for longer follow-up to assess long-term results of reductions in serum urate levels on gout. Nevertheless, in general, the results are consistent and point in the same direction in terms of efficacy and safety of the intervention, although the quantity and quality of evidence are considerably greater for groups at earlier (stages 2, 3 and 4) than end-stage (stage 5) kidney disease.

In formulating the recommendations, the GDG has taken into account that the results identified are directly applicable to our healthcare system having been obtained in similar populations and the drugs assessed are available and commonly used in our setting, with the possible exceptions of lesinurad (which has been approved recently) and pegloticase (for which there is little experience of its use in this context and which is still little used). For these reasons, the proposal is to use allopurinol at doses higher than those used to date, based on renal function as proposed by Hande in 1984, seeking to achieve greater efficacy with an acceptable level of safety. Although not backed by the same quantity and quality of clinical trials, the body of literature and extensive experience in the use of drugs such as allopurinol and benzbromarone show them to be reasonable alternatives. Nonetheless, the SmPC for benzbromarone considers that, given its liver toxicity, it should only be used in patients intolerant or refractory to allopurinol who are kidney transplant recipients and/or have severe gout with GFR over 20 ml/min. Febuxostat has been confirmed to be effective and safe even in patients with advanced CKD, who had not been included in pivotal studies of this drug. The use of lesinurad has been validated in combination with allopurinol as ULT for patients with CKD. The GDG is unable to make a specific recommendation on the use of ULT in haemodialysis patients as evidence is lacking or not applicable (in that it concerns doses that are not authorized or not marketed).

Finally, the GDG accept the recommendation of the EMA to not perform systematic HLA genotyping to screen for carriers of HLA-B*5801 in European populations¹⁹⁸. In populations with a high frequency of HLA-B58 (such as the Han ethnic group populations), the evidence suggests that genotyping might be cost-effective¹⁹⁹.

9.2 Established cardiovascular disease

Gout is associated with traditional cardiovascular risk factors such as hypertension, hypercholesterolaemia, diabetes and obesity. Some studies have concluded that hyperuricaemia is an independent cardiovascular risk factor²⁰⁰⁻²⁰⁶. Further, several different meta-analyses and SRs have evaluated the relationship between hyperuricaemia and certain types of cardiovascular disease²⁰⁷⁻²¹⁰.

In addition, gout^{92, 211} like other inflammatory joint diseases may be associated with a greater susceptibility to develop atherosclerosis and higher mortality in patients with gout has been related to high levels of serum urate and MSU crystal deposition¹⁸. Therefore, some experts

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suggest that the control of the factors associated with cardiovascular risk may be particularly beneficial for patients with gout^{7, 86, 213}.

There are several tools to estimate cardiovascular risk, including the Framingham risk score and Systematic Coronary Risk Evaluation (SCORE). On the other hand, some authors suggest the use of carotid ultrasound findings to estimate this risk more reliably²¹⁴.

The presence of cardiovascular risk factors may influence the prescribing of pharmacological treatments for inflammation or high serum urate, due to warnings and precautions or contraindications for the drugs used. For example, according to AEMPS, NSAIDs should be used at the lowest effective doses and for as little time as possible, taking into account, the cardiovascular and gastrointestinal risks in each patient²¹⁵.

Atorvastatin and losartan, indicated for the treatment of hypercholesterolaemia and hypertension, respectively, may also have a small urate-lowering effect when prescribed as a concomitant treatment for an approved indication²¹⁶.

9.2.1 Impact of gout treatment on cardiovascular disease

Clinical question 5

Are patients with gout treated with urate-lowering drugs at a higher risk of cardiovascular morbidity and mortality?

Recommendations

In patients with gout and a previous cardiovascular event, the recommendation is to use allopurinol as a first-line treatment (Grade A recommendation).

In patients with gout and a history of a cardiovascular event with a poor response or intolerance to allopurinol, it is advisable to add lesinurad (if they have had no vascular event in the last year) or change to benzbromarone as monotherapy. Another option is pegloticase, specially requested as it is a foreign medication (Grade V recommendation).

In patients with high cardiovascular risk but no history of a cardiovascular event, the benefitrisk balance should be assessed carefully if treatment with febuxostat is considered (Grade V recommendation).

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Gout is commonly associated with traditional cardiovascular risk factors such as hypertension, dyslipidaemia, obesity and diabetes, the prevalence of metabolic syndrome also being high in these patients.

Patients with gout are at higher risk of AEs and cardiovascular mortality than the general population and patients with other inflammatory joint diseases such as rheumatoid arthritis and ankylosing spondylitis. Among other factors, a higher total crystal load or amount of urate deposition has been associated with higher cardiovascular mortality in patients with gout.

On the other hand, the impact of ULT on the frequency of cardiovascular events and all-cause and cardiovascular mortality in patients with gout has been the subject of debate for several decades in relation to various issues: an effect mediated by a reduction of urate levels themselves, an effect mediated by a reduction in the inflammation associated with urate crystal deposition, a combined or associated effect related to changes in other factors, and the benefitrisk balance of ULT.

Quality of the evidence

We have included studies with both experimental and observational designs. The aim for addressing this question was to assess the safety of allopurinol, febuxostat, lesinurad, benzbromarone and pegloticase in patients exclusively diagnosed with gout. Given the paucity of evidence, however, we also have included information on the most relevant results reported for such patients in studies that included patients not diagnosed with gout.

Below, we summarize the evidence found for drugs that limit the formation of uric acid, XO inhibitors, specifically, allopurinol and febuxostat, the only XO inhibitors approved in Spain.

Regarding **allopurinol**, given the lack of evidence available for addressing the clinical question, the GDG considers worth mentioning some studies identified, that, although they do not meet all the inclusion criteria and hence have been excluded from the body of evidence, provide additional information that might help in the drafting of these recommendations. In an RCT assessing the efficacy and safety of escalating doses of allopurinol in 183 patients with gout, there were 5 deaths reported in the control group (1 due to a cardiovascular event) and another 5 in the escalation group (all due to a cardiovascular event), none being attributed to the drug¹⁰⁹. With 9% of controls experiencing serious heart-related events vs. 12% in the dose-escalation group, only one case was attributed to allopurinol. An open-label extension study of this RCT to 24 months¹⁷⁷ found a similar rate of serious heart-related events in the two groups (7.8 % vs. 7.5 %; none of them related to allopurinol), with 4 deaths in the control group (3 due to chronic

heart failure) and 3 in the dose-escalation group (1 due to acute coronary syndrome), and these were also not attributed to the drug.

For febuxostat, we have identified several RCTs and a couple of meta-analyses that address the clinical question. The Febuxostat versus Allopurinol Controlled Trial (FACT)¹¹⁷, a phase-III multicentre double-blind RCT, compared the efficacy and safety of febuxostat and allopurinol in 762 patients with gout and serum urate ≥8 mg/dL. Participants were randomized to receive febuxostat 80 mg (n=256), febuxostat 120 mg (n=251) or allopurinol 300 mg (n=253) for 52 weeks. Four of the 507 patients in the febuxostat groups died (0.8%) but none of the 253 patients in the allopurinol group. Neither of the two cardiovascular-related deaths (chronic heart failure in a patient on febuxostat 80 mg and cardiorespiratory arrest in a patient on febuxostat 120 mg) was attributed to the drug. Although no numerical or statistical differences were found (p=0.31), the results motivated a subsequent study (the CONFIRMS trial, see below) to compare the two doses of febuxostat (40 mg and 80 mg) (Level of evidence 1+). The Allopurinol- and Placebo-Controlled Efficacy Study of Febuxostat (APEX study)¹⁰⁶ compared the efficacy and safety of febuxostat in 1072 patients with serum urate >8 mg/dL and gout, with normal or impaired renal function (serum creatinine >1.5 to ≤2.0 mg/dL). It was a multicentre RCT that assessed different doses of the study drug (febuxostat 80, 120 or 240 mg), compared to an active drug (allopurinol, mainly at a dose of 300 mg) or placebo, over 28 weeks. Cardiovascular AEs were reported in 11 patients on febuxostat, 1 on allopurinol and 1 on placebo, while serious AEs that led to treatment discontinuation occurred in 3 patients in the febuxostat group, and none in the allopurinol or placebo groups, the differences not reaching significance. No deaths were reported. Febuxostat was safe and more effective than allopurinol or placebo in patients with gout, including those with mildly or moderately impaired renal function (Level of evidence 1++). The EXCEL extension study¹¹⁹ that included patients who completed the FACT and APEX trials, as well as 735 additional patients included to satisfy the requirements of the FDA, did not detect significant differences between treatment groups in total rates of AEs (including cardiovascular events) (Level of evidence 1-). The FOCUS extension study²¹⁷ assessed 5-year efficacy and safety in 116 patients who had completed the 2005 phase 2 conducted by the same authors. All the patients initially received febuxostat 80 mg and then the daily dose was fixed at 24 weeks (at febuxostat 40 mg in 8 patients, 80 mg in 79 and 120 mg 29). No cases of acute myocardial infarction were reported, but there were 5 cases of atrial fibrillation (with the 80 mg dose) and 1 case of atrioventricular block, none attributed to febuxostat (Level of evidence 1+). The CONFIRMS trial¹¹⁸ compared the efficacy and safety of febuxostat and allopurinol over 6 months in patients with gout and serum urate levels ≥8 mg/dL,

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randomized to febuxostat 40 mg (n=757), febuxostat 80 mg (n=756) or allopurinol (n=755; 610 with 300mg and 145 with adjusted doses of 200 mg due to renal impairment). The rate of cardiovascular AEs did not differ significantly between the treatment groups, 0% for febuxostat 40 mg and 0.4% for both febuxostat 80 mg and allopurinol. One patient died in each of the febuxostat groups and three died in the allopurinol group. In patients with mild-to-moderate renal impairment, both doses of febuxostat were more effective than allopurinol, with a similar safety profile. Unlike the two previous phase 3 trials that had evidenced a poorer profile for febuxostat, CONFIRMS - which included twice as many patients and avoided the 120-mg dose found similar rates of AEs and cardiovascular death. Therefore, the excess risk is attributed to the high dose of febuxostat (indirect evidence), which is not recommended by the FDA (Level of evidence 1++). In a post hoc analysis¹⁸⁴ with patients \geq 65 years old who participated in the CONFRIMS study, the rates of cardiovascular events were low and comparable (0.9% febuxostat 40 mg, 1.6% febuxostat 80 mg and 3.1% allopurinol 200/300 mg). There were only two deaths, both in the allopurinol group. In 2018, results were published from the CARES study¹²³, a multicentre double-blind non-inferiority RCT that included patients with gout and cardiovascular disease. A total of 6190 patients were randomized to febuxostat or allopurinol, stratified based on renal function (though not by cardiovascular risk, one of the limitations of the study), and followed up for a median of 32 months (maximum: 85 months; lost to follow-up: 45%, not significantly different between groups). The primary endpoint was major adverse cardiovascular event (MACE), a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization. In the intention-to-treat analysis, a primary endpoint event was recorded in 335 patients (10.8%) in the febuxostat group and 321 patients (10.4%) in the allopurinol group (hazard ratio [HR] 1.03 for febuxostat; 98.5% CI: 0.87-1.23; p= 0.002 for non-inferiority). Cardiovascular mortality was higher in the febuxostat group (4.3%) than in the allopurinol group (3.2%) (HR 1.34; 95% CI 1.03-1.73; p=0.03). In the post hoc analysis, a primary endpoint event was observed during the treatment in 191 patients (6.2%) in the febuxostat group and 199 (6.4%) in the allopurinol group (HR 0.94 for febuxostat; 97% CI: 0.76-1.17; p= 0.558). In this analysis, cardiovascular mortality was 0.7% for febuxostat and 0.5% for allopurinol (HR 1.62 for febuxostat; 95 % CI: 0.84-3.15; p= 0.152). This study concluded that in patients with gout and major coexisting cardiovascular diseases, febuxostat was not inferior to allopurinol in terms of rates of adverse cardiovascular events, though mortality was higher with febuxostat than with allopurinol (Level of evidence 1+).

The GDG also identified studies that do not meet the inclusion criteria but provide data on cardiovascular outcomes that it considers should be highlighted. A double-blind RCT¹¹³ assessing patients with early gout on febuxostat 40 mg (80 mg from day 14 if serum urate ≥6 mg/dL) or placebo reported few serious cardiovascular AEs: two in the placebo group (one death due to ventricular fibrillation in a patient with a history of arrhythmia and ischaemic heart disease; and one case of unstable angina with revascularisation) and three in the febuxostat group (one death due to heart failure not attributed to the medication in a patient with a history of chronic heart failure, ischaemic heart disease and hypertension; one case of non-fatal acute myocardial infarction; and one case of unstable angina with revascularization). A meta-analysis²¹⁸ of pooled data of RCTs of patients with chronic gout shows comparable short-term safety profiles for febuxostat and allopurinol, without significant differences in cardiovascular mortality (RR 1.69, 95 % CI 0.54-.34; p = 0.37), although the validity of these results may be limited by the heterogeneity of the populations included, variability in follow-up, and ULT type and dose. An SR²¹⁹ studied the cardiovascular effects of XO inhibitors (including topiroxostat). The study population in one of the RCTs included was composed of patients with hypertension but without gout (0.2% weight), and in another, individuals with high serum urate levels without evidence of gout (1% weight); while the rest of the studies focused on individuals with gout. The SR concludes that non-purine selective XO inhibitors do not significantly reduce or increase the risk of cardiovascular AEs. A meta-analysis²²⁰ assessing the relationship between febuxostat and MACE compared to a control treatment (allopurinol and/or placebo) did not report significant differences in the association with MACE for any dose of febuxostat (671 events; RR=1.06; 95% CI: 0.92-1.23; p=0.42), but it did observe an increase in cardiovascular mortality with respect to the control treatment (RR= 1.29; 95 % CI: 1.01-1.66; p=0.03). Despite adjusting for NSAID use, the authors do not rule out the results being explained by the use of these drugs as gout prophylaxis/treatment, given limitations in the data on this variable. We should interpret these results in the context of the number of events being low (0.05%; 0.037% of deaths in the CARES study). Another meta-analysis²²¹, with a sub-analysis by ethnic group, treatment duration and dose did not report higher overall (OR: 0.78, 95 % CI: 0.31-2.0; p=0.60) or cardiac-related mortality compared to allopurinol (OR 0.72; IC95 %: 0.24-2.13; p=0.55). Including data from the CARES study, the researchers found a borderline significantly higher cardiac-related mortality with febuxostat than allopurinol (OR: 1.29; 95% CI: 1.00-1.67; p=0.05). Analysing the CARES sample and the subgroup of studies in which patients had had ≥52 weeks of treatment together, the researchers found a higher risk of overall (OR: 1.36; 95 % CI: 1.05-1.76; p=0.02) and cardiacrelated (OR: 1.35; 95 % CI: 1.04-1.75; p=0.03) mortality. A limitation of the study was that it



considered subgroups by dose to be independent studies, meaning it was not possible to calculate the overall cumulative effect: the highest doses of febuxostat seem to be associated with a higher risk of cardiac-related mortality than allopurinol, while there may be a trend towards lower mortality with the lowest doses.

Regarding **uricosuric** agents, several studies provide data on cardiovascular safety for the agents used in Spain: benzbromarone and lesinurad.

Only medium-quality studies have been identified in the case of **benzbromarone**. A populationbased study²²¹ of 1 million individuals did not find statistically significant differences in the risk of coronary artery disease among patients with gout treated with allopurinol and/or benzbromarone and patients not treated with either of these drugs. Nonetheless, after adjusting for dose-response relationships, treatment with more than 270 DDDs of allopurinol and more than 360 DDD of benzbromarone was associated with a significantly lower risk of coronary artery disease. The authors conclude that the use of allopurinol and benzbromarone, as monotherapy or in combination, shows a dose-response relationship between the number of DDDs and risk of coronary artery disease, in particular at high doses (Level of evidence 3). The SR by Zhang *et al.*²¹⁸, on the cardiovascular safety in treatment for chronic gout with various types of ULT, includes benzbromarone in the meta-analysis, but the authors were unable to establish comparisons between the different therapeutic mechanisms of action given the small number of patients treated with uricosuric and uricolytic agents (Level of evidence 1-).

Beyond the body of evidence that met the selection criteria, we identified an 18-month real-life study assessing the safety and efficacy of this drug (median dose 100 mg daily; 25-200 mg daily) in patients with gout with a poor response (or intolerance) to allopurinol or probenecid²²². A total of 14 deaths were recorded, none of them related to benzbromarone; only 6 patients were taking this medication when they died, 3 of whom died from heart disease and 2 from stroke. The authors of this study admitted a potential underestimation of deaths (due to the study design or lack of questionnaire completion) and an overestimation of the use of benzbromarone (patient doses).

Regarding **lesinurad**, in the LIGHT trial¹²⁸, a 6-month RCT with 214 patients with gout and intolerance to XO inhibitors randomized to lesinurad 400 mg or placebo, one patient experienced a MACE in each group. The open-label extension study was stopped early, 18 months after the end of the core study, due to a marked reduction of the number of

participants, reporting 2 MACEs, 1 death and one non-fatal acute myocardial infarction (Level of evidence 1+; extension study: 1-). A phase 2 multicentre double-blind, placebo-controlled study by Perez-Ruiz et al.¹⁹¹, on 227 patients with gout with a poor response to allopurinol who were randomized to 4 weeks of treatment with lesinurad (200, 400 or 600 mg) or placebo in combination with allopurinol (200-600 mg), did not find any significant changes in vital signs or electrocardiogram findings; and nor were any deaths or serious AEs reported (Level of evidence 1+). Terkeltaub et al.²²³ analysed the data from three RCTs (CLEAR 1 and 2 and CRYSTAL) and two extension studies (those of CLEAR 2 and CRYSTAL) to assess the long-term safety (24 months) of lesinurad in combination with an XO inhibitor. Regarding MACEs in the 3 core studies, there were 4 events in 3/516 patients (0.6%) in the group on an XO inhibitor as monotherapy, 4 events in 4/511 patients (0.8%) in the group on lesinurad 200 mg plus an XO inhibitor, and 9 events in 8/510 patients (1.6%) in the group on lesinurad 400 mg plus an XO inhibitor. In the pooled analysis of MACEs in the core and extension studies, there were 17 events in 16/666 patients (2.4%) in the group treated with lesinurad 200 mg plus an XO inhibitor and 17 events in 15/666 patients (2.3%) in the groups treated with lesinurad 400 mg plus an XO inhibitor. The higher rate of MACEs in patients on lesinurad 400 mg was attributable to nonfatal acute myocardial infarction both in the core studies (7 patients with lesinurad 400 mg plus an XO inhibitor, 2 with lesinurad 200 mg plus an XO inhibitor and 1 with an XO inhibitor as monotherapy) and core plus extension studies (9 patients treated with lesinurad 400 mg plus an XO inhibitor and 5 with lesinurad 200 mg plus an XO inhibitor). To adjust for treatment duration, MACEs were expressed as exposure-adjusted incidence rates (patients with events per 100 person-years): 0.71 (0.15-2.08) with an XO inhibitor as monotherapy in the core study; 0.96 (0.26-2.47) for lesinurad 200 mg plus an XO inhibitor in the core study (1.24; 0.71-2.01 in the core plus extension studies), and 1.94 (0.84-3.82) for lesinurad 400 mg plus an XO inhibitor in the core study (1.17; 0.65-1.93 in the core plus extension studies). Angina was the most common serious cardiac-related treatment-emergent AE: 0.5 events per 100 person-years with an XO inhibitor as monotherapy in the core study; 1 event per 100 person-years with lesinurad 200 mg plus an XO inhibitor in the core study (0.5 in the core plus extension studies); and 1.5 events per 100 person-years with lesinurad 400 mg plus an XO inhibitor in the core study (0.6 in the core plus extension studies). To summarise, combination therapy with lesinurad 200 mg and an XO inhibitor did not increase the rate of cardiovascular AEs compared to an XO inhibitor as monotherapy and the safety profile in the extension studies was consistent with that in the core RCTs, with no new problems being reported (Level of evidence 1-). A meta-analysis by Wu et al.¹³⁰, with data from the blinded period of the phase 2 and 3 trials, identified 23 serious

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cardiovascular AEs in 511 patients on lesinurad 200 mg plus an XO inhibitor vs. 20 events in 516 patients on an XO inhibitor as monotherapy (RR=1.17; 95% CI: 0.58-2.35), and 18 events in 510 patients on lesinurad 400 mg plus an XO inhibitor vs. 20 events in 516 patients on an XO inhibitor as monotherapy (RR= 0.91; 95% CI 0.48-1.7). The differences between groups were not statistically significant ($X^2 = 0.27$; df= 1; p= 0.61; I²= 0 %) (Level of evidence 1-).

Finally, we summarize the evidence available on the cardiovascular safety of *uricolytic agents*. Sundy *et al.*¹²⁷ reported two RCTs on **pegloticase** in patients with chronic gout who were intolerant or refractory to allopurinol. These RCTs reported four deaths in the pegloticase group and three in the placebo group: in the pegloticase group, three deaths in the treatment period and one after the treatment (versus two in the placebo group), and two of the deaths in the treatment period were attributable to cardiovascular AEs (in patients on pegloticase fortnightly). Other cardiovascular AEs were reported in 2% (n=3) of patients on pegloticase fortnightly and 6% (n=7) of those on this drug monthly vs. none in the placebo group (Level of evidence 1+). The meta-analysis by Zhang *et al.*²¹⁸ on the cardiovascular effects of ULT (XO inhibitors and uricosuric or uricolytic agents) in patients with chronic gout includes data on pegloticase (and rasburicase which has not been approved for gout but rather for the treatment and prophylaxis of acute hyperuricaemia) extracted from the study of Sundy et al. but fails to make comparisons between the different therapeutic mechanisms given the small number of patients treated with uricosuric and particularly uricolytic agents (Level of evidence 1-).

The GDG considers that, although there is no high-quality evidence on the cardiovascular safety of allopurinol, with the data currently available, this drug remains the first-line option for ULT in gout, this recommendation being supported mainly by extensive experience with this drug, as well as its low cost.

Regarding febuxostat, although the results of the CARES study¹²³ are not directly applicable or generalizable to non-American populations, the AEMPS published a communication in June 2019 that warned about the significantly higher risk of mortality found in that study in patients with gout and a history of cardiovascular disease treated with febuxostat vs. allopurinol; and discouraged the use of febuxostat in patients with a history of serious cardiovascular disease, except in cases in which other treatment options could not be used. When interpreting these warnings, we should highlight that the CARES study has been criticised from a methodological point of view by several international experts in the management of febuxostat in patients with gout and hyperuricaemia²²⁴⁻²²⁸. This study reported a high rate of early withdrawal from the treatment (56.7%); the majority being in the first 24 months after randomisation, which may

limit its validity and have clinical implications since the mortality curves did not differ until after the second year. A post hoc analysis of data from participants who withdrew shows that the differential effect of febuxostat on cardiovascular mortality stops being significant. The majority of deaths occurred in patients in whom febuxostat or allopurinol had been withdrawn and the study does not include information on any ULT given after the treatment allocated randomly had been withdrawn: the intention-to-treat analysis may attribute the damaging cardiovascular effects of any new ULT to the treatment withdrawn previously. On the other hand, the rate of the primary endpoint (MACE, a composite endpoint) did not differ between the febuxostat and allopurinol groups and the study does not identify any mechanism by which febuxostat would increase the risk of cardiovascular death. Moreover, in the case of the secondary endpoints, there was insufficient statistical power to detect a difference. Further, there was a lack of balance in the use of antiplatelet agents and NSAIDs as gout prophylaxis (there being more patients in the febuxostat group on NSAIDs, these increasing cardiovascular risk). Finally, we should mention the lack of a placebo group (meaning that the difference is known, but not the net effect). For all these reasons, the majority of experts recommend interpreting the results of the CARES study with caution and comparing them with safety data from the CONFIRMS trial and several post-marketing studies on gout, as well as waiting for the safety results on the cardiovascular safety of the Febuxostat versus Allopurinol Streamlined Trial (FAST)²²⁹ requested by the EMA, after the approval of febuxostat in Europe.

On the other hand, we should also take into account what is stated in the SmPC of ULTs marketed in Spain with regards to cardiovascular disease. The SmPC for allopurinol²³⁰ does not contraindicate the use of this drug in patients with cardiovascular disease nor does it make specific warnings for patients with cardiovascular disease (with angina and hypertension being in the list of very rare adverse reactions, <1/1,000 cases). The SmPC for febuxostat²³¹ does not indicate that this drug is contraindicated in patients with cardiovascular disease, but does not recommend its use in patients with coronary heart disease or chronic heart failure. According to its SmPC²³², benzbromarone is not contraindicated in patients with cardiovascular disease, and nor there are specific warnings or precautions for its use in patients with cardiovascular disease. The SmPC for lesinurad²²⁹ does not state that this drug is contraindicated in patients with cardiovascular disease regularly in patients with stable cardiovascular disease, and its use is not recommended in patients with unstable angina, New York Heart Association class III or IV chronic heart failure, or uncontrolled hypertension or who have had an episode of acute myocardial infarction, stroke or deep vein thrombosis in the previous year.

9.3 Solid organ transplantation

Clinical question 6

How effective and safe is gout treatment in solid organ transplant recipients?

Recommendations

Given that there is insufficiently robust evidence, due to a lack of specifically designed studies, the GDG is unable to provide specific recommendations about the most effective and safest treatment for gout in solid organ transplant recipients (Grade V recommendation).

The GDG considers it reasonable for patients who are solid organ transplant recipients to be treated by specialist nephrology, hepatology, and rheumatology units with considerable specific experience in the treatment of gout in such patients (Grade v recommendation).

Solid organ transplant recipients have not been included in the trials for registering new drugs (febuxostat, lesinurad). For this reason, the SmPCs of these drugs recommend not to use them in solid organ transplant patients with gout.

On the other hand, although there are no trials to confirm this, the long-term use of drugs (such as allopurinol and benzbromarone, the latter being approved for use in renal transplant recipients according to its SmPC) allows us to suppose that they are sufficiently effective and safe. Given all this, it is important to know the scientific basis endorsing the use of uratelowering agents in patients with gout with regards to their efficacy or effectiveness and safety.

Quality of the evidence

We only found three papers that meet enough criteria to warrant their review, two and one on kidney and liver transplant recipients, respectively. Most studies focus on the treatment of hyperuricaemia in patients not diagnosed with gout or describe the results by group (gout or hyperuricaemia) when the population included both groups.

The study by Jacobs *et al.*²³³ describes a case series, of only five patients, in which they described a lack of apparent clinical interaction, in an unspecified follow-up, between allopurinol and mycophenolate mofetil in renal transplant recipients, which would allow us to replace azathioprine with allopurinol if necessary. As limitations of this study, as well as its small sample size and its retrospective nature, we should highlight the lack of data on safety, the mean serum



urate levels attained after the treatment being higher than the therapeutic targets and the low doses used (100-200 mg daily) (Level of evidence 3).

The study by Navascues *et al.*²³⁴ is also a case series and presents the results of treatment with low doses of allopurinol (100 mg daily) in 22 renal transplant recipients, analysing the efficacy at 30 and 60 days. The efficacy could be considered as poor, in that the mean urate level after the treatment was 8.3 mg/dL. The rate of attainment of the serum urate target was not analysed. No cases of short-term blood toxicity were detected (Level of evidence 3).

Neal *et al.*²³⁵ reported the results of treatment in 8 patients with gout among 134 consecutive liver transplant recipients, of whom nearly half (47%) had hyperuricaemia after transplantation this being associated with renal impairment and the use of ciclosporin A. Though serum urate levels normalised in all cases, together with improvements in renal function, no data are provided on serial serum urate measurements or safety (Level of evidence 3).

The GDG considers that the body of evidence identified is out of phase with current clinical practice regarding the use of drugs. That is, these results are not applicable to our healthcare setting at present, in that the treatment of transplant recipients with asymptomatic hyperuricaemia is not approved.

For this reason, the extrapolation of data (supplementary reference material) obtained from case series involving the treatment of patients with hyperuricaemia but without gout should be interpreted with caution.

The results of the studies identified are not directly applicable to our healthcare setting given that some of the therapeutic agents assessed are not commonly used in our setting, the doses are low and the body of evidence is insufficiently robust.

The GDG deems it reasonable to incline towards the prescribing of widely used drugs in these populations (allopurinol in patients not on azathioprine, or benzbromarone, if patients remain on azathioprine).

10. Role of the primary care team

Osteoarticular problems are among the most common reasons for consultation in primary care, representing up to 40% of all consultations.

The involvement of primary care is key in the pathway of patients with gout, from when the diagnosis is suspected, through treatment of the acute phase, prevention of new flares and implementation of ULT, to patient follow-up and monitoring, assessment of treatment adherence and analysis and treatment of comorbidities²³⁶.

10.1 Diagnosis in primary care

The majority of patients with gout are first assessed, diagnosed and treated in primary care or an emergency department. Given this, primary care doctors are the clinicians that are most likely to see patients with symptoms suggestive of a gout flare but who have not previously received a diagnosis²³⁷⁻²³⁹.

Key points in the diagnosis of gout in primary care

In primary care, due to the technical difficulties of demonstrating the presence of MSU crystal deposits using ultrasound scans or the gold standard method, namely, the analysis of the synovial fluid by polarized light microscopy, it is reasonable to reach a suspected diagnosis based on symptoms and signs typical of a gout flare in patients with a history of hyperuricaemia. There various diagnostic and classification criteria, these being explained in another section of this guideline, and some are specific for primary care-based diagnosis^{48, 56}. The 2018 update of the EULAR guidelines for the diagnosis of gout indicates that the following characteristics favour the diagnosis of gout: acute monoarticular arthritis involving the foot (especially the first metatarsophalangeal joint) or the ankle; previous similar acute episodes of arthritis; rapid clinical onset (with the condition reaching the most severe within the first 24 hours); presence of erythema; male sex; cardiovascular disease and hyperuricaemia⁵⁶. Along similar lines to the EULAR classification criteria, Janssens's diagnostic rule help to diagnose gout, and above all to rule it out⁸. In cases in which it is not possible to perform synovial fluid analysis, imaging techniques may also be used to demonstrate the presence of MSU crystal deposits²⁴⁰.

- In the USA, as many as a third of patients are referred to a rheumatologist²³⁹. The factors that warrant referral to specialized care are discussed in another section.

10.2 Treatment of patients with gout in primary care

Both gout and the multiple associated comorbidities are mainly managed in primary care, by nurses as well as by doctors. For this reason, both the targets and the treatment (pharmacological and non-pharmacological) must be clear to health professionals and above all to patients and their circle of care.

Treatment for lowering urate levels

Pharmacological treatment

ULT is the most important treatment, as it allows us to eliminate the pathogenic agent, namely, the MSU crystals. Allopurinol is the most widely used drug and generally the first-line treatment, febuxostat being the best option in the event of intolerance to or lack of effectiveness of allopurinol. Allopurinol hypersensitivity syndrome is the most serious AE caused by this drug. This AE has been associated with patients' renal function and starting dose of the drug. Table 9 indicates the starting dose as a function of GFR¹⁰³. Subsequently, the dose is increased until the therapeutic target set is attained. Since the progressive increase in the dose reduces serum urate levels in a more sustained manner, it reduces the likelihood of triggering new flares, this in turn, increasing treatment adherence. This strategy of starting with a low dose and progressively increasing it until the therapeutic target is attained can be used with all urate-lowering drugs. Monitoring blood tests may be carried out every 4 weeks until serum urate targets are attained²³⁹.

Non-pharmacological measures

For the general health of patients, it is very important to use non-pharmacological measures in gout²³⁶. Gout is associated with several metabolic and cardiovascular diseases that make it necessary to promote dietary and lifestyle changes, with the idea of reducing not only serum urate levels but also cardiovascular risk^{236, 241}.

We use the term "non-pharmacological measures" to refer to all activities that seek to treat patients with gout comprehensively, and these are established on a case-by-case basis with the involvement of the patient. Realistic goals are set together, and the course of the disease is monitored, changes being made as required until the previously-agreed goals are met²⁴². Given



its accessibility and closeness to patients, primary care is the appropriate setting for making recommendations on effective lifestyle change^{10, 243, 244}.

Educational and behavioural interventions can help to improve short- and medium-term outcomes in patients with gout²⁴⁵. Some authors have found that patients with gout lack awareness about the management of their condition, even in those with active gout. In general, many patients associate gout with negative stereotypes and tend to trivialize the impact of the disease despite it being serious²⁴⁶. In this context, comprehensive healthcare education can help patients with gout to understand the nature of their condition and how to control it²⁴².

Although lifestyle change may not have a significant impact in terms of controlling serum urate levels, it is necessary for reducing cardiovascular risk and patients should be given simple concise recommendations^{47, 56, 87, 241, 242, 244, 247} (see Table 10).

We should also highlight the potential role of primary care nurses in the education of patients, concerning both gout and the associated comorbidities. Nurse-led education may even have greater acceptance than physician-led education²⁴⁸. This issue is discussed in more detail in the section on the role of nurses in gout.

Treatment and prevention of gout flares

The main drugs used for the treatment of flares in primary care are NSAIDs, glucocorticoids and low-dose colchicine. In the section on treatment, we outline the characteristics of these treatments and recommendations for their use; however, there are some specific issues concerning treatment that should be taken into account by primary care doctors and hence are mentioned here:

a) Provision of information to identify gout flares and early treatment (in-the-pocket medication)

It has been shown that early initiation of anti-inflammatory treatment for gout flares can reduce their duration and severity²⁴⁰. Subsequently, it is beneficial to provide patients with information about what flares are like and train them in how to manage their treatment so that modifications can be implemented as promptly as possible, on patients' own accord, without them having to visit their general practitioner or an emergency department. For this reason, we recommend that patients carry their treatment for gout flares with them everywhere, especially when travelling, to enable prompt treatment of flares.

b) Identification of risks (concomitant treatments/interactions)

As patients with gout often have multiple associated comorbidities, it is essential to educate them not only about potential triggers of gout flares, to avoid them, but also the potential interactions of specific flare treatments with other drugs. Further, it is important to train them in the early identification of the most common and serious adverse effects of medication, such as the development of a skin rash, in order that the medication is stopped as soon as possible. Additionally, providing information about the need for regular blood tests, not only for the titration of uric acid but also to rule out any AEs, to avoid them worsening or progressing. For safety, another step that should be taken is to explain to patients with gout how medications should be adjusted or modified taking into account their comorbidities, such as avoiding diuretics in patients with hypertension and using calcium antagonists instead.

c) Colchicine, which is useful for both treatment and prophylaxis of acute gout flares, has a very narrow therapeutic index. According to its SmPC, it should not be administered at a dose higher than 2 mg/day or 6 mg in 4 days. We should be particularly cautious in patients with reduced GFR and check for the onset of symptoms of myopathy in patients on statins¹³⁹. The dose for flare prevention is 0.5-1 mg/day. The usual practice is to administer low doses of colchicine (0.5 mg/day) together with an NSAID or a corticoid in the acute phase²³⁹ and maintain that dose as prophylaxis, once the NSAID or corticoid has been withdrawn.

10.3 Assessment in specialised care

There are no data available that specify the indications for referring patients with gout to a rheumatology unit²³⁹. Below, we list the situations in which sometimes, and according to experts, we may consider referring patients to a specialist²⁴³:

- Atypical clinical presentation or difficult differential diagnosis
- Confirmation of the diagnosis by analysis of crystals in synovial fluid
- Severe gout
- Gout in complex chronic patients
 - Patients with advanced kidney disease, GFR <30 ml/min
 - Solid organ transplant recipients
 - Patients with multiple comorbidities making management of their gout difficult
- Poor course/lack of adequate response to treatments prescribed in primary care
- Need for types of treatment/ancillary tests not available in primary care.

Starting dosage of allopurinol as a function of GFR GFR (ml/min/ $1.73m^2$) **Allopurinol dosage** <5 50 mg/week 50 mg/twice a week 5-15 16-30 50 mg/48 hours 31-45 50 mg/24 hours 46-60 50-100 mg/every other day 61-90 100 mg/day 91-130 150 mg/ day

Table 9. Starting dosage of allopurinol as a function of glomerular filtration rate (GFR)²⁷

Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, *et al.* Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum. 2012 Aug; 64(8):2529-36.

Table 10. Lifestyle changes that could be proposed to patients with gout concerning the condition itself and their general health

Lose weight if overweight or obese

Reduce intake of alcohol (depending on the type of beverage and amount), above all avoiding beer and spirits.

Avoid soft drinks and sugar-sweetened beverages

Reduce intake of red meat

Increase intake of low-fat dairy products

Increase intake of plant-based protein (vegetables, pulses and nuts)

Ensure a moderate intake of fish, as this reduces cardiovascular risk

Do enough physical exercise

Do not smoke

Avoid excessive salt intake

Ensure ample fluid intake

Avoid sudden dietary changes

Boost intake of dietary fibre

Drink coffee and tea without restrictions

11. The role of nurses

Nursing staff have a key role to play in the management of gout. Their experience in the management of patients with gout, together with their knowledge and skills regarding education, health promotion and treatment adherence, make them central to achieving adequate treatment adherence and compliance with recommendations²⁴⁹.

The impact of specially-trained nurses on the management of patients with gout has been mainly demonstrated in the studies published by a group at Nottingham University in the United Kingdom.

The main barriers to achieving proper management of gout encountered by patients and health professionals are a lack of awareness concerning: the causes and consequences of the condition; its effective treatment through lifestyle change and ULT; and potential AEs of these treatments. Other barriers that hinder treatment adherence include patient age, forgetfulness, a lack of associated comorbidities and mistrust in the effectiveness of the treatment⁴.

In the case of health professionals, a lack of knowledge about the management of gout may explain inadequate management of the condition^{250, 251}.

These barriers result in poor adherence to ULT (10%-46%) in patients with gout²⁵²⁻²⁵⁵.

Several studies^{96, 245, 248, 249, 256, 257} have shown that nurse-led interventions that include tailored education, patient participation in decision making (patient empowerment) and access to expert support (from nurses) in the management of AEs may influence both lifestyle change and treatment adherence, with subsequent improvements in the rates of attainment of therapeutic targets (target serum urate levels) and clinical outcomes: adequate serum urate levels and reductions in tophi and flare rate.

The management of hyperuricaemia by nurses is cost-effective²⁴⁹ and studies have found that a nurse-led intervention, over 12 or 24 months, was associated with a successful reduction of urate levels to under 6 mg/dL in 92-95% of participants^{249, 251}.

Patients who receive nurse-led care²⁵⁴ report greater levels of satisfaction than those receiving doctor-led care, although we should be cautious about generalising this finding in healthcare in the United Kingdom to other settings.

Support by specially-trained nurses should be included in the regular follow-up of patients with gout, when the healthcare setting allows (Grade A recommendation).

12. General advice on patient management

The management of gout should take into account the characteristics of each patient.

Gout flares are often very painful and disabling. We should encourage the use of pharmacological and non-pharmacological approaches to achieve rapid and effective control of the pain and inflammation. Treatment selection should depend to a great extent on the clinical characteristics of each patient.

In consultation with the patient, the initiation of urate-lowering therapy should be considered in patients with confirmed gout, this meaning that it is essential to reach a firm diagnosis whenever feasible from the healthcare point of view.

The recommendation is to base the definitive diagnosis on the analysis of synovial fluid by optical microscopy, although a clinical diagnosis can be made based on symptoms, as well as blood tests and ancillary imaging, joint ultrasound being the technique of choice.

Although it is advisable to delay the establishment of a urate-lowering therapy by a few weeks after an arthritis flare, starting this treatment during a gout flare can be considered in patients with a complete response to anti-inflammatory treatment, in-patients with severe gout and patients with recurrent arthritis flares on IL-1 inhibitors.

During treatment with urate-lowering drugs, the following should be checked regularly: treatment adherence, renal function and potential adverse effects of the treatment, as well as serum urate levels, following a treat-to-target strategy, seeking to bring them down below 5-6 mg/dL and keep them in this range.

Joint ultrasound scanning can be a very valuable tool for assessing MSU crystal deposits, both at baseline and during the follow-up of patients with gout, during urate-lowering therapy.

Depending on disease severity (degree of joint involvement, frequency of symptomatic episodes and associated structural damage) and the characteristics of each patient (comorbidities and concomitant medications), prophylactic treatment for acute gout flares should be given during the first 6-12 months of urate-lowering therapy.

Targets should be explained and agreed upon with patients before starting treatment, as should the means to attain them, the likely time required and the benefit-risk balance of the treatment.

Treatments should be prescribed based on the principles of efficacy and clinical experience.



In the treatment of gout, it is essential to include the assessment and treatment of associated comorbidities (especially kidney and cardiovascular disease), and it is advisable to estimate cardiovascular risk using the tools available at regular intervals and manage this risk in accordance with national guidelines, preferably in cooperation with the primary care team and any relevant specialists.

Patients and also their families, caregivers and close friends should be informed about the articular and extra-articular consequences of the disease not treated properly and trained in joint self-care and self-management, and if possible, the treatment of inflammatory flares.

Health professionals should provide information and encourage patients with gout to adopt healthy lifestyles, as well as to get involved in the control of both the disease and associated comorbidities.



13. Patients' perspectives

Gathering data on how patients with gout experience and perceive their health status may help health professionals involved in their care to understand a range of factors that have an impact on the disease process. In the development of this guideline, we have included the perspective of patients with gout in three ways: 1) direct involvement of two patients with gout in the GDG; 2) inclusion of the results of an SR of research studies on the experience of patients with gout, their families and/or caregivers; and 3) inclusion of the main outcomes of a primary qualitative study, conducted as part of the background for this CPG, with patients who volunteered to recount their experiences and share their concerns.

Review of the evidence

A review was conducted of the scientific evidence available, prioritizing qualitative research studies to gather data on the worries, concerns and needs of patients with gout, their families and caregivers. The objectives were to explore the perceptions, attitudes and experiences regarding the impact of a diagnosis of gout on patients with this disease; describe experiences concerning symptoms of the disease and the treatment process (paying particular attention to treatment adherence); assess the effect of lifestyle on the development and course of the disease; identify patients' needs for information and education concerning gout; and finally, assess the quality of patient-clinician relationships.

The analysis process identified five main topics: 1) the impact of the diagnosis; 2) the symptoms of the disease; 3) the importance of treatment adherence; 4) the impact of the disease on day-to-day life; 5) family and social environment and 6) clinical care. The range of findings for each topic is shown on the thematic map (Figure 6). Below, we present the topics identified and the conclusions reached.



Figure 6: Worries, concerns and needs of patients with gout

Diagnosis	
Patients' perception of the disease:	Q+, Q++
In the gout diagnosis process, there are two different situations. On the one hand,	
there are patients for whom obtaining the diagnosis and gaining an awareness and	
understanding of the causes of the disease helps them to start to digest the news and	
search for ways to manage and adapt to the disease. Indeed, some people even seek	
to find the reasons why they have developed gout themselves because they think that	



this would help them to identify the strategy, or actions, they should later implement to address their medical condition^{258, 259}.

On the other hand, some patients are reluctant to accept their diagnosis. One study described the role of the ideal of masculinity. Some men were even reluctant to go to the doctor initially, after their first acute episode of gout, to avoid the "shame" of admitting that they were experiencing excruciating pain; despite this having a negative impact on their wellbeing, both physical and emotional, in relation to their professional and family relationships. It was also found that some women were not initially willing to accept the diagnosis of gout by their GP, due to the beliefs and stigma associated with its diagnosis ²⁵⁰.

Clinicians' vs. patients' perspectives:

A notable finding in research focused on creating and validating new classification criteria to identify gout was the differences between the views of patients and clinicians concerning which characteristics of the disease should be considered the most important. Patients believed that the inability to perform activities of daily living and walking was important from the diagnostic point of view and gave them a high rating, while doctors felt that these features had no diagnostic value at all. Patients placed more emphasis on the severity of gout symptoms, such as redness, warmth, inflammation and joint tenderness that interfere with sleep and normal daily functioning. Compared to doctors, they also rated the treatment response and triggering factors for gout flares as more important. In contrast, doctors tended to give more importance to imaging findings, the pattern of joint involvement and changes in these features over time. In general, doctors focused more on diagnostic criteria while patients placed greater emphasis on indicators of disease severity²⁶⁰. Some studies have suggested that it would be very useful for doctors to explore the perceptions of their patients about gout, at the time of the diagnosis, since certain common beliefs regarding the causes and management of gout may interfere in its effective management. That is, time invested by clinicians in countering common assumptions concerning a poor diet and excess alcohol intake as causes of gout and linking the use of urate-lowering drugs to a reduction in urate crystals in the joints would encourage a more accurate perception of the disease and its management^{258,} 261

Descriptive studies

Q+

Descriptive

studies

Q+,



Symptoms of the disease	
Pain:	
This is the symptom patients consider the most important. For many patients, living	Q++, Q+
with gout is living in pain ²⁶² . This type of pain is constant ("like constant tooth pain",	
"as if I had broken my toe"), associated with swelling, reddening, warmth, greater	
sensitivity to touch/tenderness, rigidity and sleeping problems ²⁶²⁻²⁶⁴ ; some patients	0
even expressing a "desire to amputate the area involved" ^{265, 266} .	QTT
Pain is the main symptom that makes patients seek medical attention, to control and	
avoid it ²⁶⁷ .	
<u>Tophi:</u>	
Some research has highlighted the major impact of tophaceous gout on patients'	Q+
lives. Patients most commonly report that the presence of tophi adds to the already	
heavy burden of having gout, exacerbating the impact of the disease on social and	
psychological functioning as well as physical function ²⁶⁸ .	
Flares of joint inflammation:	
Patients remember gout flares very clearly. This is primarily because, at the time of	Q+, Q++
flares, the link between the disease and pain particularly evident. Hence, for many	
patients, the clearest memory of their first flares is pain; such intense pain that they	
would never forget it ²⁵⁸ . Others highlight the severity and duration of flares ²³⁶ .	
Nonetheless, some patients believe that what gout flares reflect is the occasional	
accumulation of uric acid, and that once a flare resolves, the crystal deposits should	
have all gone; and that therefore they should not need to worry until the next	Q+
episode. On this basis, such patients consider that gout treatment only needs to focus	
on acute flares. This belief, together with a lack of understanding regarding the	
potential long-term effects of the gradual accumulation of urate crystals in the joints,	
puts these people at greater risk of irreversible joint damage (osteoarthritis) ²⁵⁰ .	
For other people, gout flares are associated with a feeling of loneliness. They are	
afraid of going out because of the symptoms themselves and also because they are	
ashamed of being seen to limp by their friends. Moreover, they are unable to drive.	
The sense of social isolation is exacerbated by the fact that they cannot attend social	0++ 0+
or family events (e.g., meals, meetings, parties, holidays, and gatherings to play or	Υ ΤΤ , Υ Τ
watch sport), unless everything is very well planned in advance ^{265, 266} .	



Treatment adherence

The patients' perspective:

Regarding the process of treating gout, there is a pattern that is found consistently
and it relates to adherence: patients' adherence to treatment is influenced by their
assumptions regarding the drugs they are taking, their experience of the disease and
their level of satisfaction with the information received about the drugs used.Q+,
Descriptive
studies

In some patients, an understanding of the long-term consequences of the disease and the possibility of adjusting doses individually to avoid new acute flares may be key in them committing to continue their treatment. If patients are not aware of the chronic nature of gout, they will be less likely to seek treatment^{257, 269}. For other patients, perceiving both that they play a key role in controlling the disease and that the medications are effective makes them more likely to adhere to their treatment^{270, 271}. Some patients are aware of the importance of the treatment of gout as a chronic illness, but not of not the potential impact of their own actions on the process²⁷².

The most notable factors that facilitate treatment adherence include: an understanding of the need to prevent acute flares of gout to avoid needing to attend the emergency department, and to free oneself from the severity and chronicity of pain and dietary restrictions; knowledge of the rarity of AEs (given the fear of AEs and the rumours that circulate about them); and trust in clinicians^{250, 262, 273}. Some patients admit that if they sometimes skip their medication it is because they are concerned about taking too many medications due to their comorbidities or because they think that the medication is not necessary when they are not in pain^{250, 267, 274}. Given this, the frequency, severity and impact of acute flares may be a key factor for patients in whether they adhere to their treatment over the long term²⁶⁹.

Q+, Q++

In contrast, a negative perception of or pessimistic attitude to the disease is associated with poorly-controlled gout, a lower level of adherence and greater musculoskeletal disability²⁷⁵.



Q++

From the point of view of clinicians, the factors involved in treatment adherence include: the number of concomitant medications, the potential adverse effects associated with medications, support from the family and the thoughts of patients themselves; additionally, the pain associated with a gout flare may strongly motivate treatment adherence²⁷⁴. Q+ Some clinicians believe that patients should take responsibility for their own health. A patient failing to properly adhere to the treatment they have prescribed and recommendations they have made results in acute episodes and this pattern of events makes them feel hopeless and frustrated; this is why they place importance on adherence²⁶⁴. Living with the disease day-to-day Lifestyle: Patient lifestyle is associated with the process of the disease. Some patients, as well Q++, Q+ as considering that medication adherence is a very important factor, believe that making lifestyle changes and adjustments, such as eating a healthier diet and being more physically active, may help them to achieve self-management of their condition. Additionally, if there is fear of pain, lifestyle changes are less difficult²⁶⁷. Nonetheless, one of the most common barriers to treatment being effective is a failure to carry out the lifestyle changes proposed by clinicians. Some patients are reluctant to accept the diagnosis of gout because it implies admitting that maybe they should change some of their lifestyle habits, a step they are not willing to take²⁵⁸. According to doctors, patients follow the recommendations they are given regarding changes in lifestyle habits at the start; but as the frequency of acute flares decreases, they adhere to these changes less well. That is, in most cases, compared to adherence to pharmacological treatment regimens, compliance with recommendations related to dietary and alcohol restrictions over the long term is much harder²⁷⁶. The majority of patients are aware that some foods and beverages are potential triggers for gout. Nonetheless, despite this, they continue consuming foods and beverages that they know are $harmful^{236,\,264,\,273,\,277,\,278}.$

The clinicians' perspective:



Mood states:	
Some studies have reported that the prevalence rates of both depression and anxiety	Descriptive
are higher in people with gout than in the general population; and they highlight the	studies
case of depression, given its potential negative influence not only on the psychological	
health of the patient but also on treatment adherence and attendance to regular	
clinical check-ups, which may negatively influence the management of the disease.	
For this reason, depression may have a negative impact on the self-management of gout ²⁷⁹ .	
Gout also impairs patients' quality of life, and this can be observed through the	
assessment of their functional, emotional and psychological limitations, as well as	
deterioration in their social relationships and difficulties in working life ^{263, 264} .	
Descriptive research has found that some ideas of people with gout concerning the	Q+,
disease are associated with the perception of a greater risk of mortality, regardless of other key clinical and demographic variables ²⁸⁰ .	Descriptive studies
Nonetheless, the message from other research is that the frustration and	
powerlessness associated with gout create a need to face up to the disease and learn	
to live with it. Accepting the disease is the most common coping strategy reported by	Q++
patients ²⁶² .	
<u>Sexuality</u>	
Patients recognize the influence of flares on a reduced desire for sexual relations. The	Q+
greatest problems in having sexual relations are related to experiencing acute and	
chronic joint pain and the physical and, above all, emotional impact of having gout	
during moments of intimacy ^{273, 281} .	
Family and social environment	
The role of the family	
Family support is very important for patients. They mainly seek physical and	Q++
emotional support, especially during acute flares. Sometimes, patients feel that other	
people do not understand the nature of gout and the effects it has on them.	
Concerning family, patients highlight their fear that other members of their family	
may also develop the disease. On the other hand, if they have known a close relative	
to have gout, this can help them to deal better with the disease ²⁶⁵ .	

Further, gout restricts lifestyle habits and therefore the quality of life not only of	
patients but also of other members of the family and caregivers, who express feelings	Q+
of unhappiness and guilt when they enjoy social activities without involving their	
relative with gout ²⁶⁴ .	
Stigmatization	
Many patients report that people around them do not really know what gout is and	0++.0+
what it means for those who have it. For patients, gout is a serious condition and	Q.,) Q.
extremely painful and they get angry when their social circle do not take them	
seriously and they make a joke out of it ²⁷⁸ . The idea that the disease carries a stigma	
persists. This makes patients try to hide the diagnosis and even lie when they talk to	
other people. In this way, they avoid comments and jokes and being mocked about	
aspects of their lives such as their diet (for example, jokes being told during family	
meals about eating seafood and drinking beer) ^{258, 264-266} .	
Some patients fear that the association of gout with excessive eating of some types	
of foods and drinking of alcohol (that is, with unhealthy lifestyle habits) makes it be	
seen by others as a self-inflicted disease. For this reason, they express a need to "cope	
with the symptoms" rather than seek medical care and be criticized and told off $^{250, 265}$.	
If instead of being called gout, this condition were to be referred to as urate crystal-	Q+, Q++
induced arthritis, the stigmatization and perception of the disease would change. A	
study was conducted in which two groups of the general population completed a	
questionnaire that was the same for both groups except regarding the term used to	
refer to the condition. When the term gout was used, people perceived it to be a	
disease caused by patients themselves behaving inappropriately, namely, eating an	Descriptive
unhealthy diet and drinking too much alcohol; gout was labelled an embarrassing	studies
disease, from a social point of view, and it was expected that its treatment would	
focus on dietary interventions. When the term urate crystal-induced arthritis was	
used, the disease cause was believed to be something related to ageing, and it was	
viewed as a more serious and chronic condition that would need to be managed with	
long-term medication ²⁶¹ .	
The stereotype of gout may contribute to patients feeling ashamed of their illness and	
isolating themselves or being shunned by others. For example, in a population for	
whom eating is an event that forms part of social and cultural relations (the Māori	

people), if someone has a gout flare, they are unable to participate in many

activities²⁶⁶.

Q+



The workplace	
Patients describe various obstacles when they talk about their functioning at work.	
Among these, the key factors patients cite are employers lacking an understanding of	Q+, Q++
the disease ²⁶⁶ ; followed by the constraints added by acute flares, such as difficulties	
wearing work uniform or shoes ^{264, 266} , and all patients would like access to flexible	
working hours and days off, especially when they have flares ^{262, 265} .	
Clinical care	
Interaction with health professionals	
Great importance is placed on doctor-patient relationships throughout the disease	Q++
process; however, the feelings about this issue differ markedly among those involved.	
On the one hand, patients emphasize the concept of "telling" versus "listening" during	
consultations. They describe that when they attend consultations, they receive talks	
from clinicians rather than being listened to by them. Health professionals tend to	
adopt an educational approach that involves them first "telling" patients what they	
should do, more than "listening" to an account of their experiences with the disease.	
Despite showing great skill in the treatment of patients, health professionals often	
find it difficult to use a patient-centred approach for communication regarding gout.	
And, as a consequence, they tend to provide information focused on biomedical	
issues which is unlikely to resonate with patients' experiences. Little effort is made to	
assess patients' understanding of the characteristics of gout or understand the	
psychological or social impact of the condition on patients ²³⁶ .	
On the other hand, from the perspective of health professionals, barriers in their	
relationship with patients can be classified into three categories:	
1) The management of the disease. First, the natural history of gout (it starting with	
occasional episodes, then progressing insidiously with acute flares, and later, being	
compounded by comorbid conditions) can itself become a barrier to effective	
management. Clinicians may have doubts and prescribe acute treatment, rather than	
a preventative treatment better suited to a chronic illness. Secondly, clinicians report	
feeling that they have little control over factors related to patient behaviour. This	
leaves them frustrated and hopeless in the face of what they see as a failure of	



patients to act responsibly regarding their own health and with a sense of uselessness	
concerning the management of gout.	
2) The healthcare system itself. The short amount of time that clinicians are able to	
dedicate to individual patients at each appointment is a substantial barrier to the	
provision of effective healthcare. With such little time to talk, it is difficult to work on	
behavioural change or provide education for patients with gout.	
3) Cultural differences. The perceptions of patients and their apparent lack of a sense	
of responsibility regarding their role in the process have been attributed to cultural	Q++, Q+
factors. Further, in some countries, there is a need to take into account differences	
between ethnic groups in terms of beliefs regarding food and drink, for example, and	
in terms of language ^{275, 277} .	
Patient education	
Where do patients get information from? Many patients initially obtain information	0+. 0++
from their primary care doctors. Nonetheless, depending on their level of education,	
sometimes they do not properly understand the information provided. There is a	
demand for more information and more patient education, as well as the use of clear	
and simple language that takes into account existing cultural differences. For	
example, to avoid potential confusion, it needs to be understood that there are	
different customs regarding food and even the terms used to refer to foods ^{250, 256, 264,}	
^{266, 274, 282, 283} . Despite this, in some studies, clinicians recognise that they do not offer	
sufficient information to their patients about gout and that patient education is very	
important to achieve proper management of the disease ^{264, 284} .	
Another source of information is the family; especially when there is a family history	Q+
of gout. On the one hand, a family history may help because patients receive support,	
understanding and strength for changing certain lifestyle habits; on the other, it has	
the disadvantage that family members may perpetuate myths and incorrect	
information ²⁶⁶ .	
Here, we should consider the distinct situation of women with gout. Some women do	
not understand the disease well and find it difficult to locate information that they	Q+
consider important, most of the information available targeting men. Gout has a	
major impact on women's identity and their roles and relationships. These findings	


are important for healthcare professionals who interact with women who have	
suspected gout or a definitive diagnosis of the disease ²⁶⁹ .	Q++, Q+
In general, patients seek to obtain the additional information they need from doctors,	
other healthcare professionals, other patients or the Internet ²⁶⁷ . Interestingly, on	
some occasions, things they find on the Internet or through mobile apps motivate	
them to change unhealthy lifestyle habits regarding diet or the management of their	
disease in ways that not even doctors had suggested to them ^{258, 285} .	
One of the benefits of having more information and knowledge about the disease is	Q+
that patients become more aware of the importance of medication; they do not think	
so much about potential AEs and their treatment adherence improves. Tailored	
programmes focused on changing perceptions of the disease may improve outcomes	
in patients with gout. This may be related to the need for health professionals to tune	
their message to the individual needs of each patient ²⁷⁵ .	
Clinicians' training needs:	
Clinicians also comment on their level of knowledge about the disease. They recognize	Q+, Q++
a need to improve continuous education in this field, in terms of both the	
management of gout itself (some clinicians approaching it as an acute illness rather	
than a chronic condition) and the information they can then provide to patients ^{274, 284} .	
When they fail to obtain sufficient information about the disease from clinicians,	
some patients seek help from pharmacists to bridge the gap. Nonetheless, when	
exploring the point of view of pharmacists, the majority of them reported a lack of	
specific professional training or continuing education on the latest approach to the	Q+
management of gout ²⁸⁶ .	



Qualitative study

To explore the experiences of gout among people with this condition in the context of our culture, a primary qualitative research study was conducted using group discussion techniques. Recordings of the discussion sessions were transcribed and categorized, to facilitate the interpretation of the results. In this way, it was possible to identify and analyse the most important issues for these patients. This information was used to complement that obtained from the SR of the literature (summarised above).

The key conclusions of the qualitative research are summarised below:

Categories	Analysis
Diagnosis	The origin of gout and explanations of the condition
	For the majority of patients, recalling and identifying their first flare of gout is
	linked to their symptoms and when the flare occurred. This tends to coincide
	with either doing physical exercise or being in a stressful situation. Many patients
	agreed that stress, personal problems and major worries play an important role
	in the process of triggering a gout flare. And this is a recurrent idea; it came up
	again and again.
	"The first time it happened to me was after doing exercise."
	"The main cause of my gout flares has been the stress I have been under."
	"Due to stress, I have had gout flares, more or less, every 6 months."
	<i>"It flares up in stressful situations."</i>
	The role of the ideal of masculinity and the fact that some men are reluctant to
	seek medical attention out of "shame", after their first flare of gout, were
	identified from the literature search. Then, from the group discussions, some
	reflections emerged that to some extent may be related to these findings and
	that are associated with concepts patients have concerning the origin of gout
	and their understanding of the aetiology of the disease. They ask themselves why
	gout is more common among men than among women.
	<i>"I'm not being sexist, but why do we men have more gout than women, when we have done always more exercise than them?"</i>
	"Why there are more men than women?
	"Maybe it is because they can detox when they have their period."



Some men with gout build a model of what is normal or the typical pattern
that influences the onset of the disease. And the most common pattern in men
does not match their model, because the behaviours that influence men's
health are related to their ideal of masculinity.
Women are labelled as weak while men are expected to be strong.
The diagnostic process and the specialists involved
The diagnostic process is described differently depending on various key issues.
The easiest path is that taken by patients who already have a family history of
gout, because the symptoms are more easily identified and because patients
tend to be referred to the rheumatologist at an earlier stage, allowing their
clinical condition to be identified more quickly. Older patients and those in whom
symptoms are associated with having performed some type of physical exercise
mention "the mistake" of being referred initially to specialists that had nothing
to do with rheumatology. The majority of these patients have had a long list of
incorrect diagnoses before arriving at gout.
"They took to while to refer me to rheumatology."
"My brother has certainly had gout flares."
"My father has had high urate all his life. One day, when I was 28, I went out after work and had some alcohol-free beers with a colleague, I went to bed and when I woke up, I couldn't walk. My ankle was so, I spent some months treating it as if it was a sprain but after a while, the penny dropped for somebody and that was it, my mistake was to think this was treated by internists and I was still in a bad way until I was seen by a rheumatologist."
Day-to-day physical symptoms
The chronic nature of the disease results in patients living with some symptoms
that can appear repeatedly and that may trigger others; this being something
that has a very negative effect on all patients. First, there is pain; and this
symptom may also reflect how patients describe their problem, there being two
types. One type of pain is undoubtedly linked to the onset and recurrence of gout
flares, and this is harder to cope with. Then, there is another type of pain that
lasts less long and appears at the start of daily activities, and this is easier to



	manage. The common characteristic of both types of pain is the associated	
	functional disability.	
	<i>"I couldn't move my legs at all, and that had a massive impact on me; I got scared and went to hospital."</i>	
	<i>"I've had to be admitted to hospital twice because I could not bear the pain in my knee, and it hurt even when I didn't walk."</i>	
	"I have had problems with my ankles; I go walking, and when I trip, I get really cross."	
	"When I get up, I can hardly move, until I walk a bit."	
	Other symptoms that are highlighted include inflammation, swelling and	
	reddening. These may also affect people with gout emotionally, because they	
	see them as a factor that, above all, reduces their quality of life.	
	<i>"It all started as if I had dislocated my ankle and big toe. Then, I started to have problems in the other ankle and it got worse, until I started walking with stiff legs when I walk, it is unbelievable, my knee swells up to the size of three knees".</i>	
	"It all started when my big toe turned red, continuing until one day I wasn´t able to walk".	
Treatment	Finding the treatment that is best, in the sense of most effective	
	In patients' experience, the choice of pharmacological treatment plays a key role.	
	For them, the aim is to find a medication that helps them to regain their health,	
	physical functioning and ability to live a life as if they did not have gout, that is, a	
	normal life. In turn, this means enabling normal social functioning. In a disease	
	like gout, receiving treatment is closely associated with the hope of being cured	
	of the disease without a heavy burden of adverse effects.	
	"When you already know what's wrong and you are being treated, you can be more relaxed."	
	"Personally, I'm worried about the future. What if so much treatment, for so many years, might be bad for me? That's what frightens me."	
	"Personally, I haven't noticed any adverse effects."	
	<i>"I've been doing well, very well with the medication for 40 years, taking very little by the end, but now they've given me strong drugs for my cancer, I can't cope any longer… with very intense pain".</i>	



Treatment adherence

There are two lines of argument for the importance of treatment adherence. In this context, we need to distinguish between the pharmacological part of the treatment and the non-pharmacological measures.

With regards to medication, one of the key factors that influences treatment adherence is patient fear of gout flares. Stopping the treatment can have bitter consequences. This is what makes patients willing to adhere to their treatment.

"My mistake was stopping the treatment ... uric acid builds up and there's a point at which it starts staying there and ... then I get a flare."

"I've started taking it more seriously and sticking more closely to the rules they set me."

The factors related to non-pharmacological measures tend to have a common thread. The difficulty revolves around adherence to dietary recommendations. Abstaining from or limiting the intake of certain foods and drinks is harder to accept. All patients agree that they have received clinical advice and/or obtained information from other sources such as the Internet; but most are not really sure about the truth behind the dietary recommendations, or more importantly, whether lack of compliance to them influences whether their gout improves. This confirms a repeated finding in numerous health problems for which there is a non-pharmacological treatment option: it is easier to "take a pill" because the effects are much faster.

"I still don't fully stick to the rules on what not to eat, but thanks to allopurinol and colchicine, I've gone more than a year and a half without any flares".

Self-medication

The discourse of some patients reveals a notable phenomenon: given their fear and desperation concerning acute flares, they have listened to the recommendations of clinicians regarding what medications they can take and how to manage their flares. These patients can be considered well informed. Nonetheless, in practice, they adapt the information they have, these recommendations, in unique ways seeking to solve the problem they face as effectively and quickly as possible. This is what is seen in the way patients use colchicine and their own decisions regarding medication, for example.

	"We already know what to do with colchicine, pop in two tablets, and after a while, two	
	more and so on, and this aives you diarrhoea, it's absolutely horrid, for 12 to 24 hours	
	you're feeling that you can't take it anymore, and after that, it's okay"	
	"One has to try to regulate oneself."	
	"Already knowing that colchicine makes you sick and gives you diarrhoea, you take it."	
	The search for solutions and alternative treatments	
	The ideal is that treatment should be tailored individually, considering the	
	characteristics of each patient. But why not try what seems to have "worked	
	well" for other people? Patients hear stories of people that have achieved	
	astonishing results. For some people with gout, this leads them to a world of	
	home remedies, secret ingredients, and advice on the latest discoveries, which	
	have no scientific or clinical basis, and they set their hope on such alternative	
	treatments working for them.	
	"When you are in a lot of pain, you look for and do anything; what you want is to get rid of it."	
	"It works for so-and-so Why don't you try it?"	
	"Drink white wine, not red, as white wine doesn't set it off."	
	"Since I've been stuck with the pain for the last year and a half, I'll look for anything."	
Living with		
gout	Understanding the meaning of gout. A stigmatized disease	
-		
	There is an aspect of the disease that ends up affecting all patients emotionally,	
	namely, the social stigma around gout. Patients feel that other people think that	
	patients themselves are to blame for having gout. Situations such as family	
	meals, planning holidays, the work environment and interactions with employers	
	and colleagues are stressful for them. Thinking that battles in these contexts are	
	a lost cause, and to avoid being laughed at by their social and family circles, they	
	opt to hide the symptoms and feelings they are experiencing.	
	"My relatives think that I've got what I deserve so I don't moan about it all my close family believe that I do things I shouldn't do."	
	<i>"If they see you drinking a beer, [they say] 'What are you doing? You're not allowed that!'"</i>	

"Gout, gout, there you go again with gout. You binge on food and drink and there you go."

"My boss says to me, 'Overdone it again, have we?'

"It irritates me so much when someone says, 'You've got a rich person's disease!'"

"My wife looks at me and says, 'There you go again! And when are we going on holiday; now don't tell me that you are going to have a flare! ... Are you going to have one or not?"

Adaptation

Adapting to a chronic illness such as gout requires time. Patients go through different stages of coping and there is no established timeframe for completing this process; but, thanks to their experiences, they gradually discover resources for coping with difficult phases of the disease and fight to stop it taking over their lives. People with gout have an ability to adapt and strengths that sometimes they themselves are not aware of.

"I've lived with gout all my life and I've become somewhat fond of it ... I try to see the positive and the positive side of gout is that it's a disease that warns you."

"I know that I might have a gout flare at any time, and I accept that's how it is."

Lifestyle change

Changing or modifying certain lifestyle habits is one of the most difficult issues for patients. Most people with gout are clear about the targets to be achieved with medication. The same is not true of changes in lifestyle habits proposed by clinicians, in particular, regarding food and drink. The main barrier is that they do not see the relationship between unhealthy habits and worsening of their symptoms or the benefits of and rewards from making changes. An explanation for this might be that people live in a setting in which, in the socialisation process and development of relationships with others, certain behaviours regarding food and drinks follow set models and norms that become lifestyle habits. *"I think that what you eat is important but not essential, as long as you don't stuff yourself*".

"I hope to find a way to continue eating everything I want ..."

"They banned me from drinking beer, and I was fed up because the months wore on, I wasn't drinking and the pain didn't ease at all, ... I went on holiday and said to myself, `Enough is enough!' And since then, I've been drinking my five beers a day and I'm exactly the same. No better, no worse."



"I don't want anyone to stop me from having a beer when I'm cooking lunch or dinner. I don't want them to stop me doing that."

When patients obtain information about the importance of physical activity in the prognosis of gout, the decision becomes easier. They agree to introduce exercise as a habit and incorporate some regular physical activity into their daily routine.

"Walking is doing me good."

"I`ve started walking now."

Employment

Gout also affects patients in the working sphere. The physical limitations have an impact on their functional capacity to work. The changes related to continuing or stopping work depend on patients and their personal and emotional status; although most prefer to stay active in the workplace.

"One can't stop working, because one needs to work to put food on the table."

"I've gone to work [even when I was] on crutches."

Attitude towards the future

When gout is perceived as a disease that is going to become a lifetime companion, it is not always easy to look to the future with optimism. If the disease is not under control, the fear of it will not go away. The present and future merge and the arguments that it's going to be possible to cope with the disease collapse.

"The future ... If I stay like this, the future looks grim"

"What I can see is that there is a cost for society, the time that passes before you are diagnosed, the time you are off work ... If the pathway were clearer: who you should be referred to, ... if rheumatologists had more training."

Healthcare process

Relationship with clinicians

The relationship between patients and clinicians is a complex issue that emerges again and again in the discourse. Doctors and patients perceive, interpret and experience this relationship differently. Therefore, it is important to assess how the relationship is built and how it deteriorates. Trust is the most influential



factor in strengthening communication, and in this context, there are various scenarios. For some patients, communication should be focused not only on the disease but also on the person. And when they feel that this is achieved, they know that they can contact their doctor at the most difficult times.

"If they tell you, 'Don't worry, in 24 hours, you'll be feeling better'. If you find a health professional who keeps an eye on you, who goes beyond their duty, who explains things to you, and says that if you have any flares, you can call them".

"Now that I've found a good rheumatologist, I really feel relieved, better... She's achieved what others haven't. There are things that I feel are not good (foods) and I don't eat them anymore".

"The truth is that finding a good rheumatologist really makes life easier".

For other patients, doctors as health professionals are seen to be superior to them, and in this context, the healthcare is perceived to be of less good quality.

"It's not my place to tell the doctor what they have to do, ... but I'd like to ask them why don't you stop giving me the tablets and see if, by now, my urate levels don't go up."

Need for information about the disease

The core message is that patients highlight the need to be given more information on the management of gout. They first seek medical attention because they have a health problem and are motivated by the fact that they do not know what it is or how to tackle it. For a doctor-patient relationship to go well, it is important to provide healthcare information to patients. And this is a key factor in enabling the expectations of patients with gout to be met. Nonetheless, the reality is that there is a lack of information about why to take or not take certain medications, and about what the disease does to the patient's body. Emphasis is also placed on the lack of personalized information and that patients have to search for such information themselves through the channels most accessible to them.

"Nobody has ever explained anything to me about the medications. The crystals are eroding your body from inside and they don't tend to tell us that."

"I've never been told that I had high uric acid levels. Never."

"You go on the Internet and you can't find much."



"I've reached the conclusion that if I go looking on the Internet, it sets my head spinning ... and I say, 'That's enough'."

Patients with little faith

Patients request more research into gout. From their point of view, it is as if clinical studies had stalled. For them, gout is an old disease and they believe that current treatments are the same as those that have been used for years and that their use is not questioned. They feel that there is a need for more research and they want to know the cause of this disease and what triggers it. They lack answers.

"Not much research is being done; if there were, they would've invented something new. We've been taking colchicine for 40 years."

"[They should] not use a treatment from 50 years ago ... they should have done a bit more research."

"Despite its reputation as the 'disease of kings' and that it's been around for so long, there's been very little research."

14. Diagnostic and treatment strategies

Algorithm 1

Diagnostic algorithm for gout





Algorithm 2

Treatment algorithm for gout





15. Dissemination and implementation: proposal of indicators

Dissemination strategy

Achieving the goal of health professionals following the recommendations in clinical practice guidelines starts with developing a strategy for their dissemination. The programme for promoting the adoption of this guideline for the management of patients with gout includes the following interventions:

• Announcement of the completion and availability of the guideline through the members' newsletter on the SER website

- Publication of the guideline in an electronic format on this website
- Dissemination of the guideline to professionals through social media: Twitter, LinkedIn and Facebook
- Formal presentation of the guideline to the scientific societies in the field

• Placing emphasis, in all presentations of the guideline, on the informative material developed for patients to encourage its distribution to all clinicians and in turn to patients with this health problem

• Publication of the guideline in scientific journals

• Targeted and effective distribution of the guideline to the relevant professional groups (rheumatologists, nephrologists, general practitioners and rheumatology nurses) to facilitate the dissemination of the guideline

• Evaluation of whether they are adopted effectively, with the setting up of clinical decision support tools, integrating the guideline and indicators selected (see below) into the computer software used in primary care

• Presentation of the guidelines at scientific events (conferences, seminars and meetings).

Proposal of indicators

The manual of the AGREE II tool highlights the importance of developing indicators that allow us to monitor and evaluate adherence to the main recommendations in the guideline. The guideline's authors have sought to provide a useful tool for health professionals interested in evaluating the care provided to patients with gout. This consists of quantitative measures which, if measured regularly, allow us to monitor the course of these patients over time. The team responsible for assessing the impact of the CPG and the care provided should select appropriate



sources of data and the most suitable time period considering the concept measured by each indicator (Table 11).

Table 11. Proposed indicators

Area	Type of indicator	Name of the indicator	Cut-off for quality	Care level* (1: primary, 2: specialised)
Referral	Process	Percentage of patients with hyperuricaemia and recurrent arthritis with a poor response after 1 year of treatment who are referred	80%	1, 2
Assessment	Process	Percentage of patients with hyperuricaemia and recurrent arthritis with a poor response after 1 year of treatment who are referred	90%	1, 2
Assessment	Process	Percentage of patients who undergo renal and liver function tests	100%	1, 2
Assessment	Process	Percentage of patients who undergo cardiovascular risk assessment	100%	1, 2
Assessment	Process	Percentage of patients who have their urate-lowering medications reviewed	80%	1, 2
Assessment	Process	Percentage of patients who have plain radiographs taken of joints that show limitations on physical examination	90%	1, 2
Assessment	Process	Percentage of patients who undergo thorough assessment of potential subcutaneous tophi	80%	2
Assessment	Process	Percentage of patients for whom the number of gout flares in the previous year are documented	80%	1, 2
Assessment	Process	Percentage of patients who undergo specific diagnostic tests: imaging (ultrasound or dual-energy computed tomography) or microscopy	80%	2
Treatment	Process	Percentage of patients with severe gout (polyarticular gout, tophaceous gout or structural damage) who initiate urate-lowering therapy	100%	1, 2
Treatment	Process	Percentage of patients who reach the maximum tolerated dose of medications	90%	2
Treatment	Process	Percentage of patients who attain adequate serum urate levels	90%	1, 2
Treatment	Process	Percentage of patients who have their serum urate levels tested at least once a year	100%	1, 2
Treatment	Process	Percentage of patients who have their flares since the previous check-up assessed	100%	1, 2

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16. Future lines of research

In the course of the development of this guideline, various priority areas have been identified for future research. In particular, these include the need for:

Asymptomatic hyperuricaemia

- Research on the influence of high urate levels on the onset of gout, stratifying by time with high urate levels, degree of serum urate elevation, current presence of MSU crystal deposits and family history of risk factors
- Studies on the development of deposits and the appearance of inflammation in patients with recent-onset hyperuricaemia
- Analysis of the cost-effectiveness of interventions for high serum urate in patients with or without MSU crystal deposits

Cardiovascular risk

- Research on the effect of ULT on the incidence of cardiovascular/renal events: drug class effect (mechanism of action); medication effect (different XO inhibitors or uricosuric agents); dose effect (and pharmacokinetic dose adjustment in the case of allopurinol) and efficacy (urate level achieved and degree of urate level elevation); and prospective cohort or case-control studies (with or without follow-up)
- More studies on the effect of colchicine treatment (dose and duration of prophylaxis), on gout flare rate, Doppler signal, inflammatory parameters and cumulative incidence of cardiovascular events, adjusted for other risk factors or characteristics of the disease

<u>Diagnosis</u>

- Research on the cost-effectiveness of ultrasound compared to other approaches (primary care/rheumatology care/availability of laboratory equipped with a microscope)
- Analysis of the cost-effectiveness of using imaging in decision making about treatment

<u>Treatment</u>

- Research on the effect of co-interventions (control of hypertension, diabetes and hyperlipidaemia) on the cumulative incidence of vascular events in patients with gout
- Research on the healthcare cost savings (reductions in emergency department resource use/primary care consultations/specialised care consultations/hospital admissions) associated with adequate control of urate levels (T2T)



- Research on the effect of the T2T strategy on other costs: social, work-related and personal, focusing on reduction in work-related costs (to employers of sick leave and presenteeism) and social costs (in terms of the economic impact on the Spanish National Social Security Institute associated with temporary/permanent incapacity to work)
- Research on optimal target serum urate levels
- Research into both the safety and efficacy of different preventative treatments (NSAIDs/colchicine/corticosteroids), including the use of preventive strategies as an active control arm in clinical trials versus other treatment options (gradual dose escalation of allopurinol)
- Investigation of the relative benefits of initiating preventative treatment (colchicine) during flares or complete treatment (of the flare and colchicine and start of escalation of ULT), assessing the efficacy, safety and impact on adherence.

APPENDICES

Appendix 1. Levels of evidence and grades of recommendation

Table 12. Scottish Intercollegiate Guidelines Network (SIGN) Levels of evidence and grades of recommendation ^{287, 288}

Levels of scientific evidence		
1++	High-quality meta-analyses, systematic reviews (SRs) of randomised clinical trials (RCTs), or RCTs with a very low risk of bias	
1+	Well-conducted meta-analyses, SRs or RCTs with a low risk of bias	
1-	Meta-analyses, SRs or RCTs with a high risk of bias	
2++	High-quality SRs of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal	
2+	Well-conducted case-control or cohort studies with a low risk of bias and with a moderate probability that the relationship is causal	
2-	Case-control or cohort studies with a high risk of bias and a significant risk that the relationship is not causal	
3	Non-analytical studies, e.g., case reports, case series	
4	Expert opinion	

Qualitative research^a

^aThis category is for studies based on qualitative methods and is not covered by the SIGN recommendations. The methodological quality of this type of research was assessed and only the most rigorous studies included.

Grades of recommendation ^b		
A	At least one meta-analysis, SR or RCT rated as 1++ and directly applicable to the target population of the guidelines; <i>or</i> a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results	
В	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; <i>or</i> extrapolated evidence from studies rated as 1++ or 1+	
с	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; <i>or</i> extrapolated evidence from studies rated as 2++	
D	Evidence of level 3 or 4; or extrapolated evidence from studies rated as 2+	



Recommended best practice based on clinical experience and consensus among the guideline development group

^bStudies rated 1- or 2- should not be used for the development of recommendations used as evidence in the development of guidelines given the high risk of bias.

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^cOn some occasions, the guideline development group identified important practical issues on which it wanted to place emphasis but related to which there was unlikely to be any supporting evidence. In general, these issues concern aspects of treatment considered good clinical practice and which are not commonly questioned. Such issues have been evaluated as questions of good clinical practice. Related suggestions are not an alternative to evidence-based recommendations, rather they should only be made when there is no other way to highlight the corresponding issue.

Q+, Q++	Evidence taken from relevant high-quality qualitative studies. This category is not considered
	in the SIGN guidelines.

Table 13. Levels of scientific evidence and the formulation of recommendations on questions related to diagnosis

(the Oxford Centre for Evidence-based Medicine system as adapted by the National Institute for Health and Care Excellence)^{287, 289, 290}

Level of scientific evidence	Type of scientific evidence
la	Systematic review (SR) with homogeneity of Level 1 studies
lb	Level 1 studies
II	Level 2 studies SR of Level 2 studies
	Level 2 studies SR of Level 3 studies
IV	Consensus, expert opinion without explicit critical appraisal
Level 1 studies	 These include: Blind comparison of the test with a validated reference standard ("gold standard") An appropriate spectrum of patients



Level 2 studies	 These have only one of the following (sources of bias): Non-representative population (the sample does not reflect the population to which the test would apply) Use of a poor reference standard (i.e., the 'test' is included in the 'reference' or the 'testing' affects the 'reference') Non-blinded comparison Case-control design.
Level 3 studies	These have two or more of the features listed above (for level 2 studies).

Grade of recommendation	Evidence
A	la or lb
В	I
C	III
D	IV

Table 14. Levels of scientific evidence and the formulation of recommendations on questions related to follow-up/prognosis

(the Oxford Centre for Evidence-based Medicine system as adapted by the National Institute for Health and Care Excellence and modified by Rector)^{287, 289-291}

Level of scientific evidence	Type of scientific evidence
la	Systematic review (SR) with homogeneity of Level 1 studies
lb	Level 1 studies
II	Level 2 studies SR of Level 2 studies
111	Level 2 studies SR of Level 3 studies
IV	Consensus, expert opinion without explicit critical appraisal
Level 1 studies	 These include: Blind comparison of the test with a validated reference standard ("gold standard") (not applicable) An appropriate spectrum of patients.



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	These have only one of the following sources of bias:
	 Non-representative population (the sample does not reflect the population to which the test would apply)
	 Use of a poor reference standard (the test is included in the reference or the testing affects the reference) (not applicable)
Level 2 studies	 Assessment of the test on follow-up not blinded to clinical assessment or gold standard test results if available (modified)
	– Losses to follow-up (Rector, 2012)
	 Secondary analysis based on data gathered for other purposes (Rector, 2012)
	 Retrospective design (modified)
	 Case-control design (not applicable).
Level 3 studies	These have two or more of the features listed above (for level 2 studies).

*Modified incorporating some of the items proposed by Rector in 2012 for judging study quality²⁹¹.

Recommendation	Evidence
A	la or lb
В	II
С	
D	IV



Appendix 2. Information for patients



Aprendiendo a convivir con la **Gota**

Información para el paciente

Preguntas y respuestas para las personas que tienen gota, sus familiares y cuidadores.



Esta información ha sido realizada por la Unidad de Investigación de la Sociedad Española de Reumatología (SER) y el Grupo de trabajo de la Guía de Práctica Clínica para el manejo de pacientes con gota. Está disponible en formato electrónico en la página Web de la Sociedad Española de Reumatología (SER): www. ser.es. En esta página puede consultarse, además, la versión completa de la Guía.

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01 Presentación

La información que recoge esta Guía está orientada a personas que tienen gota, también a sus familiares y cuidadores. Le podrá ayudar a conocer más esta enfermedad, para que pueda cuidarse mejor y aumentar así su calidad de vida. Puede que tenga que leerla varias veces o utilizar las diferentes secciones dependiendo de cuándo necesite la información.

Este documento recoge información sobre la enfermedad, el diagnóstico y el tratamiento; además incluye consejos sobre cómo puede manejar la enfermedad en su día a día y otros recursos de utilidad como los contactos de asociaciones de pacientes o recursos de Internet. Debe tener en cuenta que toda la información recogida aquí no sustituye la opinión ni los consejos de su médico o de otros profesionales como enfermeras especializadas. Se trata de un documento que le ayudará a complementar la información ofrecida por el equipo sanitario que le atiende.

Disponer de una definición válida de qué es la gota va a ser de gran utilidad para entender su importancia clínica y sus posibles complicaciones, así como los tratamientos de los que se dispone para tratarla. La gota es una enfermedad rodeada de mitos y conocimientos populares que deben ser matizados para que no enturbien

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prejuicios y las creencias sobre la naturaleza de la enfermedad que todavía siguen vigentes hacen que el manejo de la misma no siempre sea el más adecuado.

Este documento ha sido realizado por la Unidad de Investigación de la Sociedad Española de Reumatología (SER). Las recomendaciones que en él se recogen se han elaborado basándose en la literatura científica existente y en el consenso y experiencia del grupo de profesionales expertos en el tema (reumatología, Atención Primaria y enfermería especializada). También se han tenido en cuenta otros materiales informativos sobre gota elaborados por sociedades científicas y organismos oficiales en España y en otros países. Además, se ha utilizado la información derivada de un estudio de necesidades y preferencias de los pacientes con gota que ha elaborado la propia Unidad de Investigación de la SER.

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02 Diagnóstico de la enfermedad

¿Qué es la gota?

La gota se define como una **enfermedad de depósito**, es decir que su forma de hacer daño es mediante el acúmulo en los tejidos de **ácido úrico** en forma de cristales (cristales de urato). Para que se produzca la **gota** es necesario la presencia de inflamación articular como consecuencia de depósitos de cristales de urato en las articulaciones. La gota provoca **brotes de inflamación articular** que pueden ser muy dolorosos e invalidantes. Los depósitos de ácido

Pie sano



)C

Pie con acumulación de ácido úrico



D

úrico pueden aparecer en las articulaciones y en otros tejidos como tendones, piel, cartílagos (por ejemplo, orejas), riñon, entre otros. La gota se asocia a padecer con más frecuencia de lo esperado una enfermedad renal crónica y enfermedades cardiacas.

Clásicamente la gota se ha definido como una enfermedad crónica. Sin embargo, hoy en día se dispone de tratamientos capaces de eliminar los depósitos de ácido úrico que provocan los síntomas y las complicaciones y, por lo tanto, la gota es una enfermedad curable.

¿Es lo mismo tener el ácido úrico alto en la sangre que tener gota?

No, no es lo mismo. Hay que conocer bien estos dos conceptos y saber diferenciarlos. El primero, la hiperuricemia, significa tener unos niveles de ácido úrico en sangre elevados, aunque eso no quiera decir que se tiene gota. Definir exactamente los niveles elevados de ácido úrico no es sencillo. El nivel de ácido úrico en sangre a partir del cual empieza a depositarse en los tejidos es de 6,8mg/dL a temperatura de 37°C, que es la temperatura habitual de nuestro cuerpo. En zonas corporales con temperatura más baja, por ejemplo, en el dedo gordo del pie, el depósito de ácido úrico se produce en torno a 6,4mg/dL, lo que podría explicar que esta sea la zona más habitual donde precipitan los crista-



les de urato. Por lo tanto, la hiperuricemia es un valor analítico y no una enfermedad como tal. **No todos los pacientes con hiperuricemia van a desarrollar gota, de hecho, solo un 20-30% de pacientes con niveles de ácido úrico elevado en sangre desarrollarán gota.**

¿Cuáles son las causas que la producen?

La gota se puede producir por una **disminución de la eliminación** por la orina del ácido úrico o por un **aumento de su producción**. Básicamente, una gota es **primaria** cuando es desencadenada por causas genéticas o bien por causas desconocidas mientras que la gota es **secundaria** cuando está relacionada con enfermedades o medicamentos que provocan un aumento de producción de ácido úrico o una disminución de su eliminación, generalmente por los riñones. Si quiere ampliar esta información puede ir al anexo 1 donde se ven las distintas causas que se engloban dentro de estos grupos generales.

¿Cuáles son los síntomas?

Los síntomas de la gota se manifiestan generalmente en las articulaciones (artritis), los tendones (tendinitis) y algunas bolsas que rodean las articulaciones (bursitis). En estos tejidos, la gota produce **inflamación rápida e intensa**, que suele ser muy dolorosa y puede ser invalidante. La articulación afectada aumenta de tamaño, puede ponerse roja y caliente (especialmente las articulaciones de las manos o los pies) y debido





al **dolor** no se puede mover de forma normal. A veces la zona inflamada está tan sensible que el simple roce puede provocar molestias.

Los episodios de inflamación son más habituales en los miembros inferiores, sobre todo en el primer dedo del pie (lo que se denomina clínicamente **podagra**), así como en los tobillos, los empeines de los pies y las rodillas. Lo más habitual es que sean episodios que afectan a una sola articulación, aunque cuando la gota tiene más tiempo de evolución estos ataques pueden ser más aparatosos, apareciendo en varias articulaciones a la vez y provocando un estado de malestar general que puede asociarse con fiebre. Los episodios al inicio son aislados y muchas veces limitados en el tiempo; pero si la gota no se trata adecuadamente los brotes puede presentarse de una manera más frecuente, más intensa y de más duración. Además de las articulaciones, los tendones, las bolsas de las articulaciones e incluso la piel de alrededor pueden verse afectados por la inflamación.

Los pacientes con gota a los que no se les aplica un tratamiento adecuado pueden desarrollar acúmulos de cristales de urato (la sal del ácido úrico) en forma de nódulos en diferentes tejidos que se denominan **tofos**. Cuando esto ocurre, la gota se denomina tofácea y puede producir lesiones de los huesos y las articulaciones (gota erosiva o artropatía gotosa).

¿Qué articulaciones pueden verse afectadas?

Prácticamente cualquier articulación del cuerpo puede verse afectada por la gota. Lo más fre-





cuente, como ya hemos dicho, es que afecte a los miembros inferiores, siendo la **podagra**, la inflamación de la primera metatarsofalángica del dedo gordo del pie, la más característica. La afectación en miembros superiores es más habitual en gotas avanzadas, aunque hay subgrupos de pacientes, como las mujeres postmenopáusicas, que pueden tener la primera manifestación de la enfermedad en articulaciones de las manos. La afectación en codos es muy frecuente, sobre todo en gotas tofáceas.

La gota sin un control médico adecuado puede llegar a ser una enfermedad que destruye las articulaciones.

¿Afecta a otros órganos del cuerpo además de a las articulaciones?

Como se ha comentado previamente, la gota es una enfermedad que afecta a diversas partes del cuerpo. A día de hoy la gota se considera como una enfermedad inflamatoria, que al igual que ocurre con otras enfermedades reumatológicas como la Artritis Reumatoide incrementa el riesgo cardiovascular y favorece que se puedan sufrir con más frecuencia de lo esperado **infar**tos de miocardio o cerebrales. En este sentido tanto el ácido úrico elevado como la gota clínica están relacionados con el llamado síndro**me metabólico** (conjunto de factores de riesgo para la aparición de diabetes y enfermedad cardiovascular formado por obesidad abdominal, triglicéridos altos, colesterol tipo HDL bajo, diabetes e hipertensión arterial). Esta relación con las enfermedades cardiovasculares refuerza la importancia del tratamiento y el seguimiento de los pacientes con gota, más allá de sus posibles complicaciones puramente articulares.

Otro de los aspectos a tener en cuenta es la relación de la gota con el riñón. Además de por sus efectos nocivos ya comentados a nivel circulatorio, puede asociarse a mayor frecuencia de enfermedad renal; además, los antiinflamatorios que generalmente se autoadministran de forma recurrente para tratar los ataques de gota pueden dañar a largo plazo los riñones.

¿Cómo se diagnostica?

El diagnóstico de certeza de la gota se hace mediante el estudio al microscopio del líquido articular extraído de alguna articulación afectada por la enfermedad. Esto habitualmente se hace en la articulación que presenta inflamación, pero en ocasiones puede ser útil sacar líquido de una articulación que no presente síntomas. En este análisis se observan cristales de urato dentro de células blancas (neutrófilos).





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En ocasiones, una valoración clínica (síntomas, signos o lo que se llama una historia natural) muy típica y algunas otras pruebas complementarias, como la ecografía o la radiografía simple, pueden ayudar a hacer un diagnóstico muy aproximado para empezar el tratamiento sin necesidad de extraer líquido articular.





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¿ A qué médico se debe consultar?

Habitualmente, la mayor experiencia clínica a la hora de abordar la gota reside en los **especialistas en Reumatología**. La colaboración con los médicos de familia y con otras especialidades afines como los especialistas en riñón (nefrólogos y urólogos) juega un papel importante en el manejo diario de los pacientes con gota.

¿Puede heredarse la gota?

El riesgo de que un paciente pueda desarrollar gota es un complejo conjunto de características (sexo, edad, raza, estilo de vida) en el que la herencia es un componente más. Se conocen alteraciones genéticas que predisponen a la hiperuricemia que se describen en la tabla 1 del anexo. Un estudio reciente ha mostrado que hijos de pacientes con gota pueden tener mayor predisposición a presentar depósitos de ácido úrico.



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03 Tratamiento y seguimiento de la gota

El objetivo del tratamiento en la gota es reducir el nivel de ácido úrico en sangre para disolver los depósitos de cristales de urato formados en los tejidos y así prevenir los ataques de gota y evitar que se produzcan a largo plazo daños irreparables en las articulaciones. El tratamiento variará en cada paciente dependiendo de la intensidad y extensión de las articulaciones inflamadas y del motivo por el que se ha producido el aumento del ácido úrico.

¿Cómo manejar los ataques agudos?

Los ataques de gota se suelen manejar con colchicina y antiinflamatorios, empleados durante varios días, hasta la resolución del dolor y la hinchazón. Los antiinflamatorios, ya sean los tradicionales (naproxeno, ibuprofeno, indometacina, diclofenaco, etc.) o los inhibidores de COX-2 (etoricoxib, celecoxib) deben intentar evitarse en enfermos con enfermedad renal y/o cardiovascular significativa, o al menos tratar siempre de minimizar el tiempo de uso para evitar efectos secundarios.

La colchicina es uno de los tratamientos más usados para los ataques agudos y se emplea también como preventivo cuando se inician fármacos que bajan el ácido úrico, a veces duran-




te muchos meses, siempre que se tolere bien. Aunque actualmente las dosis que se emplean son bajas y tiene buena seguridad cardiovascular, en algunos enfermos renales se tiene que reducir o evitar el uso de colchicina.

En ciertos casos es necesario emplear esteroides (derivados de la cortisona) para reducir la inflamación articular, aunque no conviene abusar de ellos, porque pueden agravar la gota a largo plazo y producir efectos adversos. Como a la hora de introducir cualquier medicamento, se ha de tener en cuenta posibles interacciones con otros tratamientos del enfermo y seguir las recomendaciones dadas por el médico dependiendo de cada caso particular.



En los ataques de gota, aparte del tratamiento farmacológico, también suele resultar beneficioso colocar la pierna o el pie en alto (caso de que la articulación inflamada se localice en miembro inferior), así como aplicar frío local en la zona afectada (varias veces al día durante varios minutos), además de guardar un reposo relativo y beber abundante agua. No suele ser necesario vendar la articulación o zona afecta

¿Cuáles son las opciones de tratamiento crónico de la gota?

Actualmente hay diferentes medicaciones muy eficaces para reducir los niveles de ácido úrico en sangre que evitan su acumulación en los tejidos y favorecen que los depósitos ya existentes se disuelvan. Hay cuatro medicamentos que reducen el nivel de ácido úrico en la sangre: el alopurinol, el febuxostat, el lesinurad y la benzobromarona. Los dos primeros reducen la formación de ácido úrico y los dos últimos ayudan a que el riñón elimine mejor el mismo. Lesinurad en combinación o benzobromarona son alternativas cuando con alopurinol o febuxostat no se consigue bajar lo suficiente el ácido úrico o disolver los tofos.



Su reumatólogo decidirá el tratamiento farmacológico más adecuado para usted. Como en otras enfermedades, suele empezarse por una dosis baja, subiéndola de forma progresiva según tolere y necesite el enfermo. El objetivo será alcanzar un ácido úrico en sangre por debajo de 5-6 mg/dl (en algunos pacientes más bajo aún) a fin de evitar los ataques de gota y hacer desaparecer los acúmulos de cristales de urato de las articulaciones y otros tejidos (como los tofos palpables debajo de la piel). Como con todos los medicamentos, los utilizados para bajar el ácido úrico pueden causar efectos secundarios que el paciente y el médico deben vigilar, aunque suelen ser poco frecuentes y casi siempre tolerables. En aquellos pacientes con gota grave o resistente en que se hace necesario combinar lesinurad o benzobromarona con alopurinol o febuxostat, los controles analíticos y clínicos suelen ser más frecuentes, sobre todo al inicio, por la seguridad del enfermo. En caso de cualquier duda o evento adverso es recomendable ponerlo en conocimiento del médico para registrarlo y solucionarlo.

A pesar de un tratamiento adecuado, al empezar con cualquiera de estos medicamentos para la gota el enfermo puede sufrir, aunque solo inicialmente, un ataque de inflamación articular. **Es importante no considerar esto un fracaso y abandonar el tratamiento.** Para evitarlo o minimizarlo (prevención de brotes), suele recetarse durante varios meses colchicina o algún antiinflamatorio a baja dosis. Esto hace que el paciente tenga menos problemas al empezar a tratar su enfermedad y contribuye a que no retire la medicación necesaria para curarse (el cumplimiento del tratamiento es fundamental).

Realizando bien el tratamiento y siendo persistente, los brotes de gota acaban desapareciendo, el ácido úrico baja en sangre, los acúmulos de cristales se disuelven y el paciente se cura.

¿Cómo bajar el ácido úrico en sangre?

El ácido úrico en sangre se puede conseguir bajar por medio de dos mecanismos, que incluso pueden combinarse (el médico decidirá en cada caso particular cuál emplear):

• "Cerrar el grifo de entrada": rebajando o moderando el aporte de alimentos ricos en purinas (que derivan posteriormente en ácido úrico al ser metabolizadas) y, sobre todo, mediante fármacos (inhibidores de la xantina oxidasa) que disminuyan la formación de ácido úrico en nuestro organismo. Así funcionan el alopurinol y el febuxostat.

• **"Abrir el grifo de salida"**: aumentando la eliminación de ácido úrico por el riñón mediante medicamentos como el lesinurad o la benzobromarona.

¿Qué efectos secundarios pueden tener los tratamientos farmacológicos?

Generalmente los tratamientos son bien tolerados, pero los medicamentos para la gota, como cualquier fármaco, pueden tener efectos secundarios. Dependerá de la dosis empleada, así como de otros factores individuales (genéticos, étnicos, edad, enfermedades y tratamientos asociados, etc.).

Fundamentalmente han de vigilarse tres cosas:

• **Tolerancia digestiva**: comprobar si el tratamiento produce alguna molestia abdominal, diarrea o alteración analítica del perfil hepático (transaminasas). • **Tolerancia renal:** tanto a nivel de analítica (creatinina u otros parámetros de función renal), como a nivel de cólicos renales (por cálculos o piedras de ácido úrico).

• **Tolerancia cutánea**: picor, erupciones o cualquier otra lesión cutánea de tipo alérgico.

Para minimizar los riesgos, suele aconsejarse empezar a dosis baja la medicación que reduce el ácido úrico en sangre (alopurinol o febuxostat), subiendo después poco a poco la misma si el enfermo y su analítica muestran una buena tolerancia. Como ya se ha comentado, para minimizar la posibilidad de ataques de gota al disolver los depósitos de cristales con medicamentos como alopurinol o febuxostat es conveniente añadir los primeros meses colchicina o algún otro medicamento antiinflamatorio.





¿Cuánto tiempo debe mantenerse el tratamiento? ¿Cuál es el objetivo?

El tiempo que un paciente ha de recibir un tratamiento para bajar el ácido úrico es muy variable, ya que depende del tipo y gravedad de su gota, de la duración de esta, de la cuantía o volumen total del depósito de cristales de urato en su organismo, etc.

Por lo general, el tratamiento dura varios años, pues la disolución de los cristales de urato es lenta. Sin embargo, la mejoría en los síntomas suele ser rápida. El paciente debe tomarse con disciplina la medicación, seguir una serie de consejos y recomendaciones, e intentar llevar una vida saludable. Se recomienda el empleo de medicamentos siempre que se necesiten para mantener el ácido úrico < 6 mg/dl a largo plazo; en caso contrario, la gota reaparecerá.

Para dejar de padecer ataques, disminuir las secuelas articulares, renales o cardiovasculares, y curar definitivamente la enfermedad han de disolverse los depósitos de cristales de urato. El **objetivo clínico** de la curación se puede alcanzar si se consigue el **objetivo analítico:** lograr niveles de ácido úrico en sangre **inferiores a 6 mg/dl** (incluso inferiores a 5 mg/dl en gotas graves o con tofos). Si se consigue reducir el ácido úrico en sangre a valores bajos no sólo se impedirá que siga acumulándose cristal, sino también que se disuelva el que ya está formado o depositado, para así lograr la curación.

Una vez que han desaparecido los tofos y que el paciente lleva años sin ataques, con niveles bajos



de ácido úrico en sangre, se puede intentar bajar la dosis de la medicación (e incluso en algunos suspenderse), tratando de que la uricemia no suba a más de 7 mg/dl. Algunos enfermos necesitan medicación toda la vida; otros, en cambio, no. La genética y otros factores son importantes, pero en cualquier paciente es posible la disolución de los depósitos cristalinos.

Medicamentos para otras enfermedades que pueden resultar perjudiciales o beneficiosos para el control del ácido úrico.

Algunos fármacos pueden resultar beneficiosos, como el losartán (medicamento usado en hipertensión arterial), simvastatina, atorvastatina y fenofibrato (empleados para bajar los lípidos), o la leflunomida (inmunomodulador); aunque no están aprobados específicamente para el tratamiento de la gota, sino para el de otras enfermedades.

Sin embargo, otros medicamentos afectan negativamente a la eliminación renal del ácido úrico, como es el caso de los diuréticos (furosemida, hidroclorotiazida, etc.), muy empleados en hipertensión arterial y otras enfermedades cardiovasculares y renales. También pueden resultar perjudiciales los salicilatos, la ciclosporina, algunos antiparkinsonianos y ciertas quimioterapias. No obstante, no siempre es recomendable suspenderlos, ya que eso puede poner en peligro su salud.

¿Puede uno curarse sin medicamentos?

Si un paciente no recibe tratamiento adecuado, principalmente con medicamentos, el objetivo de conseguir un nivel de ácido úrico en sangre lo más bajo posible (siempre por debajo de 5-6mg/dL) será difícilmente alcanzable. Cuando se consiguen eliminar completamente los depósitos de ácido úrico del organismo, el uso de medicamentos puede reducirse y en casos muy concretos eliminarse. En ese momento las medidas no farmacológicas seguirán teniendo su importancia para evitar volver a desarrollar depósitos de cristales de urato.

¿Cuál es la evolución de los pacientes con gota?

La gota, si se deja evolucionar libremente, nunca suele ir a mejor, sino a peor. El depósito de cristales de urato en las articulaciones y en otras localizaciones va en aumento con el tiempo, de forma que cada año existe más daño acumulado y más ataques (más numerosos, en más articulaciones y más agresivos cada vez). Por el contrario, si la gota se trata, el depósito disminuye y así lo hacen los síntomas y el daño global.

¿Puede llegar a curarse la enfermedad?

Sí, si el tratamiento se hace con la intensidad y la disciplina requeridas durante el tiempo necesario. La práctica totalidad de los enfermos ve cómo se reducen e incluso remiten los síntomas cuando lleva varios meses con el tratamiento adecuado.

¿La enfermedad puede dejar secuelas?

En efecto, la gota puede deformar las articulaciones causando cojera, deformidad de las articulaciones de las manos e incluso amputaciones, pero también puede afectar a otros sistemas como el urinario (cálculos y deterioro del filtrado del riñón) o el cardiovascular (aterosclerosis prematura). Todas las secuelas pueden minimizarse o incluso impedirse si se introduce un tratamiento lo antes posible y durante el tiempo pertinente en cada caso.



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04 Vivir con Gota

¿Qué debo tener en cuenta cuando acuda al centro de salud o si voy al hospital?

Para el adecuado control de la gota es importante seguir las recomendaciones de los profesionales sanitarios (reumatólogos y médicos de familia) que le ayudarán al cumplimiento tanto de los tratamientos como de las medidas relacionadas con el estilo de vida. En el ámbito ambulatorio el médico de familia puede aportar información sobre el objetivo de control del ácido úrico en sangre y llevar a cabo analíticas



tanto para esto como para valorar los posibles efectos secundarios de la medicación. También puede facilitar orientación dietética y de estilo de vida. En las consultas hospitalarias, principalmente en reumatología, se pueden resolver todas las dudas acerca de síntomas habituales. tiempo de duración de cada tratamiento, expectativas a corto, medio y largo plazo, así como posibles complicaciones derivadas tanto de la enfermedad como de los tratamientos. En este sentido, puede ser muy útil preparar todas estas dudas antes de la consulta para exponérselas luego al médico, o preparar incluso una lista de cuestiones que le vayan surgiendo a lo largo del seguimiento para aclararlas durante la consulta médica. También es posible que desee que le acompañe un familiar o un amigo. A veces es difícil recordar todo o que se le olvide contestar algo referido a algunas de estas preguntas y así su acompañante puede completar la información que a usted se le haya pasado.

No tenga reparo en preguntar por aquellas cuestiones que no le han quedado claras, o comente que le expliquen las cosas en un lenguaje sencillo y comprensible. También puede tomar notas o solicitar alguna información por escrito.

¿Qué consejos sobre cuidados en la vida diaria debo seguir?

La siguiente información puede ayudarle a controlar la gota y a mejorar su calidad de vida.

Reposo o ejercicio

Hay que saber elegir el momento adecuado para añadir el deporte como medida no farma-

Antes de su cita médica con el especialista prepare brevemente lo que quiere decir o consultar. En su primera visita al reumatólogo es conveniente que, de antemano, prepare algunas respuestas a posibles preguntas que le van a realizar y que van a ser importantes para su diagnóstico y tratamiento, como:

¿Qué tipos de síntomas tiene? ¿Cuándo empezaron? ¿Qué articulaciones se nota dolorosas o limitadas? ¿Hay alguna actividad o posiciones que hacen que sus síntomas mejoren o empeoren? ¿Alguno de sus familiares cercanos (padres, hijos, hermanos) tiene problemas articulares? ¿Qué medicamentos toma usted? ¿Ha probado ya algún tratamiento para reducir el ácido úrico o para tratar la gota? ¿Ha sido eficaz alguno de ellos? Se puede vivir bien con gota. Cuando la persona logra controlar la enfermedad pueden mejorar sus síntomas y su calidad de vida. Lo más importante es seguir las recomendaciones farmacológicas, los controles habituales en las consultas de Reumatología y Atención Primaria y evitar situaciones de estrés. Los siguientes consejos le pueden ayudar, pero en ningún caso podrán sustituir a los medicamentos que se le recomiendan en consulta. cológica en relación con la gota. En el momento agudo, por ejemplo, cuando la articulación está inflamada, se recomienda no realizar ejercicio y mantener en reposo dicha articulación. Una vez que el mencionado cuadro inflamatorio esté resuelto, usted podrá incorporarse a su ritmo habitual de vida. Y en este ritmo habitual será fundamental añadir el deporte, principalmente para evitar la obesidad como factor cardiovascular y como un culpable más de la elevación de ácido úrico en sangre. Lo más adecuado será realizar un ejercicio monitorizado que le ayude a mantener su peso ideal, como puede ser la carrera continua, evitando el asfalto, la bicicleta estática o la natación.



Alimentación: comida y dieta

Hay que tener en cuenta que las medidas dietéticas en la gota tienen un papel modesto en el control del ácido úrico, pero puede ayudar a que la enfermedad tenga una mejor evolución. Efectivamente, hay alimentos que son más ricos en ácido úrico (purinas de origen animal) y que se deben que tomar con moderación. Las carnes rojas, las vísceras, el marisco, las bebidas alcohólicas (incluida la cerveza sin alcohol) y las bebidas con azúcares pueden hacer que los niveles de ácido úrico en sangre suban y que pueda tener nuevos ataques de gota. Pero si se hace un consumo moderado de estos alimentos en su cantidad y en su frecuencia, se puede llevar una dieta equilibrada y completa.

En relación a las purinas de origen vegetal, sigue habiendo muchos falsos mitos, pero no hay investigaciones suficientes que coincidan en que hay que restringir dichos alimentos. Algunos estudios sugieren que el bajo contenido de purinas en estos alimentos hace que no tengan prácticamente impacto en los niveles de ácido úrico en sangre, ni en un posible aumento en los episodios agudos de gota. Ni siquiera en vegetales con un contenido más elevado de purinas como la soja, que están teniendo además un repunte



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de consumo por el mayor número de personas que optan por una alimentación vegetariana o vegana. Por lo tanto, alimentos tradicionalmente proscritos como el tomate, las espinacas, las acelgas, la coliflor o las judías podrán ser tomadas de manera habitual sin peligro de empeorar de manera determinante los niveles de ácido úrico o la clínica articular aguda. Si necesita ampliar esta información puede consultar al anexo 2 donde se recoge gráficamente la pirámide con las recomendaciones alimentarias para pacientes con gota.



Si el paciente cumple el tratamiento farmacológico y las visitas habituales con su médico, la dieta será mucho más flexible de lo que realmente se ha creído tradicionalmente. Hay dos conceptos fundamentales en relación con los alimentos: **la cantidad y la periodicidad.** Un paciente **con un adecuado nivel de ácido úrico en sangre podrá hacer una vida prácticamente normal,** si evita consumir excesivas cantidades de los alimentos más ricos en purinas. El consumo de carnes rojas, mariscos, vísceras, cerveza (con y sin alcohol) y otros alimentos (bebidas con alto contenido de azúcar, p.ej.) aumentan las cifras de ácido úrico. Mientras que otros alimentos como son las frutas, las verduras o el pescado azul ayudan a la disminución del ácido úrico por lo que deben de ser priorizadas en la alimentación diaria.

Hidratación

Es importante asegurar un adecuado consu**mo de líquidos**, especialmente agua o zumos ricos en vitamina C que facilitan la eliminación del ácido úrico por la orina. En momentos especialmente delicados como el verano esto debe hacerse con mayor hincapié, ya que no es raro que aumenten los ataques de gota durante estas fechas al existir insuficiente hidratación y una mayor pérdida de líquidos. El consumo medio de agua debe ser de unos dos litros, aumentándolo ligeramente en verano o en pacientes con cálculos renales. Hay que tener en cuenta, de todos modos, que algunos pacientes con patología renal pueden tener restringida la toma de líquidos, por lo que en estos casos es fundamental tener una recomendación personalizada del especialista en este sentido.

Dejar de fumar

El tabaco no ha demostrado una relación directa con los niveles de ácido úrico en sangre ni con el aumento de ataques de gota. Pero teniendo en cuenta la relación directa de la gota con los **factores de riesgo cardiovascular**, es recomendable que los pacientes con gota abandonen el





hábito tabáquico. Además, el tabaco está relacionado estadísticamente con un mayor consumo de alcohol, lo que también tendrá, como se explica a continuación, un efecto negativo en la evolución de la gota.

Dejar de consumir alcohol

Evitar el consumo excesivo de alcohol es uno de los mayores retos en los pacientes con gota. La **relación del alcohol con el empeoramiento tanto de los síntomas como de los niveles de ácido úrico está bien demostrada**. Más de la mitad de los pacientes con gota beben alcohol en exceso. El alcohol provoca que el ácido úrico se elimine peor en el riñón y además es capaz de hacer que se cree más ácido úrico en el propio organismo.

No todos los tipos de bebidas alcohólicas tienen la misma influencia en la gota. La cerveza es quizá la más perjudicial, no solo por su contenido en alcohol, sino por sí misma, por su alto contenido en purinas, por lo que hay que limitar su consumo incluso en las presentaciones sin alcohol. Los combinados o bebidas llamadas "espirituosas": ron, ginebra, whiskey, etc., también tienen un impacto negativo en la gota, pero menor que el de la cerveza. Por el contrario, el vino no ha demostrado que sea perjudicial (ni tampoco beneficioso) para la gota.

El consumo de alcohol está fuertemente arraigado en nuestra sociedad, en nuestra forma de relacionarnos con los demás y de celebrar cualquier evento, por lo que



una prohibición absoluta difícilmente va a ser eficaz. Si usted cumple su tratamiento farmacológico y sus visitas médicas periódicas y mantiene un adecuado nivel de ácido úrico en sangre, podrá tomar de vez en cuando (y en cantidades moderadas) cualquier tipo de alcohol sin grandes perjuicios para su enfermedad.

Entorno familiar y laboral

La gota repercute no sólo en quien la padece, sino también en su entorno. Aunque históricamente es una enfermedad con "mala fama" y se tendía a culpar al paciente de padecerla, la realidad es que se trata de una enfermedad que puede resultar muy incapacitante, impidiendo la realización de las tareas cotidianas, preocupando e implicando muchas veces a familiares y amigos.

Puede producir dolor muy intenso y cojera, además de deformidades y/o limitaciones articulares crónicas de diferente tipo si se deja sin tratar, lo que puede impedir o afectar la actividad profesional. Es responsable de muchas bajas laborales en nuestro país y en el resto del mundo

Además, el paciente suele acabar temiendo el efecto desencadenante de ataque de gota de ciertas comidas y bebidas, de desplazamientos o viajes largos, o de la práctica de deporte, etc.; lo cual limita su vida social y recreativa.

Las repercusiones físicas y emocionales de la gota son distintas en cada paciente y dependen

de la gravedad de la enfermedad, de su actitud ante la misma, de la disposición para intentar adaptarse a su vida cotidiana y del apoyo de su entorno.

Sus amigos y familiares pueden ayudarle con apoyo emocional, comprendiendo y aceptando sus limitaciones y prestándole ayuda física si la necesita.

En cuanto a su actividad laboral, asesórese sobre sus derechos y las opciones para adaptar su puesto de trabajo a sus necesidades.

Estados de ánimo

Si se la deja evolucionar, la gota puede deformar articulaciones por inflamación y erosiones, así como por el propio depósito de urato, muchas veces visible bajo la piel en zonas como pies, rodillas, codos o manos.



Esto, igual que pueda suceder con enfermedades cutáneas como la psoriasis, tiene impacto en la imagen corporal de la persona e influye, por tanto, en su estado anímico. De hecho, numerosos trabajos de investigación han demostrado la relación entre la gota, la depresión y la merma en la calidad de vida.

El tratamiento de la gota puede revertir todo esto, haciendo que los depósitos de cristales disminuyan progresivamente, desapareciendo poco a poco la inflamación y las deformidades, mejorando también la movilidad articular y el dolor. Si la gota mejora, la calidad de vida y el ánimo del paciente mejoran al mismo tiempo, lo cual refuerza positivamente el esfuerzo por intentar alcanzar la curación.

Aprenda a afrontar su enfermedad. Los pensamientos positivos pueden ayudarle a mejorar el estado de ánimo.

Controles clínicos

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Si la enfermedad no está bien controlada se pierden más oportunidades de que tenga una buena evolución. Para que la gota no se convierta en una enfermedad deformante, desde el punto de vista de las articulaciones, y grave, desde el punto de vista de ciertas complicaciones, como las cardiovasculares y renales, lo más importante será un buen seguimiento médico y cumplir adecuadamente el tratamiento. Por esto es importante confiar en su médico.

Al principio, los controles clínicos deberían ser más a menudo para poder aclarar cuestiones como:

- Las características de la enfermedad.
- Posibles complicaciones si no se hacen bien las cosas.
- Posibles tratamientos con todos sus pros y contras.

También hay que definir bien cuál es el objetivo a alcanzar con el tratamiento. Para conseguirlo habrá que tener un control más estrecho porque habrá que ajustar las medidas farmacológicas y no farmacológicas. Cada paciente necesita un control individualizado y no se pueden hacer recomendaciones absolutas; pero una vez se vayan consiguiendo los objetivos, las visitas y las pruebas complementarias se podrán ir espaciando con el fin de realizar un mantenimiento adecuado.

Si durante el inicio del tratamiento presenta efectos secundarios, principalmente cutáneos, tendrá que informar inmediatamente a su médico para aclarar qué está pasando, ya que, aunque raros, pueden ser el inicio de cuadros clínicos graves. Una vez conseguida la dosis efectiva concreta del tratamiento, las visitas se espaciarán en el tiempo, necesitando controles cada tres o seis meses, y más adelante incluso anuales.

Acuda a las revisiones. Realice los análisis y pruebas que se le indiquen. Aproveche para consultar a su médico las dudas que tenga sobre la enfermedad o su tratamiento.

MANEJO DE POSIBLES COMPLICACIONES

Precauciones en cirugías y/o ingresos hospitalarios

Si una persona con gota acude con una o varias articulaciones inflamadas a Urgencias debe comunicar al médico que allí le atienda que padece gota, haya o no haya tenido previamente esas mismas articulaciones inflamadas, pues puede tratarse de un ataque de su enfermedad. Asimismo, durante el ataque **no** se debe suspender los medicamentos que bajan el ácido úrico, como alopurinol, febuxostat, benzobromarona o lesinurad.

Por otro lado, cuando deba ser ingresado en el hospital por otro motivo o someterse a una operación quirúrgica, debe advertirlo a los médicos responsables para que tenga en cuenta la gota y su tratamiento habitual.

En los ingresos hospitalarios puede haber ciertos factores que desencadenen o empeoren la gota: estrés, desajuste de los líquidos del organismo, introducción de medicamentos que produzcan elevación de ácido úrico, etc. Es fundamental, como en otras patologías, que como paciente con gota no suspenda su medicación durante el ingreso o el perioperatorio, salvo que sea mandatorio.

Si existe algún tipo de duda antes de una cirugía programada, el anestesista o usted mismo pueden consultar con el reumatólogo para resolverla.

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Enfermedades relacionadas con la gota

Numerosas enfermedades se asocian frecuentemente con la gota: hipertensión arterial, dislipemia (hipercolesterolemia, hipertrigliceridemia), resistencia a la insulina o diabetes, obesidad, hígado graso, enfermedad renal crónica, cardiopatía isquémica, enfermedad cerebrovascular... Muchos de estos componentes se retroalimentan entre sí, dando lugar muchas veces al llamado síndrome metabólico.

Manejo de riesgo cardiovascular en pacientes con gota

El enfermo con gota es un paciente con importante riesgo cardiovascular y este a veces se subestima.

Es importante tratar de controlar los factores de riesgo tradicionales de riesgo cardiovascular; reduciendo el consumo de alcohol y eliminando el del tabaco, cuidar el peso corporal, practicar actividad física, vigilar la tensión arterial y los niveles de lípidos y glucosa en sangre y mantener una correcta ingesta de líquidos. Asimismo, hay que reducir, en la medida de lo posible, la toma de antiinflamatorios; limitar o disminuir la dosis de medicamentos que suben el ácido úrico (diuréticos como furosemida o hidroclorotiazida, por ejemplo), y favorecer el uso de medicaciones seguras o que bajen los niveles de úrico en sangre (losartán, atorvastatina, etc.).

En muchas ocasiones se hace necesaria la colaboración entre diferentes especialistas para que el manejo del riesgo cardiovascular sea el adecuado. Los expertos en Reumatología, Cardiología, Nefrología, Endocrinología y Medicina de Familia son importantes en el abordaje integral del paciente con gota.

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05 Más información y recursos adicionales

¿Dónde puedo aprender más sobre la gota?

Para cualquier duda, debe de consultar con su reumatólogo o médico de familia.

Por lo que respecta a las asociaciones de pacientes, no existe como tal una específica de pacientes gota, pero sí puede obtenerse información en LIRE (Liga Reumatológica Española) y Conartritis (Coordinadora Nacional de Artritis, que disponen de página web propia y presencia en redes sociales con cuenta de Twitter.

También hay información complementaria en diferentes páginas de internet. Por otro, lado, periódicamente se realizan campañas poblacionales de información y concienciación sobre la enfermedad, como la iniciativa "No des pie a la gota" o "Un paso más en gota".

Recursos de internet

Sociedad Española de Reumatología. https://inforeuma.com/enfermedades-reumaticas/ gota/

Vídeos

https://www.youtube.com/watch?v=n2Y0mYNAa44

https://www.youtube.com/watch?v=iMg3avVAbSI

https://www.youtube.com/watch?v=mpiqQTOx6WY

Términos médicos

• Ácido úrico: El ácido úrico es un compuesto orgánico formado por carbono, nitrógeno, oxígeno e hidrógeno que se forma cuando el cuerpo descompone sustancias llamadas purinas.

• Alopurinol: medicamento para la gota que reduce el ácido úrico en sangre impidiendo la formación de este y promoviendo la disolución de los cristales de urato.

• Artritis: es la inflamación de una o más articulaciones. Una articulación es la zona donde dos huesos se encuentran.

• Benzobromarona: medicamento que desciende los niveles de úrico en sangre favoreciendo la eliminación por el riñón. Promueve también la disolución de los depósitos cristalinos.

• Bursitis: es la inflamación de la bursa. Una bursa es una bolsa pequeña llena de líquido que protege y amortigua los huesos y otras partes del cuerpo como los músculos, tendones o piel.

• Colchicina: medicamento con propiedades antiinflamatorias e inmunomoduladoras empleado habitualmente en el tratamiento de la gota, tanto para calmar el ataque agudo como para evitar nuevos ataques.

• Cristales de urato: cristales de una sal derivada del ácido úrico.

• Ecografía articular: técnica de imagen que ayuda al médico en el diagnóstico o seguimiento de la gota. Permite ver el depósito de cristales de ácido úrico y la inflamación secundaria a los mismos en muchos enfermos.

• Enfermedad sistémica: que afecta a diferentes sistemas o aparatos del organismo.

• Erosiones: lesiones en los huesos de las articulaciones en forma de mordisco debido a la inflamación causada por los cristales de ácido úrico.

• Excreción: eliminación de una sustancia de nuestro organismo por orina, heces, etc.

• Febuxostat: medicamento que reduce la concentración de ácido úrico en sangre impidiendo su formación. Promueve la disolución de los depósitos cristalinos de urato.

· Gonagra: afectación gotosa de la rodilla.

• Gota: enfermedad causada por depósito de cristales de ácido úrico en los tejidos, más frecuentemente en las articulaciones.

• Hipercolesterolemia: niveles de colesterol en sangre por encima de lo normal.

• Hipertrigliceridemia: niveles de triglicéridos en sangre por encima de lo normal.

 Hiperuricemia: niveles de ácido úrico en sangre elevados por encima de lo normal (>7 mg/dl; >6 mg/dl en mujeres).

• Infarto cerebral: sucede cuando el flujo de sangre a una parte del cerebro se detiene

 Infarto de miocardio: tipo de cardiopatía isquémica (IC), es decir una enfermedad provocada por el deterioro y la obstrucción de las arterias del corazón, provocando que el corazón no reciba suficiente sangre y la muerte de células cardíacas.

• Lesinurad: medicamento reductor de uricemia utilizado en el tratamiento de la gota. Favorece la eliminación renal de ácido úrico y ayuda a disolver los depósitos cristalinos.

• Líquido articular: fluido presente habitualmente en las articulaciones de forma fisiológica o normal. Puede hacerse patológico o excesivo (derrame) cuando la articulación se irrita o inflama, como en la gota.

• Podagra: inflamación de la primera articulación metatarsofalángica del primer dedo del pie debido a la gota.

• Primera metatarsofalángica: articulación que une el dedo gordo al resto del pie.

• Purinas: producto final del metabolismo de las proteínas de nuestro propio cuerpo y de las que provienen del exterior (alimentos y otros). Se degradan en nuestro organismo dando lugar al ácido úrico. • Quiragra: afectación gotosa de la mano o muñeca.

• Síndrome metabólico: grupo de trastornos que se presentan al mismo tiempo y aumentan el riesgo de enfermedad cardíaca, accidente cerebrovascular y diabetes tipo 2. Estos trastornos incluyen aumento de la presión arterial, niveles altos de azúcar en sangre, exceso de grasa corporal alrededor de la cintura y niveles anormales de colesterol o triglicéridos.

• Tendinitis: es la inflamación o irritación de un tendón. Un tendón es el tejido (o estructura fibrosa) que une el músculo al hueso

• Tofo: acúmulo, muchas veces visible bajo la piel, de numerosos cristales de ácido úrico rodeados de células inflamatorias y colágeno. Pueden aparecer en articulaciones, pero también en otras localizaciones superficiales o profundas del organismo.

• Urato o urato monosódico: sal de ácido úrico que cristaliza y se deposita en los tejidos cuando se supera el nivel de saturación en sangre.

• Úrico o ácido úrico: sustancia soluble derivada de las purinas cuyo exceso en sangre puede dar lugar a saturación y depósito en los tejidos en forma de cristales.

• Uricemia objetivo: nivel recomendado de ácido úrico en sangre para disolver los depósitos cristalinos de los tejidos y, por tanto, la curación de la gota. Actualmente es de <6 mg/dl (<5 mg/dl en gota tofácea o grave).

Anexo 1. Información avanzada sobre la Gota

TABLA 1. CAUSAS DE HIPERURICEMIA Y GOTA

HIPERURICEMIA PRIMARIA	HIPERPRODUCCIÓN ÁCIDO ÚRICO	HIPOEXCRECIÓN ÁCIDO ÚRICO
	Causa desconocida	Causa desconocida
	Déficit de hipoxantina-guani- na-fosforribosil-transferasa: *Síndrome Kelley-Seegmi- ller: déficit parcial. *Síndrome Lesch-Nyhan: déficit completo	Nefropatía familiar con hiperuricemia
	Déficit de fosfofructoaldo- lasa	
	Hiperactividad de fosforribo- sil-pirofosfato-sintetasa	
	Glucogenosis (tipos I, III, V y VIII)	
	HIPERPRODUCCIÓN ÁCIDO ÚRICO	HIPOEXCRECIÓN ÁCIDO ÚRICO
HIPERURICEMIA SECUNDARIA	Aporte exógeno por alimentación: *Alcohol *Alimentos ricos en purinas *Dieta hipercalórica Enfermedades con elevado recuento celular: *Psoriasis *Anemia hemolítica crónica *Enfermedades mieloprolife- rativas crónicas o agudas	Fármacos: *Diuréticos: sobre todo tiazidas, furosemida. *Salicilatos (dosis bajas) *Ciclosporina Insuficiencia renal crónica Otros: *Hipotiroidismo *Hiperparatiroidismo

Anexo 2. Recomendaciones alimentarias para los pacientes de Gota



EJERCICIO DIARIO Y CONTROL DEL PESO CORPORAL

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Aprendiendo a convivir con la **Gota**

Información para pacientes, familiares y cuidadores sobre la gota

La información contenida en este documento pretende ofrecer consejos y pautas prácticas y sencillas a personas que tienen gota, a sus familiares y cuidadores. Es una ayuda para conocer mejor la enfermedad y deeste modo aprender a cuidarse mejor y mejorar la calidad de vida. Les ayudará a complementar la información ofrecida por el equipo sanitario que les atienden.

También se recogen otros recursos, como asociaciones de pacientes y páginas disponibles en Internet, que les puedan ayudar igualmente con información adicional en el manejo de la gota.

Disponible en: www.ser.es





Appendix 3. Recommendations in the GuipClinGot 2013 guideline

Gold standard

Recommendation 3: In cases of arthritis of unknown origin, gout should be included in the differential diagnosis (LE 5; GR D; DA: 92%).

Assessment

Recommendation 9: In all patients with gout, both the aetiology and the mechanism inducing hyperuricemia must be assessed (LE 5; GR D; DA 92%).

Recommendation 10: In the first assessment of a patient with gout, a complete history should be taken, and a complete general and musculoskeletal physical examination should be performed (LE 5; GR D; DA 100%).

Recommendation 11: Special attention should be paid to cardiovascular risk factors, using any of the available risk estimation tools (LE 5; GR D; DA 92%).

Recommendation 12: The panel recommends to evaluate, in patients with gout, the magnitude of the attack and severity of the disease (LE 5; GR D; DA 92%).

Recommendation 14: Once the acute episode is overcome, the patient with gout should be studied by blood and urine analysis for determination of the following parameters: complete blood count, blood chemistry panel, liver and kidney functions, acute phase reactants and study of urinary uric acid clearance (LE 5; GR D; DA 100%).

Recommendation 15: Once urate-lowering treatment has been initiated, laboratory tests should be performed to verify the achievement of the therapeutic goal (serum uric acid levels <6 mg/dL), and to monitor possible comorbidities and drug toxicity (LE 5; GR D; DA 100%).

Treatment

Recommendation 45: Lifestyle changes should be suggested and, if necessary, drug treatment should be prescribed to reduce serum uric acid levels after diagnosis of gout, but taking into account patient characteristics and comorbidities (LE 5; GR D; DA 92%).

Recommendation 49: Urate-lowering treatment should be started from low doses, progressively stepping-up if necessary, until reaching effective doses to achieve a therapeutic serum uric acid level (LE 1b; GR A; DA 100%).

Recommendation 50: Currently, it is not possible to recommend one urate-lowering drug over another (LE 5; GR D; DA 80%).

Recommendation 51: The selection of the urate-lowering drug will be based on data regarding efficacy, safety and experience of the prescribing physician, the patient's clinical

profile – severity of illness and comorbidity – and indications, recommendations and restrictions described in each product's SmPC (LE 5; GR D; DA 91%).

Recommendation 52: It is advisable to begin urate-lowering treatment in patients who have not achieved the therapeutic goal of uric acid (<6 mg/dL) with dietary health measures (LE 5; GR D; DA 85%).

Recommendation 53: Treatment for the prevention of acute episodes of inflammation should always be prescribed unless contraindicated, at least during the first six months of uratelowering treatment (LE 2b; GR B; DA 100%).

Recommendation 54: Urate-lowering therapy should be maintained in the long term to achieve complete dissolution of the crystals and prevent recurrence of hyperuricaemia (LE 5; GR D; DA 100%).

Recommendation 55: There must be close monitoring both in terms of efficacy and safety when drugs are used for the treatment of gout (LE 5; GR D; DA 92%).

Recommendation 56: Evaluation of response to urate-lowering treatment may be made based on a number of variables, including: frequency of acute attacks, serum uric acid levels, presence and number of MSU crystals in synovial fluid, and number and size of tophi (LE 5; GR D; DA 91%).

Recommendation 58: NSAIDs are effective in acute gout attacks. Maximum dosage is recommended in the absence of contraindications and suspension as soon as the attack is resolved. Dose reduction can be assessed after the first 2-3 days of treatment if there is clinically significant improvement (LE 5; GR D; DA 83%).

Recommendation 59: In acute gout attacks, COXIBs can be considered an alternative to traditional NSAIDs in patients with high or medium gastrointestinal risk, administered with or without PPI, depending on the type of patient (LE 2a; GR B; DA 83%).

Recommendation 60: In acute gout attacks, corticosteroids are recommended for patients with contraindications to NSAIDs/COXIBs. They can be administered either by intraarticular injection in the case of monoarthritis, or systemically in cases with more extensive joint involvement (LE 2b; GR B; DA 100%).

Recommendation 61: The early use of low-dose colchicine is effective in controlling acute gout attacks and so it should be considered in these cases (LE 1b; GR A; DA 86%).

Recommendation 62: It is generally not advisable to combine two urate-lowering drugs with the same mechanism of action (NE5; GR D; DA 100%).

Recommendation 63: There are no robust studies on the safety or possible pharmacokinetic interactions of different combinations of urate-lowering drugs. Consequently, caution in prescribing and close monitoring of their safety is recommended (LE 4; GR C; DA 100%).

Recommendation 64: The AEMPS withdrew the authorization of drugs with allopurinol benzbromarone in a fixed dose combination for safety reasons. Therefore, if they are chosen, it is recommended to request authorization for their off-label prescription use (NE4; GR C; DA 70%).

Recommendation 65: From a clinical standpoint, the effect of fenofibrate and losartan is marginal, but both compounds could be useful in selected cases. Both probenecid and sulfinpyrazone are not available in Spain, so they must be requested as special drugs (LE 3a; GR C; DA 100%).

Recommendation 66: Canakinumab, rilonacept and anakinra may be effective in the treatment and prevention of acute episodes of inflammation. They could be considered in conditions other than those authorized – canakinumab and anakinra – or as a drug not licensed in Spain – rilonacept – in acute episodes of refractory inflammation or for prophylaxis when other approved therapeutic options cannot be used in patients with severe gout, specifically with chronic inflammation or very frequent acute episodes of inflammation (LE 1b; GR B; DA 78%).

Recommendation 67: Rasburicase may be an alternative for off-label use in patients unresponsive or intolerant to all approved urate-lowering compounds. Pegloticase could be requested for use as a drug not licensed in Spain (LE 4; GR C; DA 78%).

Gout and kidney failure

Recommendation 16: In patients with CKD, the use of oral colchicine can be assessed to reduce the severity of an acute attack, following SmPC specifications (LE 1b; GR A; DA 92%).

Recommendation 17: In patients with CKD, consider discontinuing statins while using colchicine (LE 3a; GR B; DA 70%).

Recommendation 18: In cases of CKD and diabetes, a therapeutic option for the treatment of acute gout may be colchicine rather than NSAIDs or corticosteroids (LE 3a; GR B; DA 75%).

Recommendation 19: In cases of CKD, note that corticotropin has similar indications and efficacy to corticosteroids in the treatment of acute gout attacks (LE 1b; GR A; DA 82%).

Recommendation 20: In patients with CKD and gout, NSAIDs are not recommended for the prevention of new attacks (LE 3a; GR B; DA 92%).

Recommendation 21: In patients with CKD and gout the use of colchicine for prophylaxis of new attacks can be assessed using the SmPC (LE 2b; GR B; DA 92%).

Recommendation 23: In patients with CKD, administering potassium citrate (30-80 mEq/day) helps keep urinary pH above 6 and dissolve renal calculi formed by uric acid (LE 3a; GR B; DA 70%).

Recommendation 26: The use of high permeability haemodialysis membranes with high clearance power could allow safe use of colchicine in patients with CKD, but we must remember that in Spain this indication is not reflected in its SmPC (LE 3a; GR B; DA 78%).

Recommendation 27: In haemodialysis patients who require prophylaxis of acute episodes, it would be advisable to use high permeability membranes and to prescribe a dose of 0.5-0.6 mg of colchicine after dialysis, but it must be noted that this is not approved in the current SmPC (LE 4; GR C; DA 78%).

Recommendation 33: If it is necessary to use colchicine in patients with kidney transplant and cyclosporine A, it is recommended to reduce the dose of colchicine to one-third in acute episodes and to one-fourth in prophylaxis (LE 2b; GR B; DA 77%).

Recommendation 34: In kidney transplant patients, corticosteroids may be a therapeutic option in the treatment of acute attacks (LE 3b; GR B; DA 90%).

Recommendation 35: In patients with kidney transplant, corticotropin is a potential therapeutic alternative for the treatment of acute attacks (LE 4; GR C; DA 70%).

Management in primary care

Recommendation 39: Although the gold standard for the diagnosis of gout is the visualization of crystals, in patients with typical symptoms such as intermittent arthritis with complete resolution at the first metatarsophalangeal joint (podagra) in the presence of prior hyperuricaemia, clinical diagnosis may be a reasonable alternative for the PC doctor up to definitive diagnosis (LE 5; GR D; DA 91%).

Recommendation 41: The choice of treatment will give special consideration to comorbidities and possible interactions with drugs used to treat them. During acute episodes of inflammation urate-lowering drugs should not be prescribed, suspended or changed in dose (LE 5; GR D; DA 100%).

Recommendation 42: Primary care should play a role in the assessment and management of comorbidities present in patients with gout (LE 5; GR D; DA 100%).

Recommendation 43: In primary care, low-dose aspirin for cardiovascular event prevention should not be suspended patients with gout (LE 5; GR D; DA 100%).

Recommendation 44: Primary care patients with gout and hypertension should be assessed for suspension of thiazide and loop diuretics and initiation of treatment with angiotensin receptor antagonists (especially losartan) or calcium channel blockers (LE 5; GR D; DA 100%).



Nursing perspective

Recommendation 37: The rheumatology nurse can provide the patient with a gout-specific education program, defined as a set of structured activities aimed at increasing the level of knowledge about the experience of being a patient with gout and promoting healthy lifestyles (LE 5; GR D; DA 93%).

Recommendation 38: The education program for patients with gout (individual or group) will address the following key issues: therapeutic target, diet and alcohol consumption, pain management, cardiovascular risk management, weight control, exercise, and information about the treatments prescribed in order to improve adherence and patient safety (LE 5; GR D; DA 86%).

LE: level of evidence; GR: grade of recommendation; DA: degree of agreement

GuipClinGot. Clinical practice guidelines for the management of gout. Spanish Society for Rheumatology. 2013. <u>https://www.ser.es/wp-</u> <u>content/uploads/2015/09/GuipClinGot_1140226_EN.pdf</u>.²⁹²


Appendix 4. Glossary and abbreviations

Glossary

Burden of disease: an indicator that allows us to measure the loss of health due to the fatal and non-fatal consequences of a disease (mortality and morbidity) in a population. It is measured in disability-adjusted life years (DALYs).

Case series: a type of study that describes a series of patients with a given disease or outcome.

Case-control study: a study that identifies people with a disease (cases), for example, lung cancer, and compares them with a group of people without the disease (controls). The relationship between one or various disease-related factors (for example, smoking) is assessed by comparing the rate of exposure to these or other factors between cases and controls.

Clinical practice guideline: a set of recommendations based on a systematic review of the evidence and the assessment of the risks and benefits of the options available, seeking to optimize the healthcare provided to patients.

Cohort study: a study that involves following up of one or more cohorts of individuals with different levels of exposure to a risk factor and assessing whether they develop the disease or condition of interest.

Confidence interval: the range in which the true magnitude of the effect (never accurately known) lies with a given level of certainty or confidence. It is common to talk about "a 95% confidence interval". This means that the true value of the study effect will lie in this interval in 95% of trials. Note: the confidence interval reflects the likelihood of random errors, but not of systematic errors (bias).

Cross-sectional descriptive study: a study that describes the rate of an event or exposure at a specific time (single measurement). Also called a prevalence study, it allows us to examine the relationship between a risk factor (or exposure) and an effect (or outcome) in a given population at a given time (cut-off point).

Discussion group: a qualitative research technique used for investigating attitudes, opinions, appraisals or perceptions among a group of individuals regarding something or someone.

Efficacy: the degree of beneficial effect of an intervention under ideal circumstances (vs. **effectiveness**: the degree of beneficial effect of an intervention under in real-world settings).

Heterogeneity: In the context of meta-analyses, heterogeneity refers to variability or differences between studies in the estimates of effects. It is important to differentiate between "statistical heterogeneity", that is, differences between the reported effects, and "clinical heterogeneity",

that is, differences between studies in the main characteristics of participants, interventions or outcome measures. Tests for statistical heterogeneity are used to assess whether the variability observed in results is greater than that which would be expected due to chance alone.

In-depth interview: a qualitative research technique to obtain data through a conversation between an informant who has pre-established characteristics and a skilled interviewer.

Indirect evidence: a type of information obtained when direct comparisons between the interventions of interest are not available, and when there are major differences between the studies available and the population, interventions or outcomes considered in the question of interest.

MEDLINE/PubMed: PubMed is a search engine that accesses the references and abstracts of the biomedical literature in the MEDLINE database maintained by the US National Library of Medicine.

Meta-analysis: a statistical approach that makes it possible to combine the results of different studies (diagnostic test studies, clinical trials, cohort studies, etc.) to evaluate the heterogeneity and obtain overall results. This term is also used to refer to systematic reviews that include meta-analysis.

Morbidity: having an illness or the symptoms of an illness or medical problems associated with a treatment or the amount of illness (incidence or prevalence) in a given population.

Mortality: the rate or proportion of people in a given population that die from a given disease in a given period of time.

National Institute for Health and Care Excellence: a public body in the United Kingdom that is independent of the National Health Service (NHS), whose role is to improve outcomes for people using the English and Welsh NHS and other public health and social care services by, among other activities, providing clinicians, public health and social care practitioners with access to the best available scientific evidence, in the form of clinical guidelines and advice concerning public health and healthcare technologies.

Odds ratio (OR): is a measure of the strength of association between two variables, e.g., an exposure and an outcome, and hence, serves as an indicator of the efficacy or effectiveness of a treatment. If the OR is 1, the effect of the treatment is not different from that observed in the control group. If the OR is above (or below) 1, the effect of treatment is higher (or lower) than that observed in the control group. It should be noted that the effect being measured may be negative (e.g., death or disability) or positive (e.g., smoking cessation).

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Open trial: 1. Clinical trial in which the researcher knows details about the intervention given to the participant. 2. Clinical trial with an open sequential design.

Placebo: an inactive substance or procedure administered to a participant, to compare its effects with those of the intervention under study. Placebo is used in clinical trials to blind participants to their treatment allocation. To ensure appropriate blinding, the placebo should not be distinguishable from the intervention substance or procedure.

Prevalence: the rate or proportion of people in a given population who have a given condition or finding at a given time.

Primary research: the type of research that collects original data. Primary studies are different from reviews or syntheses which are based on data from individual primary studies. They also differ from systematic reviews that summarise the results of a set of primary studies.

Qualitative research: a concept that covers a wide range of theoretical, methodological and technical approaches and is characterised by studying phenomena in their natural context, attempting to make sense of, or interpret, them based on the meanings people attach to them. To this end, it uses the types of empirical material (interviews, observations, texts, etc.) that may best describe both routine and problematic situations, and what they mean in the lives of individuals.

Randomised clinical trial: an experimental study in which participants are assigned randomly (at random) to a specific treatment or intervention among two or more possible options. One of the groups tends to receive the conventional treatment (control group), for comparison purposes, while the other group receives the treatment under study (experimental group). Both groups are monitored to assess any potential differences in outcomes.

Scottish Intercollegiate Guidelines Network (SIGN): A Scottish network of multidisciplinary groups that develop clinical practice guidelines containing recommendations based on the best available scientific evidence, as well as documents concerning the methods used to develop the guidelines.

Single- or double-blind trial: a clinical trial in which the participants (single blind) or neither the participants nor the clinicians involved (double blind) know which intervention each individual is receiving.

Systematic review: a summary of the evidence on a specific question gathering the results of relevant studies, using explicit and systematic methods for identifying, critically appraising and synthesising the scientific literature. It may or may not include a meta-analysis.

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Abbreviations

- ACP: American College of Physicians
- ACR: American College of Rheumatology
- AE: adverse events

AEMPS: Spanish Agency of Medicines and Medical Devices (Agencia Española del Medicamento

- y Productos Sanitarios)
- BSR: British Society for Rheumatology
- CHF: chronic heart failure
- CI: confidence interval
- CKD: chronic kidney disease
- COX-2: selective cyclooxygenase-2
- CPG: clinical practice guideline
- CVD: cardiovascular disease
- DALYs: disability-adjusted life years
- DDD: defined daily dose
- DECT: dual-energy computed tomography
- EMA: European Medicines Agency
- EPISER: Study on the prevalence of rheumatic disease in the adult population in Spain (*Estudio de prevalencia de las enfermedades reumáticas en población adulta en España*)
- EULAR: European League Against Rheumatism
- FDA: Food and Drug Administration
- FER: Foundation of the Spanish Society of Rheumatology (SER)
- GDG: guideline development group
- GFR: glomerular filtration rate
- GFR: glomerular filtration rate
- HR: hazard ratio
- MACE: major cardiovascular events
- MSU: monosodium urate
- NSAID: nonsteroidal anti-inflammatory drug
- OR: odds ratio
- PICO: Patient/Intervention/Comparison/Outcome
- PPV: positive predictive value
- RCT: randomised clinical trial
- RR: relative risk
- SCAR: serious cutaneous adverse reaction
- SER: Spanish Society of Rheumatology (Sociedad Española de Reumatología)
- SIGN: Scottish Intercollegiate Guidelines Network
- SPICE: Setting, Perspective, Intervention, Comparison and Evaluation framework



SR: systematic review T2T: Treat to Target ULT: urate-lowering therapy VAS: visual analogue scale XO: xanthine oxidase YLD: Years lived with disability YLL: years of life lost

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Appendix 5. Declaration of interests

Fernando Pérez Ruiz has received speaker and consultancy fees from Amgen, Astellas, Astra-Zeneca, Grünenthal Pharma, Menarini and FER; and funding from Grünenthal Pharma, Biocruces Bizkaia Health Research Institute, Lilly, Menarini, Novartis and the Foundation of the Spanish Society of Rheumatology (FER) for attending courses/conferences, and from Astra-Zeneca, Grünenthal Pharma, Menarini and FER for running educational programmes and courses. He has been the principal investigator in clinical trials for Biogen, Gilead and Novartis; and has received funding from Cruces Hospital's Association for Rheumatologists for research, publishing and attending scientific events.

Petra Díaz del Campo works at the SER Research Unit, which develops clinical practice guidelines funded by numerous pharmaceutical companies.

Mariano Andrés Collado has received funding from Menarini and Astra-Zeneca for attending courses and conferences; speaker fees from Menarini; and fees from Astra-Zeneca, Grünenthal Pharma and Horizon for consultancy work for pharmaceutical and tech companies.

Enrique Calvo Aranda has received funding from Grünenthal Pharma, Menarini, Roche and Sobi for attending courses and conferences; speaker fees from Grünenthal Pharma, Janssen, Lilly, Menarini and Roche; funding from the SER for participating in a research project; and fees from Grünenthal Pharma for consultancy work for pharmaceutical and tech companies. He has also received funding from a private company in the health sector (private consultation).

Eugenio De Miguel Mendieta has received speaker fees from Grünenthal Pharma and Menarini; and fees from Grünenthal Pharma for consultancy work for pharmaceutical and tech companies.

César Díaz Torne has received funding from Menarini and FER for attending conferences; speaker fees from FER; fees from Grünenthal Pharma for consultancy work for pharmaceutical and tech companies; and funding from the same company for a research study.

Iván Fernández Alonso has no conflicts of interest to declare.

Gorka García Erauzkin has received speaker fees from Grünenthal Pharma and Menarini.

Juan Carlos Hermosa Hernán has received speaker fees from Esteve, Menarini, semFYC and Madrid Health Service (SERMAS); and funding from Menarini, FER and the Spanish Society of Family and Community Medicine (semFYC) for attending courses and conferences, from Menarini, Grünenthal Pharma and semFYC for running educational programmes and courses,



and from MSD to participate in a research study. He has also received fees from Grünenthal Pharma for consultancy work for pharmaceutical and tech companies.

Mercedes Jimenez Palop has received funding from MDS and Pfizer for attending courses and conferences; and speaker and workshop-related fees from Roche, Rubio, FER and the Society of Rheumatology in the Madrid region (SORCOM).

Luis Mora Calleja has no conflicts of interest to declare.

Jose Antonio Narváez García has received funding from Rovi for attending courses and conferences; and speaker fees from Abbvie and BTG-Covidien.

Rocío Segura Ruiz has received funding from Lilly and Novartis for attending courses and conferences.

Francisca Sivera Mascaró has received funding from Menarini and Grünenthal Pharma for attending courses and conferences; speaker fees from Grünenthal Pharma and Menarini; and fees from Grünenthal Pharma, Astra-Zeneca and Horizon for consultancy work for pharmaceutical and tech companies.

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