

TITLE PAGE

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Title of the article: “Efficacy and safety of non-biologic immunosuppressants in the treatment of non-renal systemic lupus erythematosus: a systematic review”

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## ABSTRACT

Objective: to analyze the efficacy and safety of non-biologic immunosuppressants in the treatment of non-renal systemic lupus erythematosus (SLE).

Methods: Systematic review. We conducted a sensitive literature search in Medline, Embase, and the Cochrane Central Register of Controlled Trials up to October 2011.

Selection criteria: a) population: adult patients with SLE, b) intervention: treatment with non-biologic immunosuppressant, c) comparator: placebo or active comparator, d) outcome measures assessing efficacy and/or safety. Meta-analyses, systematic reviews, clinical trials and cohort studies were included. The quality of each study was evaluated using the Jadad's scale and Oxford Levels of Evidence.

Results: one hundred fifty-eight articles were selected for detailed review of the 2,827 initially found. Finally, 65 articles fulfilled the predetermined criteria. Overall, they were low-quality studies with only 11 randomized clinical trials (RCT). Cyclophosphamide demonstrated efficacy for neuropsychiatric SLE preventing relapses with additional steroid-sparing effect although its use was associated with cumulative damage, development of cervical intraepithelial neoplasia and ovarian failure. Other immunosuppressants (azathioprine, methotrexate, leflunomide, mycophenolate mofetil and cyclosporine A) demonstrated efficacy in reducing non-renal activity and flares with a steroid-sparing effect, although on occasions in non placebo-controlled RCTs of small number of patients.

Conclusion: several immunosuppressants have demonstrated their safety and efficacy in non-renal SLE. A specific drug for each particular manifestation cannot be recommended although cyclophosphamide may be kept to be used in more severe cases and methotrexate may be the first option in most cases of moderately active SLE. High-quality RCTs of a larger number of patients are needed.

## SIGNIFICANCE AND INNOVATIONS

There are only 11 randomized clinical trials (RCT) assessing the effect of the different non-biologic immunosuppressants in the treatment of non-renal systemic lupus erythematosus (SLE).

In those circumstances, several immunosuppressants have demonstrated their safety and efficacy in reducing non-renal activity with a steroid-sparing effect.

Cyclophosphamide in more severe cases and methotrexate in most cases of moderately active SLE may be the first therapeutic options.

High-quality RCTs of a larger number of patients are needed.

Systemic lupus erythematosus (SLE) is a heterogeneous disease that may affect all organ systems. The disease may be highly active, requiring aggressive therapy in one or a few systems but inactive in all the others. To date, there have been few randomized controlled trials (RCTs) addressing the efficacy and safety of the available treatments on specific manifestations of SLE. The first controlled clinical trials were conducted in the 1980s and 1990s by Mayo Clinic and National Institute of Health (NIH) researchers and focused primarily on lupus nephritis(1-3). Over the last decade, most RCTs that investigated the effect of different therapies, mainly cyclophosphamide (CYC), azathioprine (AZA) and mycophenolate mofetil (MMF), on lupus also focused primarily on lupus nephritis(4-10). Recently, several biologic therapies have been studied for the treatment of renal and non-renal manifestations of SLE(11-18). The heterogeneity of the disease means that a trial showing that a treatment is effective against one manifestation of lupus cannot necessarily be extrapolated to other types of organ involvement. To date, few RCTs have analyzed the effect of the available therapies on non-renal manifestations of SLE. Specifically, there is limited evidence on the efficacy of non-biologic immunosuppressants for the treatment of non-renal manifestations of the disease. In spite of that, several of those manifestations are frequently treated with off-label medications such as methotrexate (MTX), MMF, etc. Thus, the objective of our work was to systematically review the available literature regarding the efficacy and safety of non-biologic immunosuppressive therapies in the treatment of non-renal manifestations of SLE.

## **MATERIALS AND METHODS**

This study was performed by experts of the Evidence-Based Medicine Study Group and the Systemic Autoimmune Diseases Study Group of the Spanish Society of Rheumatology.

### **Search strategy**

The studies were identified by sensitive search strategies in the main bibliographic databases: Medline since 1961 to October 2011, Embase since 1980 to October 2011, and the Cochrane Central Register of Controlled Trials up to October 2011. An expert librarian checked the search strategies. Finally, a hand search was performed by reviewing the references of the studies included. Details about strategies are available in a supplementary file (Appendix 1).

### **Selection of studies**

Initially, we performed a systematic literature review on the efficacy and safety of biologic and non-biologic immunosuppressive drugs in the treatment of non-renal manifestations of SLE.

The studies retrieved by the mentioned strategies were finally included if they met the following pre-established criteria: a) population: adult patients diagnosed with SLE, b) intervention: treatment with non-biologic immunosuppressive agent, c) comparator: placebo or active comparator, d) outcome measures assessing efficacy: non-renal manifestations, scores by activity indices, SLE flares, steroid-sparing effect, etc., and e) outcome measures assessing safety: infections, cardiovascular events, malignancies, etc.

Only meta-analyses, systematic reviews, clinical trials and cohort studies were included.

We excluded studies specifically about efficacy in lupus nephritis or discoid lupus, those assessing antimalarials medications or biologic therapies and those with insufficient data for analysis.

### Screening of studies, data collection and analysis

The titles and abstracts of all articles retrieved by the search strategy were independently reviewed for selection criteria by two reviewers (TCI and ELS). They collected the data from the studies included by using *ad hoc* standard forms. One of the reviewers (TCI) entered the data from the forms into spreadsheets. In case of any discrepancy between the information of both reviewers, a consensus was reached by reading the original article or by asking the mentor.

The level of evidence and grades of recommendation were established by a reviewer (TCI) based on the scale of the Oxford Centre for Evidence-Based Medicine(19). The Jadad's scale was additionally used to grade quality in case the study was a RCT(20).

See supplementary file (Appendix 2) for definitions.

Evidence tables were produced with all the included studies and a qualitative analysis was performed (Supplementary file, Appendix 3).

### RESULTS

The complete literature search produced 2,827 items. After removing the 359 items that were duplicated, 2,468 studies were revised and 65 finally included. The result of the search strategies is shown in Figure 1.

The excluded studies and reasons for exclusion are available in a supplementary file (Appendix 4). Most of the items included were cohort studies and only 11 were RCTs.

The detailed information from these RCTs is shown in Table 1.

The inclusion criteria and non-renal manifestations analyzed in the diverse studies were very varied. Likewise, the outcome variables used to measure the effects of the drugs were diverse: disease activity and clinical response measured by different indices, flares, serological response, other specific testing variables, corticoids requirement, adverse events, etc.

The main recommendations, level of evidence and grade of recommendation from our review are shown in Table 2.

### **Cyclophosphamide**

There were 29 studies that evaluated the efficacy and/or safety of CYC in the treatment of non-renal manifestations of SLE: 4 unblinded RCTs(21-24) (Table 1), 1 open prospective study(25) and 24 cohort studies(26-49) that included 3,742 patients overall.

Different non-renal manifestations were treated although neuropsychiatric (NP) SLE was studied in a more rigorous way(21,23,24). The regimes and duration of CYC treatment and the co-medication allowed in those studies were varied. The outcome variables used were varied, the most frequent being clinical response to treatment measured by different activity and response indices, serological response, rate of disease flares, decrease in the dose of prednisone and adverse events.

Some of the studies specifically addressed safety issues such as ovarian failure, neoplasias or association with damage. The main conclusions and quotes of these studies are shown in Table 2.

In summary, the evidence for use of CYC in the treatment of non-renal SLE is based on studies of a larger number of patients than those that assess any other non-biologic agent and RCT information is available particularly for NP-SLE. However, only a small percentage of the patients were included in high quality studies.



### **Azathioprine**

There were only two articles that assessed the efficacy and/or safety of AZA in the treatment of non-renal SLE: 1 unblinded RCT(50) (Table 1), and 1 cohort study(51) that included 85 patients overall.

The retrospective cohort study analyzed the influence of AZA ( $\geq 2\text{mg/Kg/day}$ ) and prednisolone (7-12mg/day) on the frequency of SLE flares and evaluated the predictors of these flares in 61 patients (38 without renal disease) over a mean follow-up period of 7.5 years(51). In comparison with the preceding period without AZA, that combined regimen resulted in a significant reduction in flares and an increase in flare-free patient years.

In summary, there is little evidence for use of AZA in the treatment of non-renal SLE as there is only an unblinded, non-placebo controlled RCT of a small number of patients.

### **Methotrexate**

Seven articles evaluated the efficacy and/or safety of MTX in the treatment of non-renal manifestations of SLE: 2 double-blind, placebo-controlled RCTs(52,53), 1 crossover open study(54), and 5 cohort studies(55-9) that included 230 patients overall.

The detailed information on both RCTs is shown in Table 1.

The crossover open study(54) assessed the efficacy of oral MTX (7.5mg/week) in SLE patients without major organ involvement and active disease despite  $>10\text{mg/day}$  of prednisone. The patients received treatment for 2 periods: a) 3 months (followed by a control 3-month period without treatment), and then b) 6 months (followed by a control 6-month period without treatment). In the 13 patients who finished the study, there was a significant reduction of the lupus flares during the periods of MTX use compared with the control phases ( $p = 0.02$ ) without significant differences in the requirements of prednisone.

In summary, the evidence for use of MTX in non-renal SLE is based on high quality studies, two double-blind, placebo-controlled RCTs. However, a small number of patients were included in these studies (only 61 patients treated with MTX).

### **Leflunomide**

Two articles assessed the efficacy and/or safety of leflunomide (LEF) in the treatment of non-renal SLE: 1 double-blind, placebo-controlled RCT(60) (Table 1) and 1 cohort study(61) that included 30 patients overall.

The cohort study assessed retrospectively the efficacy and safety of LEF (100mg/day for 3 days followed by 20mg/day) in 18 SLE outpatients(61). After 2-3 months of therapy, most of the patients had subjective improvement and significantly lower Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores.

In summary, there is very little evidence for use of LEF in non-renal SLE as the only double-blind, placebo-controlled RCT that has been reported included only 6 patients treated with the drug.

### **Mycophenolate mofetil**

Eight articles evaluated the efficacy and/or safety of MMF in the treatment of non-renal manifestations of SLE: 1 RCT(62) (Table 1), and 7 cohort studies(63-9) that included 769 patients overall.

The RCT by Ginzler(62) *et al.* explored, as secondary end points, the non-renal findings of the Aspreva Lupus Management Study (ALMS)(70), a prospective, open-label, parallel-group RCT that assessed the effect of MMF compared with CYC as induction treatment for lupus nephritis.

Some cohort studies specifically addressed safety issues and their main results and quotes are shown in Table 2.

In summary, the evidence for use of MMF in non-renal SLE is based on studies of a larger number of patients and RCT information is available. However, most patients were included in low quality studies and the RCT assessed the non-renal response in patients with lupus nephritis that received induction treatment including high-dose corticosteroids.

### **Cyclosporine A**

Eight articles evaluated the efficacy and/or safety of cyclosporine A (CyA) in the treatment of non-renal SLE: 2 unblinded RCT(71-2) (Table 1), 1 prospective open study(73), and 5 cohort studies(73-8) that included 319 patients overall.

The prospective open study investigated the effect of CyA (2.5-5mg/Kg/day) in 16 patients with active SLE over an average treatment period of 30.3 months(73). The European Consensus Lupus Activity Measurement score decreased significantly ( $p<0.005$ ) after 6 months but not at the end of the observation period. The most frequent side-effects were hypertension and deterioration of renal function (3/16) and hypertrichosis (5/16).

In summary, there is little evidence for use CyA in non-renal SLE as one of the two unblinded, non-placebo controlled RCTs that assessed this drug included only 10 patients being treated with CyA, and almost one third of all patients discontinued the drug due to adverse events or lack of efficacy in the second one.

### **Tacrolimus**

Two studies assessed the efficacy and/or safety of tacrolimus (TAC) in the treatment of non-renal manifestations of SLE: 2 cohort studies(79-80) that included 31 patients.

In the open-label prospective 24-week study by Suzuki(79) *et al.*, 21 patients with mild active SLE treated with oral TAC (1-6 mg/day) were studied. The mean SLEDAI decreased significantly at 24 weeks ( $p <0.01$ ). In 8 cases, treatment was discontinued

within 24 weeks due to inefficacy (6 cases) and adverse effects (2 cases). Non-serious side effects were observed in only five cases (23.8%).

The retrospective cohort study investigated whether oral TAC (1-3 mg/day) was effective for treating SLE patients without active nephritis (n=10)(80). The mean SLEDAI and the mean dose of prednisolone decreased significantly after 1 year ( $p < 0.05$ , both). Four of the 10 patients had adverse events and 2 patients discontinued treatment.

In summary, there is very little evidence for use of TAC as only two small studies have been reported, neither were RCTs and almost one third of all patients studied discontinued the drug due to lack of efficacy or adverse effects.

#### **Combination of non-biologic immunosuppressants**

Six articles assessed the effect of several regimes combining different non-biologic immunosuppressants in the treatment of non-renal SLE: 6 cohort studies(81-6) that included 2,262 patients. Although there were no RCTs, some interesting results were found. One study that analyzed risk factors for thrombosis in a large (n=1,930), multiethnic SLE cohort found that history of treatment with AZA (OR 1.36,  $p=0.023$ ) and CYC (OR 1.42,  $p=0.025$ ) were significant risk factors for thrombosis(83). Noel(84) *et al.* carried out a retrospective study to analyze infectious complications and their risk factors in a cohort of 87 SLE patients finding that intravenous corticosteroids and immunosuppressants (oral or pulse CYC, AZA or MTX) were independent risk factors for infection.

In summary, there is very little evidence for use of combinations of non-biologic immunosuppressants in non-renal SLE as there is not any RCT and the vast majority of patients were included in low quality studies that were not designed to assess efficacy.

## DISCUSSION

We have conducted a systematic review of the literature to analyze the efficacy and safety of non-biologic immunosuppressive drugs in the treatment of non-renal manifestations of SLE. Three facts justify the interest of our review: a) to date, the vast majority of the studies have focused on the effect of the different available therapies on renal SLE, b) a treatment may not be effective for all but for specific manifestations of SLE, and c) non-biologic immunosuppressants are frequently used off-label for the treatment of non-renal SLE even when there are no clear recommendations for their use in those situations. There is actually very little RCT data for most of the treatment that we are currently using.

In our systematic review, we found a great number of studies although in general their quality was low and the number of patients included in high quality studies was small. Although there are several RCTs addressing the treatment of non-renal SLE, it is almost impossible to combine the data in a single meta-analysis due to an important variability in selected patients, treatment doses and outcome measures.

The main objective of any treatment for SLE in clinical practice is decrease in disease activity. Most of the studies we have analyzed use some validated activity indices although there is no uniformity regarding them. An additional aim of using an immunosuppressant is the reduction of the doses of steroids used to control disease activity preventing their side effects. Several of the immunosuppressants analyzed demonstrated their efficacy and safety in the treatment of non-renal SLE with a steroid-sparing effect.

Our systematic review demonstrated that MTX has the strongest level of evidence for the treatment of non severe extrarenal SLE, with two double-blind, placebo-controlled RCTs that show the same results(52-53). The design of both trials and the

characteristics of the recruited patients were similar with more than 90% of them having musculoskeletal and/or cutaneous manifestations, particularly arthralgias/arthritis, malar rash and discoid lesions. These studies demonstrated the efficacy of the drug in reducing global, cutaneous and articular activity with an additional steroid-sparing effect in the short and medium-term (6-12 months) with a good safety profile. Thus, our systematic review supports the use of MTX as the first immunosuppressive therapy recommended in the treatment of moderately active non-renal SLE.

CYC was successfully tested in difficult clinical situations such as NP-SLE(21,23,24) and pulmonary hypertension due to SLE(22). Although it is not possible to establish a general CYC schedule, maintenance therapy with CYC is associated with a significant reduction in NP relapses. However, our systematic review demonstrated that CYC is an important risk factor for cumulative damage, including ovarian failure and different neoplasias. Thus, although CYC may be recommended as the first immunosuppressive agent in the treatment of more severe cases of non-renal SLE, decisions about CYC use must be evaluated as a balance between the benefits of treating life-threatening complications of SLE and risks of severe adverse events that are generally associated with longer duration and higher cumulative dose of both i.v. and oral CYC.

Although AZA is one of the immunosuppressants most frequently used in combination with steroids in non-renal SLE, there is very little evidence supporting its use. AZA was tested in one unblinded, non placebo-controlled RCT of very small number of patients treated with the drug (n=11) that was unable to show any benefit of AZA plus prednisone over prednisone alone in any of the non-renal clinical manifestations in the short term (3 months) and in the long term (24 months) or in the reduction of the doses of steroids(50). However, a recommendation about this result cannot be made as there is

an important design bias: both groups remained on high-dose prednisone (40-60mg/day) during 4-6 months and that may explain the absence of differences.

LEF also was more effective than placebo in treating mild to moderate active SLE patients with a favourable safety profile although more RCTs assessing this drug in a greater number of patients are required.

The evidence of the efficacy of MMF for the treatment of non-renal SLE is limited as comes from low quality studies and the evaluation of the secondary end-point (non-renal features of SLE) of the ALMS, a RCT specifically designed to evaluate MMF in comparison with CYC for the induction treatment of lupus nephritis(8,62). However, although induction treatment for lupus nephritis with high-dose corticosteroids and i.v. CYC or MMF is recommended in clinical practice, these regimes are not the standard of care in SLE patients with non-renal SLE. Therefore, the results of this study cannot be extrapolated to patients with non-renal SLE who are usually treated less aggressively. Further well designed RCTs assessing the efficacy and safety of MMF as primary end-point for the treatment non-renal SLE are eagerly awaited.

There is very little evidence for the use of calcineurin inhibitors as CyA was assessed in 2 small unblinded, non-placebo controlled RCTs(71-72) and TAC in 2 small low quality non RCTs(79-80). The withdrawal rate was high for both drugs so concern about their side effects is a barrier to generalize their use.

Based on its clinical and serological heterogeneity, some authors have recently considered SLE as a syndrome rather than a single disease(87). This approach to SLE and the accumulated knowledge on its different pathogenic factors might allow a better classification of this syndrome and the use of targeted therapies for specific manifestations of SLE in the future. Until then, our approach to the treatment of SLE should be more general and based on the data of the literature that we have reviewed.

In conclusion, several immunosuppressants have demonstrated their efficacy, safety and steroid-sparing effects in the treatment of non-renal SLE. However, the number and quality of the studies are limited. A specific drug for each particular manifestation cannot be recommended although CYC may be kept to be used in more severe cases and MTX may be the first option in moderately active SLE. The results of our review may help the clinician to make better therapeutic decisions and serve as a reference for further development of clinical practice guidelines or clinical trials addressing system specific non-renal manifestations in larger populations of SLE patients.

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Accepted Article

Table 1. Randomized controlled trials assessing non-biologic immunosuppressants in the treatment of non-renal systemic lupus erythematosus

Author, year, design, FU	Population	Intervention	Outcome measure	Efficacy	Safety	Comments
Stojanovich, 2003 (21) Open RCT ≥6 months	n=60 IC: NP-SLE EC: LN, others	iv CYC (200-400mg/month x 6m) + PRD 20.5mg/d (n=37) vs PRD 20.5mg/d (n=23)	Clinical improvement Relapses EEG improvement EP improvement AE	Clinical improvement at 6m: 62.2 vs 21.7% (p=0.005). Relapses at 3m: 37.8 vs 78.3% (p=0.005). EEG recovered: 75 vs 18% (p=0.003). EP recovered: 80 vs 0% (p=0.003)	2 herpes zoster	-Oxford 3a -Jadad 1
Gonzalez-Lopez, 2004 (22) Open RCT 6 months	n=34 IC: PAH due to SLE (SPAP >30mmHg) EC: embolism, pulmonary fibrosis, asthma, COPD, others	iv CYC: 0.5g/m <sup>2</sup> /month x 6m (n=16) vs enalapril 10mg/d x 6m (n=18)	↓ SPAP NYHA functional class improvement AE	↓SPAP: from 41 to 28mmHg (p<0.001) vs 39 to 27mmHg (p=0.02). Significant difference (p=0.04). Only CYC improves NYHA class (p=0.02)	CYC: more infections (RR=1.6; 95% CI: 1.001-2.47) and more G-I AE (RR=14.6; 95% CI: 2.15-99.7)	-Jadad 3
Barile-Fabris, 2005 (23) Open RCT 24 months	n=32 IC: new onset NP-SLE EC: NP-APS, CNS infection, metabolic encephalopathy, others.	iv MP (1g/d x 3d) + iv CYC (0.75g/m <sup>2</sup> /month x 12m, then every 3m x 1 year (n=19) vs iv MP (1g/d x 3d + MP 1g/d x 3d/month x 4m, then 3d/2m x 6m and then 3d/3m x 12m (n=13) Co-medication: PRD 1mg/kg/d and ↓	Response to treatment: ≥20% improvement in clinical, serological and neurological measures AE	Response rate at 2y: 95 vs 46.2% (p<0.03).	AE: no difference	-Jadad 3 36.8% (CYC) and 76.9% (MP) were lost to FU
Petri, 2010 (24) Open RCT 30 months	n=47 IC: moderate/severe SLE and lack of response to moderate to high dose steroids or IS	iv CYC 0.75g/m <sup>2</sup> /month x 6m, then every 3m x 2 years (n=26) vs high-dose iv CYC 50mg/kg x 4 d (n=21)	RIFLE (complete or partial response, no change, or worsening) AE	Complete response at 30m: 65 and 48%; partial response at 30m: 10 and 19% (p=ns both, overall and by major organ system)	No difference in serious AE, hospitalizations, infections, deaths and ovarian failure	-Jadad 3 -Oxford 2b
Hahn, 1975 (50)	n=24 IC: active, life-threatening	AZA 3-4mg/kg + PRD 60mg/d (n=11) vs PRD 60mg/d (n=13)	Clinical improvement	Clinical improvement: no difference at 3,6,12,18 and 24w	No difference in AE due to steroids. In AZA	-Jadad 3 The majority

Open RCT 24 months	SLE, and no IS or >20mg/d the preceding 6 weeks EC: drug-induced SLE	Co-medication: PRD 40-60mg/d x 4-6m; if failure to respond: double PRD dose 4-6w. If no response: removal from study. If response: ↓PRD	Mean PRD dose AE	in arthritis, serositis, dermatitis, polyneuritis, CNS involvement, fever, hemolytic anaemia, thrombocytopenia. Mean dose PRD: no difference	group: hepatotoxicity in doses ≥200mg/d Deaths: 2 vs 4; 5/6 due to SLE activity	in AZA group were white and in PRD group were black
Carneiro, 1999 (52) Double- blind, PCB- controlled RCT 6 months	n=41 IC: SLE, PRD <0.5mg/kg/d, at least one: arthralgia>3 joints, arthritis, discoid lesion or malar rash, pleuritis, pericarditis, vasculitis, proteinuria or urinary casts. EC: creatinine ≥2mg/dl, recent loss of renal function, IS use ≥4months, others	Oral MTX 20mg/week if >50Kg and 15mg/week if <50Kg (n=20) vs PCB (n=21) Co-medication: stable PRD dose the first month, then ↓↑ depending on activity	SLEDAI VAS for joint pain ↓PRD dose Joint and skin improvement AE	SLEDAI: MTX↓ (p<0.05) vs PCB↑ at 6m (p<0.05) VAS: MTX↓ vs PCB↑ at 6m (p<0.05) ↓PRD: in 65% MTX patients vs 5% PCB patients, p<0.001 Arthralgia/arthritis and discoid SLE/malar rash: significant improvement with MTX vs PCB (p<0.001, both)	70% MTX vs 14% PCB patients: side effects, mainly dyspepsia and hepatotoxicity	-Jadad 5 -Oxford 1b Similar withdrawal rates No intent to treat analysis
Fortin, 2008 (53) Double- blind, PCB- controlled RCT 12 months	n=86 IC: moderate SLE (SLAM- R ≥8), SDI ≤15 EC: CYC or AZA in the last 4 weeks, renal failure, lupus nephritis, others	MTX 7.5mg/week and ↑ to 20mg/week (n=41) vs PCB (n=45) Co-medication: folic acid 2.5mg/d, 6 d/week, PRD Stable PRD, antimalarials and NSAIDs dose the previous 4w	SLAM-R ↓PRD dose AE	MTX ↓SLAM-R at 12m: -0.86 (96% CI -1.71, -0.02), p=0.039 MTX ↓SLAM-R in patients with SDI=0 at 12m: -1.41 (96% CI - 2.42, -0.39), p=0.008 MTX ↓mean PRD daily dose at 12m: -22.3 (96% CI -36.2, -5.4), p=0.010	No difference in AE overall. Differences in G-I (56.1 vs 33.3%), and psychological AE (9.8 vs 0%), p=0.05 both	-Jadad 5 Intent to treat analysis No difference in % lost to FU
Tam, 2004 (60) Double- blind, PCB- controlled RCT 24 weeks	n=12 IC: active SLE (SLEDAI ≥6), PRDL <0.5mg/kg/d EC: need for CYC or AZA	LEF 100mg/d x 3d, then 20mg/d (n=6) vs PCB (n=6) Co-medication: HCQ, PRDL 15mg/d and ↓, NSAIDs	SLEDAI Proteinuria, C3, anti-dsDNA, PRDL dose AE	↓SLEDAI at 24w: 11.0±6.1 vs 4.5±2.4 (p=0.02) Similar changes in proteinuria, C3, a-dsDNA, PRDL dose	AE: no difference	-Jadad 5 No difference in % lost to FU
Ginzler,	n=370 IC: SLE and LN	MMF 0.5g/12h and ↑ to 1.5g/12h (n=185) vs iv CYC 0.5-	Non-renal outcomes	No difference in non-renal outcomes in: %patients with	Non reported	-Jadad 3 Similar

2010 (62) Open RCT 24 weeks	EC: $\geq 2$ week dialysis before randomization, anticipated dialysis for $\geq 8$ weeks	1g/m <sup>2</sup> /month x 6m (n=185) Co-medication: PRD 60mg/d and similar $\downarrow$ in both groups	BILAG SELENA-SLEDAI Flares	unchanged BILAG, %patients with improved BILAG, mean change in SELENA-SLEDAI and remission, BILAG and SELENA-SLEDAI flares		withdrawal rates
Dammacco, 2000 (71) Open RCT 12 months	n=18 IC: moderate SLE EC: severe SLE, others	iv MP (1g/d x 3d) in both groups, then CyA <5mg/kg/d and $\downarrow$ + PRD 0.5-1mg/kg and $\downarrow$ to 5mg/d (n=10) vs the same doses of PRD only (n=8)	SLEDAI Mean cumulative PRD dose AE	$\downarrow$ SLEDAI at 12m: 16.3 vs 11.6 (p<0.05) Mean cumulative PRD dose at 12m: 179.4 $\pm$ 40.1 vs 231.8 $\pm$ 97.1 (p<0.005)	AE: 60 vs 62.5%. No differences per each AE	-Jadad 1 1 vs 5 patients were lost to FU by worsening
Griffiths, 2010 (72) Open RCT 12 months	n=89 IC: severe SLE (requiring a new IS and PRDL $\geq 15$ mg/d) EC: hypertension, abnormal serum creatinine, others	CyA 1mg/kg/d and $\uparrow$ to 2.5-3.5mg/kg/d (n=47) vs AZA 0.5mg/kg/d and $\uparrow$ to 2-2.5mg/kg/d (n=42) Co-medication: stable PRDL, antimalarials and NSAIDs	Mean change in PRDL dose BILAG BILAG flares AE	$\downarrow$ Mean PRDL dose at 12m by over 50% in both groups (p<0.001). No difference in the change between groups (p=0.2) No differences in BILAG activity and BILAG flares	No patient had severe hypertension or persistent rise in creatinine One third of patients in both groups discontinued the drugs due to AE or lack of efficacy	-Jadad 3 CyA group was younger, had more non-Caucasians and more damage on the SDI

FU: follow-up, RCT: randomized clinical trial, IC: inclusion criteria, NP-SLE: neuropsychiatric systemic lupus erythematosus, EC: exclusion criteria, LN: lupus nephritis, CYC: cyclophosphamide, PRD: prednisone, EEG: electroencephalogram, EP: evoked potentials, AE: adverse events, PAH: pulmonary arterial hypertension, SPAP: systolic pulmonary artery pressure, COPD: chronic obstructive pulmonary disease, NYHA: New York Heart Association, RR: relative risk, CI: confidence interval, G-I: gastrointestinal, NP-APS: neuropsychiatric antiphospholipid syndrome, CNS: central nervous system, MP: methylprednisolone, IS: immunosuppressant, RIFLE: responder index for lupus erythematosus, AZA: azathioprine, PCB: placebo, MTX: methotrexate, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, VAS: visual analogue scale, SLAM-R: Systemic Lupus Activity Measure-Revised, SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, NSAIDs: non-steroidal antiinflammatory drugs, PRDL: prednisolone, LEF: leflunomide, HCQ: hydroxychloroquine, MMF: mycophenolate mofetil, BILAG: British Isles Lupus Assessment Group, SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI, CyA: cyclosporine A.

Table 2. Main recommendations and conclusions, level of evidence, and grade of recommendation from the review of the evidence of the use of non-biologic immunosuppressants in non-renal SLE.

Recommendation/Conclusion	LE	GR
<b>Cyclophosphamide</b>		
i.v. CYC may be useful for the treatment of NP-SLE and reduction of relapses.	3a	C
i.v. CYC plus prednisone is better than prednisone for the short-term treatment of NP-SLE and reduction of relapses.	3a	B
i.v. CYC is better than MP for the long-term treatment of NP-SLE and reduction of relapses.	2b	B
High-dose i.v. CYC has the same efficacy in the treatment of non-renal SLE and the same adverse event rate than the traditional i.v. CYC regimen	2b	B
i.v. CYC is better than enalapril to improve the NYHA functional class and reduce the SPAP for the treatment of PAH in SLE although has a higher non severe infection rate.	2c	B
i.v. CYC use is associated with cumulative damage(28,38).	2a	B
i.v. CYC use is associated with development of CIN(41).	2c	B
i.v. CYC decreases leukocyte, neutrophil, and lymphocyte count but the effect size is very small so severe myelotoxicity is unfrequent(32).	2b	B
In SLE women, oral or i.v. CYC is independently associated in the short term with ovarian failure(27).	2a	B
In SLE women, the risk of ovarian failure increases with the cumulative dose of oral or i.v. CYC and is higher with longer i.v. CYC regimes(25,37,47).	2b	B
In SLE women, the risk of ovarian failure is associated with an older age at commencement of both oral and intravenous CYC. Age itself is a risk factor for ovarian failure(29,30,39).	2c	B
<b>Azathioprine</b>		
The association of AZA with prednisolone treatment might reduce flare rate.	2c	B
<b>Methotrexate</b>		
In patients with active non-renal SLE manifestations in spite of prednisone, the association of MTX (15-20 mg/day) reduces in the short term (6 months) the global, articular and cutaneous activity of the disease with an additional short-term steroid-sparing effect.	1b	A
In patients with moderate activity and non-renal SLE manifestations in spite of prednisone, NSAIDs and antimalarials, treatment with MTX (20 mg/day) reduces in the medium term (12 months) the activity of the disease, particularly in patients without damage, with an additional medium-term steroid-sparing effect.	1b	A
<b>Leflunomide</b>		
In patients with mild to moderate active SLE in spite of prednisolone, addition of LEF is more effective than placebo in improving the activity of	1b	C



the disease with similar short-term (6 months) side effects.		
<b>Mycophenolate mofetil</b>		
MMF can be used for the treatment of non-renal SLE manifestations in patients with lupus nephritis as it is not inferior to i.v. CYC to decrease activity, induce remission, and to reduce flares of non-renal manifestations, and to improve serological parameters.	2b	B
MMF is safer on the haematological system than AZA and MTX, and may increase platelet and leukocyte count and haematocrit(64).	2b	B
MMF can be used to improve non-renal activity in patients with non-renal and/or renal refractory SLE, and to reduce need for corticosteroids.	3a	B
MMF may prevent short-term (6 months) SLE flares when added to the treatment of patients with increasing anti-dsDNA titre.	2b	C
In patients with renal and/or non-renal SLE, MMF may cause non-dose dependent adverse events (particularly, in the gastrointestinal system) and the medium-term (12 months) drug survival is acceptable with a low withdrawal rate due to adverse events(69).	3a	C
<b>Cyclosporine A</b>		
In patients with renal and/or non-renal SLE refractory to steroids, the addition of CyA may improve disease activity, and induce remission in the short term but causes frequent adverse events.	2c	B
In patients with renal and/or non-renal SLE refractory to steroids, the addition of CyA may improve disease activity and have a steroid-sparing effect in the long term but causes frequent adverse events.	2b	B
In patients with active SLE refractory to steroids, CyA is not less effective than AZA in reducing renal and/or non-renal activity and both drugs have similar steroid-sparing effect in the medium term with no significant difference in adverse events.	2b-c	B
<b>Tacrolimus</b>		
In patients with active non-renal SLE in spite of conventional treatment, the addition of TAC may be useful to improve disease activity in the medium term but causes frequent adverse events.	2c	C

SLE: systemic lupus erythematosus, LE: level of evidence, GR: grade of recommendation, CYC: cyclophosphamide, NP: neuropsychiatric, MP: methylprednisolone, NYHA: New York Heart Association, SPAP: systolic pulmonary artery pressure, PAH: pulmonary arterial hypertension, CIN: cervical intraepithelial neoplasia, AZA: azathioprine, MTX: methotrexate, NSAIDs: nonsteroidal anti-inflammatory drugs, LEF: leflunomide, MMF: mycophenolate mofetil, CyA: cyclosporine A, TAC: tacrolimus.

Figure 1. Flow chart with the results from the search strategies

