Clinical Science

Leflunomide versus azathioprine for maintenance therapy of lupus nephritis: a prospective, multicentre, randomised trial and long-term follow-up

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ABSTRACT

Objectives Previous studies have compared mycophenolate mofetil and azathioprine as maintenance therapy for lupus nephritis (LN). Leflunomide is an immunosuppressant widely used in the treatment of rheumatoid arthritis. The aim of this investigator-initiated study was to compare the efficacy and safety of leflunomide versus azathioprine as maintenance therapy for LN.

Methods 270 adult patients with biopsy-confirmed active LN from 7 Chinese Rheumatology Centres were enrolled. All patients received induction therapy with 6–9 months of intravenous cyclophosphamide plus glucocorticoids. Patients who achieved complete response (CR) or partial response (PR) were randomised to receive prednisone in combination with leflunomide or azathioprine as maintenance therapy for 36 months. The primary efficacy endpoint was the time to kidney flare. Secondary outcomes included clinical parameters, extrarenal flare and adverse effects.

Results A total of 215 patients were randomly allocated to the leflunomide group (n=108) and azathioprine group (n=107). Kidney flares were observed in 17 (15.7%) leflunomide-treated patients and 19 (17.8%) azathioprine-treated patients. Time to kidney flare did not statistically differ (leflunomide: 16 months vs azathioprine: 14 months, p=0.676). 24-hour proteinuria, serum creatinine, serum albumin, serum C3 and serum C4 improved similarly. Extrarenal flare occurred in two patients from the azathioprine group and one patient from the leflunomide group. The incidence of adverse events was similar in the 2 groups: leflunomide 56.5% and azathioprine 58.9%.

Conclusions The efficacy and safety profile of leflunomide are non-inferior to azathioprine for maintenance therapy of LN. Leflunomide may provide a new candidate for maintenance therapy in patients with LN.

Trial registration number NCT01172002.

INTRODUCTION

Lupus nephritis (LN) is a common severe complication of systemic lupus erythematosus (SLE) and a major cause of morbidity and mortality. Approximately 50%–60% of adult patients with SLE develop kidney involvement during their illness. In addition, 10%–30% of patients with LN progress to kidney failure requiring kidney replacement therapy. Although the kidney failure rate associated with LN has substantially increased since the 1970s, the rate of kidney replacement therapy has remained consistent and appears to have increased since 2000. Therefore, there are still significant unmet needs in the management of LN.

The guidelines for LN treatment have been updated recently by the European Association of Associations for Rheumatology and Kidney Disease Improving Global Outcomes. The initial phase of treatment is termed the induction phase, which is followed by a prolonged maintenance phase of treatment to achieve durable remission, and limit the risk of LN flare. Maintenance therapy lasts 2–3 years or longer, depending on the risk of relapse. Mycophenolate mofetil (MMF) and azathioprine (AZA) are commonly used in maintenance therapy.
The long-term use of these drugs is associated with considerable toxicity and is not effective in all patients.

Leflunomide (LEF) is a prodrug that is rapidly converted to its active metabolite A771726, which inhibits de novo pyrimidine nucleotide biosynthesis mediated especially by dihydroorotate dehydrogenase, thereby preventing DNA synthesis. LEF is a recommended disease-modifying anti-rheumatic drug for the treatment of rheumatoid arthritis. Its use has been reported in other autoimmune diseases, such as psoriatic arthritis, antineutrophil cytoplasmic autoantibody-associated vasculitis, SLE and Takayasu disease. Preclinical studies found that LEF reduced the amount of autoantibodies and immune complex deposits on glomeruli in MRL/lpr mice. A couple of clinical trials have evaluated LEF in the treatment of immune-related kidney diseases. The results showed that the efficacy of LEF was non-inferior to cyclophosphamide (CYC) as induction therapy for LN, and it was also effective in immunoglobulin A nephropathy by improving kidney function while decreasing loss of urine protein. Here, we reported the results of a 36-month study comparing LEF and AZA as maintenance therapy for LN patients who showed a complete response (CR) or partial response (PR) to induction therapy with the NIH-CYC regimen. The results provided the first evidence supporting that LEF may be an effective and safe choice for maintenance therapy in patients with LN.

METHODS

Study design

We conducted a prospective, multicentre, randomised, open-label trial comparing LEF with AZA for the maintenance of remission in patients with LN. The study comprised two phases. In phase 1, active biopsy-proven LN patients were recruited and treated with the standard NIH-CYC regimen for induction therapy. After 6–9 months of the induction phase, those who achieved CR or PR were admitted into the second maintenance phase. Patients were randomised into the LEF group or AZA group. Criteria for CR included the following: 24-hour urine protein quantity <0.5 g/24 hours, inactive urinary sediment (red blood cell (RBC) <5/high-power field (HPF), white blood cell (WBC) <5/HPF), normal serum albumin and improved or stabilised kidney function (serum creatinine (SCr) change was within ±25% of baseline value). PR was defined as significant improvement in 24-hour urine protein (at least a 50% decrease in the 24-hour urine protein to <3 g/24 hours if the baseline urine protein was >3.5 g/24 hours, or to ≤1 g/24 hours if the baseline urine protein did not reach the level of nephrotic syndrome), serum albumin ≥30 g/L and stable or improved kidney function (SCr change was within ±25% of baseline value). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. Details of the protocol are available in the online supplementary methods.

Study participants

For the first induction phase of the study, patients with active LN were recruited. The inclusion criteria were: age 18–65 years, SLE according to the American College of Rheumatology classification criteria, biopsy-proven class III/IV/V active LN diagnosed by International Society of Nephrology/Renal Pathology Society 2003 (biopsy performed less than 3 months before study entry), 24-hour proteinuria ≥1 g and SLE Disease Activity Index (SLEDAI) score ≥8. The exclusion criteria were treatment with CYC within 3 months, pulse intravenous glucocorticoids (GCs) (methylprednisolone: >200 mg/day) within 6 weeks, severe infection, severely abnormal kidney function with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², pregnant, breast feeding, previous malignancy, previously documented allergy to CYC, AZA or LEF (see online supplementary methods, p5–p6). Patients who showed a clinical response (CR or PR) 6–9 months after induction treatment were randomly assigned (in a 1:1 ratio) to AZA or LEF groups in the subsequent maintenance phase of the study.

Randomisation and masking

Patients fulfilling the inclusion/exclusion criteria were allocated to the LEF or AZA group by randomisation. Randomisation was performed using a computerised, interactive voice-response system with stratification according to centre, age, gender and kidney biopsy classification. This is an open label study without masking.

Intervention and assessment schedule

During the induction phase, all patients received intravenous pulse CYC therapy (0.5–1 g/m²) once a month for 6 months combined with oral GCs (with an initial dose equivalent to 1 mg prednisone/kg/d for 4 weeks that was tapered by 10% every 2 weeks to no more than 10 mg/day at the end of the induction phase). If necessary, induction therapy was extended to 9 months for those who showed inadequate clinical response after 6 months of treatment.

During the maintenance phase, patients were randomised to receive LEF (Airuhua) (20 mg/d) or AZA (initial dose 50 mg/d, target dose 100 mg/d). Patients received prednisone or its equivalent (maximum dose, 10 mg per day) with dose reduction based on the investigator’s judgement. The protocol suggested that the GC dose be reduced to 7.5 mg/day at months 9–12 and 5 mg/day at months 12–15. Patients were assessed every 2 months until month 12, followed by every 4 months until month 36, early withdrawal, or termination due to treatment failure.

OUTCOMES

The primary endpoint was the time to kidney flare during 36 months of maintenance-phase follow-up. A kidney flare was defined as (i) the recurrence or development of nephrotic syndrome (24 hours proteinuria ≥3.5 g and serum albumin <30 g/L), (ii) abnormal kidney function (>30% increase in SCr within 1 month directly attributed to lupus and confirmed 2 weeks later, or (iii) 2-fold increase in proteinuria (24 hours proteinuria >1 g in patients with CR or doubling of proteinuria in patients with PR at the end of induction). A kidney flare could occur with or without new or increased haematuria (>5 RBC/HPF) or the appearance of cellular casts.

Key secondary endpoints included the number of patients achieving CR; kidney-associated variables, including 24 hours proteinuria, SCr and serum albumin over time; frequency of extrarenal flares; immunologic variables (C3, C4, and anti-double-stranded DNA antibodies); and safety profile in each group. Disease activity was measured by the SLEDAI-2000 (SLEDAI-2K) scoring system.

Sample size

This study was designed as a non-inferiority trial. The non-inferiority margin was set at 12% for the primary outcome (flare at 36 months of maintenance-phase follow-up), meaning that the lower bound of the two-sided 95% CI for the difference in flare rates between LEF and AZA (as reference) should exceed −12%.

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A previous study in patients with SLE reported flare rates of 15% in the LEF arm and 20% in the AZA arm. Assuming that the flare rates in LEF and AZA groups at 36 months would differ by 5%, a sample size of 158 patients was needed to yield a power of 80% and establish the non-inferiority of LEF to AZA, with a one-sided α level of 0.025. The sample size calculation made the conservative assumption that the dropout rate would be as high as 20%. Therefore, the required sample size was 200.

**Patient and public involvement**
See online supplementary methods section (page 13–14).

**Statistical analysis**
IBM-SPSS (version number: 25.0) was used for data statistics and analysis. The difference between groups for all data was considered significant at p<0.05. Details of the statistical analysis are available in the online supplementary methods.

**RESULTS**

**Patients and treatments**
270 biopsy proven active LN patients were treated with CYC regimen combined with GCs from seven centres in mainland China. After 6–9 months of the induction therapy, 215 patients achieved CR/PR (41 patients received an extended 9 month CYC treatment, and among them, 29 patients achieved clinical response (11 CR patients and 18 PR patients)). Detailed characteristics were listed in online supplementary table 1, and online supplementary figure 1). This intention-to-treat population was randomly assigned to the LEF group (n=108) or AZA group (n=107) for a 36 month maintenance therapy from August 2010 to November 2018. The demographics and baseline disease characteristics did not significantly differ between the two groups, as described in Table 1. A total of 137 patients (63.7%) completed the 36 months of maintenance treatment: 72 (66.7%) in the LEF group and 65 (60.1%) in the AZA group (figure 1).

**Treatments**
Most patients received 20 mg/day of LEF or 100 mg/day of AZA in the maintenance phase (mean body weight in AZA group was 55.8 kg (±7.5 kg) and mean dose of AZA was 1.5–2 mg/kg/day). For 14 patients in the LEF group, the dosage was temporarily reduced to 10 mg/day due to adverse events (AEs) (mild elevation in liver enzymes or decrease in white blood cells) but returned to 20 mg/day within 2 months. For 9 patients in the AZA group, the dosage was temporarily reduced to 50 mg/day due to AEs but increased to 100 mg/day shortly after.

At baseline, the mean dosage of GCs was approximately 10 mg/day (prednisone or equivalent) (Table 1). Patients in both groups underwent GC dosage reduction to 7.5 mg/day and 5 mg/day afterward. The proportion of patients treated with 5 mg/day GCs was 86.3% in the LEF group (69/80) and 94.7% in the AZA group (71/75) at 24 months. At 36 months, 24 patients in the LEF group and 18 patients in the AZA group had their GC dosage further decreased to 2.5 mg/day.

**Study endpoints**
The time to kidney flare, the primary endpoint of the study, was compared between the groups using Kaplan-Meier survival curves. Time to kidney flare was not statistically different in the LEF group (17/108 patients, 15.7%; median time: 16 months) compared with that in the AZA group (19/107 patients, 17.8%; median time 14 months) during the 36 months of follow-up (figure 2). During the first 6 months, 5 in the LEF group and 5 in the AZA group experienced kidney flare. Afterward, there were around four–five cases with kidney flare per year in both groups. One patient from the LEF group and 3 patients from the AZA group met the criteria for a kidney flare based on the recurrence/development of nephrotic syndrome, and 16 from the LEF group and 16 from the AZA group were diagnosed with kidney flare based on proteinuria increases. Kidney flare combined with new or increased haematuria were found in 6 patients (3 in the LEF group and 3 in the AZA group, respectively). In both groups, no kidney flare event was based on abnormal kidney function.

**Key secondary endpoints** were also comparable between LEF and AZA groups. The proportion of patients who achieved and maintained CR over 36 months was similar between LEF and AZA groups (61 (56.4%) in the LEF group vs 58 (54.2%) in the AZA group).

For other kidney-associated parameters, there were no significant differences between LEF and AZA groups with respect to 24-hour proteinuria, serum albumin, SCr and eGFR over a 3-year period (figure 3A–D and online supplementary table 2). Sustained doubling of SCr or kidney failure was not observed in both groups. Subgroup analysis revealed that patients who had

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**Table 1**

| Characteristics                      | LEF group | AZA group |
|--------------------------------------|-----------|-----------|
| Age (year)                           | 30±8.9    | 33±10.9   |
| Female sex—no. (%)                   | 98 (90.7%)| 92 (86.0%)|
| Race or ethnic group—no. (%)         |           |           |
| Hispanic                             | 100%      | 100%      |
| Body weight (kg)                     | 56.2±8.3  | 55.8±7.5  |
| Systolic BP (mm Hg)                  | 123.8±10.4| 122.7±10.0|
| Diastolic BP (mm Hg)                 | 77.6±7.5  | 76.6±8.4  |
| Duration of LN (months)              | 12.8±28.0 | 14.7±31.0 |
| Clinical remission—no. (%)           |           |           |
| CR                                   | 69 (63.9%)| 72 (72.0%)|
| PR                                   | 39 (36.1%)| 30 (28.0%)|
| Kidney biopsy class—no. of patients (%)|           |           |
| III or III-V                         | 33 (30.6%)| 29 (27.1%)|
| IV or IV-V                           | 67 (62.0%)| 62 (57.9%)|
| Pure V                               | 8 (7.4%)  | 16 (15.0%)|
| Urinary protein (mg/24 hours)        | 542±502   | 451±426   |
| Active urine sediment—no. of patients (%)| 5 (4.6%) | 9 (8.4%)  |
| SCr (μmol/L)                         | 67.2±20.8 | 66.8±19.0 |
| Estimated GFR (mL/min/1.73 m²)       | 132.6±44.0| 132.7±38.3|
| Estimated GFR category—no. (%)       |           |           |
| ≥60 mL/min/1.73 m²                   | 73 (98.6%)| 75 (98.7%)|
| ≥90 mL/min/1.73 m²                   | 63 (85.1%)| 65 (86.7%)|
| Immunologic factors                  |           |           |
| Serum C3 (mg/dL)                     | 848±236   | 891±203   |
| Serum C4 (mg/dL)                     | 180±103   | 194±70    |
| Patients receiving drugs at baseline |           |           |
| Prednisone use (mg/day)              | 9.9±0.8   | 9.8±0.8   |
| HCQ use—no. (%)                      | 89 (82.4%)| 93 (86.9%)|
| ACEI/ARB use—no. (%)                 | 31 (28.7%)| 26 (24.3%)|
| SLEDAI score                         | 2.3±2.9   | 2.1±3.0   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; AZA, azathioprine; BP, blood pressure; CR, complete response; GFR, glomerular filtration rate; Han, the Han nationality; HCQ, hydroxychloroquine; LEF, leflunomide; LN, lupus nephritis; PR, partial response; SCr, serum creatinine; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.
Systemic lupus erythematosus

CR at baseline during the remission phase appeared to have a lower risk of kidney flare if they were allocated to the LEF group (6.7%) compared with the AZA group (14.3%), but the difference was not statistically significant.

Regarding extrarenal flare, there was one case in the LEF group and two cases in the AZA group. For the case in the LEF group, the patient had headache, arthritis and fever, with a SLEDAI score of 13. In the AZA group, one case presented with rash and vasculitis (SLEDAI score=12), and the other case showed rash, arthritis and a low platelet count (SLEDAI score=11). Disease activity represented by SLEDAI scores and C3 and C4 levels did not differ over time between the two groups (figure 2).

Safety and tolerability

There was no difference between the two groups in terms of the incidence of AEs: 56.5% (61 of 108 patients) in the LEF group and 58.9% (63 of 107 patients) in the AZA group (table 2). There were no events of death, severe infection or malignancy in the study. There was no serious AE during the study. Haematological abnormality and liver dysfunction were the most common AEs in both groups. However, most AEs were mild, and patients recovered after routine management. The proportion of patients with AEs leading to permanent treatment discontinuation was similar between the LEF group (2/108 patients: 1 case of leucopenia and 1 case of liver dysfunction) and AZA group (5/107 patients: 3 cases of leucopenia, 1 case of thrombocytopenia and 1 case of liver dysfunction).

Long-term extended follow-up

After the 3-year study, many patients maintained in remission and continued to be followed up. For those in sustained remission, immunosuppressive drugs were further tapered or stopped. For LEF, the dosage was gradually reduced from 10 mg/day to 10 mg every other day. Similarly, AZA was reduced from 50 mg/day to 50 mg every other day. The target GC dosage was 2.5 mg/day (prednisone or equivalent). Patients were not encouraged to stop GCs.

90 patients continued using study drugs for more than 4 years, including 48 in the LEF group and 42 in the AZA group. The reasons that patients stopped LEF or AZA treatment included kidney flare (7 in the LEF group from the 4th–6th year and 6 in the AZA group), intention for pregnancy (6 in the LEF group and 2 in the AZA group), sustained remission and lost to follow-up. At the end of 5 years, 37 patients continued LEF or AZA treatment (22 in the LEF group and 15 in the AZA group), and 19 patients had been treated for more than 6 years (10 in the LEF group and 9 in the AZA group). There was no kidney failure event during the study. Only one patient stopped AZA because of intolerance during the extended follow-up, suggesting the long-term safety of both LEF and AZA.

DISCUSSION

Maintenance therapy is important in the treatment of LN and SLE disease. The aim of maintenance therapy is to consolidate
responses into durable complete remissions and limit the risk of disease flare-up. It is well recognised that sustained remission effectively reduces cumulative damages and improves the quality of life for patients with SLE. In the current study, we compared the time to and rate of kidney flare between patients in LEF and AZA groups after they achieved CR or PR with initial CYC-based induction therapy. In our study, the rate of kidney flare was 15.7% in the LEF group and 17.8% in the AZA group during the 36 months of follow-up. In the previous 3-year maintenance study in Aspreva Lupus Management Study (ALMS) patients, kidney flares were observed in 15 of 116 patients given MMF (12.9%) compared with 26 of 111 patients given AZA (23.4%). MMF was significantly more effective than AZA in the 3-year maintenance treatment. In contrast, MMF was not superior to AZA in the MAINTAIN Nephritis Trial, in which the two drugs were compared after a short course of the Euro-CYC regimen. Kidney flare occurred in 19% of patients in the MMF group (10/53) compared with 25% in the AZA group (13/52) after a mean follow-up of 4 years. During a 10-year follow-up, the MAINTAIN Trial did not reveal an advantage of MMF over AZA as maintenance therapy for LN. Therefore, compared with the previous two maintenance studies of LN, the rate of kidney flare in our cohort appeared to be lower, particularly in the AZA group, but still comparable. The reason behind this discrepancy might be as follows. (1) All participants in our study were Chinese compared with the 100% Caucasian cohort in the MAINTAIN study and ~70% non-Asian ancestry patient population in the ALMS study. Racial differences may partially account for treatment responses. (2) Patients in our study were given more vigorous induction therapy with higher CYC dosages and thus might have been in a more stable condition when enrolled. At baseline, the mean 24-hour urinary protein was ~500 mg/24 hours in the current study, which was notably lower than that in the ALMS study (906±819.93 mg/24 hours in the MMF group and 820.0±754.33 mg/24 hours in the AZA group). As an early proteinuria response is associated with favourable long-term kidney outcomes, the baseline disease status likely contributes to the future risk of kidney flares.

LN is a disease with significant unmet clinical needs. In addition to the increasing list of new medications introduced into this field, drug repurposing has also attracted substantial interest. LEF has been extensively used in the treatment of rheumatoid arthritis worldwide, with a good safety profile and long-term use experience. In the current study, LEF was non-inferior to AZA in terms of effectiveness and AEs in the long-term treatment of patients with LN. Our findings support LEF as a potential candidate treatment for LN during the maintenance phase. The 6 years of data provide evidence that LEF is not only effective in controlling kidney and extrarenal flares but is also quite safe and well tolerated. Transient liver dysfunction and mild leucopenia were common AEs. Compared with calcineurin inhibitors, kidney injury was rarely reported for LEF, supporting its extended use in patients with kidney diseases. Pregnancy is a concern with LEF treatment. Patient dropouts because of pregnancy or pregnancy planning were more frequently observed in the LEF arm compared with the AZA arm. For patients wanting to conceive, administering cholestyramine could effectively remove the drug from the body.

Table 2 Summary of patients with AEs over the 3 year study.

| Safety population, n (%) | LEF | AZA |
|--------------------------|-----|-----|
| Any AEs                  | 61  | 63  |
| AEs occurring in ≥5% of patients in either treatment group |     |     |
| Leucopenia               | 31  | 31  |
| Anaemia                  | 13  | 13  |
| Thrombocytopenia         | 7   | 6   |
| Elevated liver enzymes   | 23  | 22  |
| Irregular menstruation or amenorrhoea | 7   | 5   |
| Any grade 3 AEs          |     |     |
| Leucopenia               | 0   | 1   |
| Cerebrovascular accident | 0   | 1   |
| Elevated liver enzymes   | 4   | 2   |
| Any AEs leading to permanent treatment discontinuation |     |     |
| Leucopenia               | 1   | 3   |
| Elevated liver enzymes   | 1   | 0   |
| Thrombocytopenia         | 0   | 1   |
| AE, adverse events; AZA, azathioprine; LEF, leflunomide. |     |     |
Adding LEF to the LN treatment strategy is of clinical significance. First, only a few clinical randomised controlled trials have investigated maintenance therapy for LN, and they required long-term follow-up and were limited by a low frequency of events. The current study provides a relatively high level of evidence supporting LEF in the maintenance treatment of LN with comparable efficacy to the standardised regimen of AZA. We recognise the increasing use of MMF as the first-line treatment for LN, and the ALMS study supported the superiority of MMF over AZA in the maintenance therapy for LN, despite the negative findings from the MAINTAIN study. However, they should not prevent the use of AZA or the potential use of LEF in LN treatment because MMF is not appropriate for all patients. For example, the significantly increased risk of infection remains a concern for MMF use in Asians, therefore, most of our patients could not tolerate the recommended dosage of MMF for induction therapy (up to 3 g/day). The dose of MMF used in ALMS study was 2 g/day, while the recommended dosage of MMF for maintenance therapy was 1–2 g/day. This might potentially limit the performance of MMF in real-world practice as compared with that in the clinical trial. Second, LEF is a drug with a new mechanism of action in the treatment of LN. Thus, LEF might improve the effectiveness of LN treatment and potentially act as an adjunct therapy or a candidate for combination/multitarget therapy. Although it is beyond the scope of this study, investigating combination therapies in future studies is intriguing. Finally, LEF has several advantages, including easy accessibility, long-term safety profile and cost effectiveness, that may benefit patients, especially those in developing countries with limited access to new drugs or with tolerance and efficacy issues with current drugs.

There are several limitations to the current study. First, the study was an open-label study, not a double-blinded trial. However, the primary outcome (kidney flare) was strictly defined by objective lab examination results and, therefore, unlikely to have been influenced by the open-label design. Second, the current study is a multicentre study based in mainland China. Whether the results can be verified in patients from other ethnic groups requires larger international studies. Third, the trial was designed for 3 years. Therefore, it is still too early to conclude the long-term effectiveness of LEF in terms of hard outcomes, such as death and kidney failure. However, according to our experience, no patients in the study population have developed kidney failure in the study before taking part.

In summary, to the best of our knowledge, this multicentre, randomised-controlled, open-label study is the first to report the non-inferiority of LEF to AZA for the maintenance therapy of LN in terms of its efficacy and safety profiles. Therefore, LEF may provide a candidate drug in the treatment of LN.

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Correction notice This article has been corrected since it published Online First. Affiliation number 4 has been corrected.

Contributors LL and CB wrote the first draft of the study protocol. JX, LS, XZ, LH, ZL and LD provided modification comments and final approval. CW, MD and SW were responsible for data collection. QF, CW and MD were responsible for data management and statistical analysis. QF, LL and CB accessed and verified the underlying data. The first draft of the manuscript was completed by QF and CW. All authors reviewed the subsequent manuscripts and approved the final version. LL and CB are the guarantors.

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Competing interests None declared.

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Patient consent for publication Not applicable.

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REFERENCES
1 Tektöndüsi MI, Daşqua A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971-2015: a systematic review and Bayesian meta-analysis. *Arthritis Rheumatol* 2016;68:1432–41.
2 Fanoukakis A, Kostopoulou M, Cheema K, et al. 2019 update of the joint European League against rheumatism and European renal Association-European dialysis and transplant association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis* 2020;79:713–23.
3 Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. *Kidney Int* 2021;100:753–79.
4 Pinto P, Dosugadis M. Acta Reumatol Port. In: Leflunomide in clinical practice., 2006; 31, 215–24.
5 Bartlett RR, Popovic S, Raiss RX. Development of autoimmunity in MRL/lpr mice and the effects of drugs on this murine disease. *Scand J Rheumatol Suppl* 1988;75:290–9.
6 He C, Lu X, Yan Z, et al. Therapeutic effect of leflunomide on the development of experimental lupus nephritis in mice. *Rheumatol Int* 2012;32:633–8.
7 Zhang M, Qi C, Zha Y, et al. Leflunomide versus cyclophosphamide in the induction treatment of proliferative lupus nephritis in Chinese patients: a randomized trial. *Clin Rheumatol* 2019;38:859–67.
8 Yi J, He Z, Xu S, et al. Efficacy and safety of leflunomide in IgA nephropathy: a systematic review and meta-analysis. *Int Urol Nephrol* 2019;51:1897–98.
9 Hochberg MC. Updating the American College of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis & Rheumatism* 1997;40:40.
10 Gladman DD, Baier D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288–91.
11 Parikh SV, Almaaen S, Brodkay S, et al. Update on lupus nephritis: core curriculum 2020. *Am J Kidney Dis* 2020;76:265–81.
12. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 2011;365:1886–95.
13. Houssiau FA, D’Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the maintain nephritis trial. *Ann Rheum Dis* 2010;69:2083–9.
14. Tamirou F, D’Cruz D, Sangle S, et al. Long-term follow-up of the maintain nephritis trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. *Ann Rheum Dis* 2016;75:526–31.
15. Cao H, Rao Y, Liu L, et al. The efficacy and safety of leflunomide for the treatment of lupus nephritis in Chinese patients: systematic review and meta-analysis. *PLoS One* 2015;10:e0144548.
16. Brent RL. Teratogen update: reproductive risks of leflunomide (Arava): a pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. *Teratology* 2001;63:106–12.
17. Hahn BH, McMahon MA, Wilkinson A, et al. American College of rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res* 2012;64:797–808.
18. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009;20:1103–12.
19. Koo HS, Kim YC, Lee SW, et al. The effects of cyclophosphamide and mycophenolate on end-stage renal disease and death of lupus nephritis. *Lupus* 2011;20:1442–9.