

Risk of adverse events from different drugs for SLE: a systematic review and network meta-analysis

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ABSTRACT

Objective The comparative safety of immunosuppressive drugs, biologicals and glucocorticoids (GC) for patients with SLE remains controversial. We aimed to investigate the specific side effects of the available SLE drugs in this population of patients.

Methods Electronic databases were systematically searched through September 2017 for randomised trials in patients with SLE. The primary outcomes were all-cause mortality and withdrawal related to adverse events (AEs). We performed a random-effects network meta-analysis to obtain estimates for primary and secondary outcomes and presented these estimates as ORs with 95% CIs.

Results Forty-four studies comprising 9898 participants were included in the network meta-analysis. No drug regimen was considered to be safer for reducing all-cause mortality. However, compared with cyclophosphamide, azathioprine (OR 3.04, 95% CI (1.44 to 6.42)) and cyclosporine (OR 3.28, 95% CI (1.04 to 10.35)) were significantly less safety in AE-related withdrawals, and GC was ranked lowest and led to higher withdrawal rates. Tacrolimus (TAC) was ranked high and showed a benefit in many outcomes. Biologicals and chloroquine also showed good safety in all of the available outcomes, while the beneficial effects of other immunosuppressive drugs were not substantial in different types of serious adverse events.

Conclusions TAC is the safest strategy for patients with SLE. Biologicals and chloroquine are also fairly safe for patients with SLE. The use of other immunosuppressive drugs and GC needs to be balanced against the potential harms of different types of AEs, and the practical safety of drug combinations still requires further trials to evaluate.

INTRODUCTION

SLE is known as an autoimmune disease with complex pathogenic mechanisms that always lead to multisystem damage; the long duration of use of immunosuppressive drugs and glucocorticoids (GCs) increases the risk of premature death.^{1–3}

During the treatment, nearly all patients report one or more adverse events (AEs), and these AEs shape doctors' preferences, especially when two drugs are considered to be equivalent. Serious AEs (SAEs) refer to events that result in death, are life threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation,

result in persistent or significant disability/incapacity, lead to a congenital anomaly/birth defect or that require intervention to prevent permanent impairment or damage; these effects can directly demonstrate the safety of available drugs in different aspects, eliminating the interference of more mild AEs. However, mainly because of an absence of head-to-head trials and SAE data, the comparative safety is largely unknown.

In a network meta-analysis published in 2017, researchers found that, in patients with proliferative lupus nephritis, mycophenolate mofetil (MMF) combined with calcineurin inhibitor therapy was less likely to cause ovarian failure, while the regimens generally had similar odds of major infection.⁴ Another network meta-analysis published in 2016 showed that tacrolimus (TAC) compared with other agents can reduce the risk of serious infection in lupus nephritis.⁵ Limited by the differing inclusion criteria, the divergence between these two studies cannot be ignored. To obtain an impartial comparison of the important AEs among the available drugs for all patients with SLE, the aim of our study was to assess the comparative effects of all available effective agents in patients with SLE using network meta-analysis.

MATERIALS AND METHODS

Search strategy

A systematic search of the scientific literature was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis. The searches included PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and Embase (from their inception to September 2017) using a combination of keywords and search strategies with Medical Subject Headings (online supplementary appendix 1). The search included only randomised controlled trials (RCTs) that reported the outcomes of interest. Additionally, reference lists from

trials, review articles and reports were manually scanned to identify any other eligible studies.

Study selection

To make a comprehensive evaluation of the risk of AEs with agents used to treat SLE, our exposure of interest was treatment with immunosuppressants or biologicals (we only included rituximab (RTX) and belimumab due to their validated efficacy) or GC. Patients who met the 1987 American College of Rheumatology Classification criteria for SLE were included. Our primary outcomes were all-cause mortality and AE-related withdrawals. Secondary outcomes included AEs, SAEs, cardiovascular events (CVEs) (acute coronary syndrome, chronic ischaemic heart disease, coronary revascularisation, cardiovascular disease (CVD) death, cerebrovascular events or peripheral vascular events), serious infections (serious infection, major infection, severe infection, sepsis, cardiovascular infection or bacterial pneumonia), bone toxicity (avascular necrosis or fracture), malignant transformation, serious gastrointestinal events (leading to dose reduction or withdrawal), ovarian failure (sustained amenorrhoea), menstrual disorder, new-onset hypertension, serious leucopenia (white cell count $<2 \times 10^9$ L leading to dose reduction or withdrawal), leucopenia and hyperglycaemia (hyperglycaemia or new-onset diabetes).

Duplicate reports, studies that did not report on the outcomes of interest or in which all arms had 0 events, studies that lasted 24 weeks or less, studies that included children younger than 10 years old or women during pregnancy or lactation and studies that included fewer than 20 patients. All lupus nephritis diagnoses should have been confirmed by biopsy. We also excluded scientific reports that presented pooled trial data for which the individual trials could not be identified to prevent double counting.

Screening and data extraction

Standardised data forms and data extraction training exercises were developed to achieve a high level of consensus between reviewers. Two reviewers independently assessed the full text of the articles to confirm their eligibility. Any disagreement was resolved by consensus discussion.^{6 7} All studies included were listed in online supplementary appendix 2.

Assessment of methodology quality

Two authors evaluated the eligible studies from seven domains in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews (online supplementary appendix 3).

Statistical analysis

First, we conducted pairwise meta-analyses using the random-effects model.⁸ All results are expressed as ORs with 95% CIs. The heterogeneity of the data was assessed using the I^2 test, with a $p < 0.05$ indicating significant heterogeneity.

We then performed network meta-analyses to obtain estimates for primary and secondary outcomes and presented these estimates as ORs with 95% CIs.⁹ Network meta-analyses assumes transitivity, which means one can learn about treatment A versus treatment B via treatment C (eg, learning about cyclophosphamide (CYC) vs TAC) via MMF). We implemented network meta-regression within the frequentist framework for outcomes to evaluate the assumptions in the studies and provide graphical representation of the results.

We investigated the extent of heterogeneity in every network by comparing the magnitude of τ for the network with an empirical distribution of heterogeneity variances specific to the types of outcomes and treatments being compared.¹⁰ Values lower than 0.1 were considered low, outcomes from 0.1 to 1.0 were considered moderate and outcomes higher than 1.0 represented high heterogeneity.

Disagreement between direct and indirect evidence can suggest that the transitivity assumption might not hold. We used a loop-specific approach to investigate the consistency within every closed triangular or quadratic loop in every network as the difference between direct and indirect estimates for a specific treatment comparison (RoR - ratio of odds ratio) in the loop.^{11 12} We identified inconsistent loops as those yielding a 95% CI excluding 1. This approach can be easily applied and indicate loops with large inconsistency but cannot infer consistency of the entire network or identify the particular comparison that is problematic. To check the assumption of consistency in the entire network, we then used the design-by-treatment interaction model that provides a single inference, and the χ^2 tests were adopted.¹³ For the generalisability of the findings, sensitivity analyses were then assessed by restricting analyses to studies with the following design characteristics: patients with lupus nephritis, follow-up longer than 24 months and without the use of biological agents.

To rank the treatments for an outcome, we calculated different ranks possibility of each agent, and then reported probabilities for all ranks and created a line graph showing cumulative ranks. In the line graph, each column represented a treatment, and different safety ranks were represented by different colours; the percentage of a colour was corresponding to the possibility of certain rank. The default was set to report only the probabilities of being the treatment with minimum frequency in the outcome, so the treatment that had the largest proportion of first rank colour in the graph indicated the safest treatment for the outcome. We also used forest plots to obtain an intuitive and full comparison of the safety of these agents.^{14 15}

RESULTS

A total of 2377 relevant articles were searched, and 44 studies with 9898 patients were finally identified and included.¹⁶⁻⁵⁹ Of the RCTs included in the systematic review, nine were three-arm trials, one was a four-arm

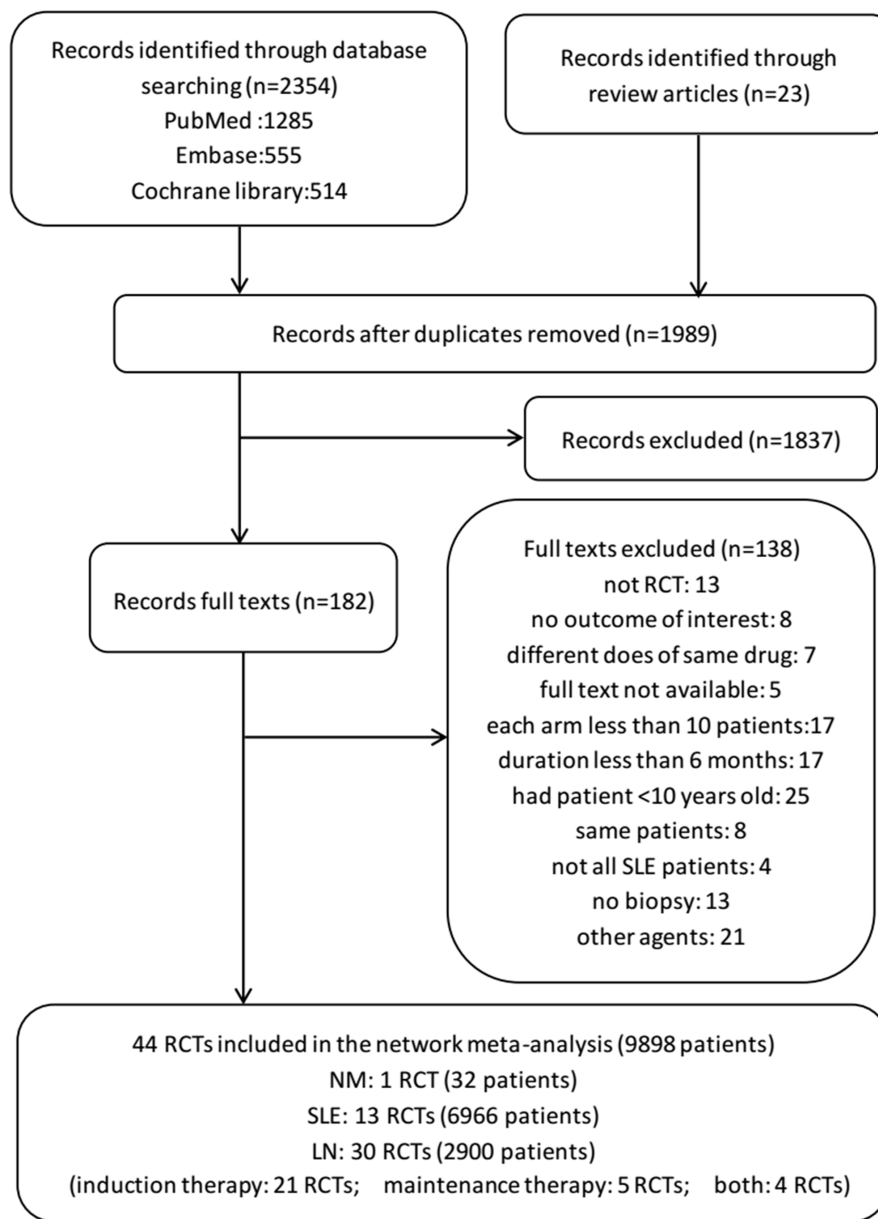


Figure 1 Summary of evidence search and selection. A total of 19 immunosuppressants or biologicals alone or in combination were involved in our analyses: intravenous CYC (0.5–1 g/m² body surface area monthly) (21 trials), AZA (1–4 mg/kg/day) (12 trials), MMF (500–3000 mg/day) (12 trials), TAC (0.05–0.1 mg/kg/day) (four trials), oral CYC (1–4 mg/kg/day) (two trials), CSA (1–5 mg/kg/day) (five trials), MTX (7.5–20 mg/week) (three trials), RTX (1 g/day) (two trials), LD belimumab (1 mg/kg) (four trials), MD belimumab (4 mg/kg) (one trial), HD belimumab (10 mg/kg) (five trials), SC belimumab (200 mg/week) (one trial), LEF (1 mg/kg/day) (one trial), chloroquine (150 mg/day) (one trial), AZA+GC (one trial), MMF+TAC (two trials), intravenous CYC+MMF (one trial), CYC-AZA (two trials) and AZA+CYC (one trial). AZA, azathioprine; CSA, cyclosporine; CYC-AZA, CYC followed by AZA; CYC, cyclophosphamide; GC, glucocorticoid; HD, high dose; LD, low dose; LEF, leflunomide; MD, moderate dose; MMF, mycophenolate mofetil; MTX, methotrexate; RCT, randomised controlled trial; RTX, rituximab; SC, subcutaneous; TAC, tacrolimus, NM, neurological manifestations; LN, lupus nephritis

trial and one was a five-arm trial. The selection process, reasons for exclusion and information for interventions are detailed in [figure 1](#). Networks of eligible comparisons for the primary outcomes are presented in [figure 2](#).

Risk of bias

The risk of bias in studies contributing to the primary outcomes was generally low, suggesting no evidence of small-study effects in the network. Moreover, in the

risk of bias summary graph, the risk of bias was determined to be low for most criteria and unclear for some criteria (online supplementary appendix 3).

Heterogeneity and inconsistency

In pairwise comparisons of the primary outcomes, no evidence of statistical heterogeneity was seen in general (online supplementary appendix 5). In the network meta-analyses, statistical heterogeneity was

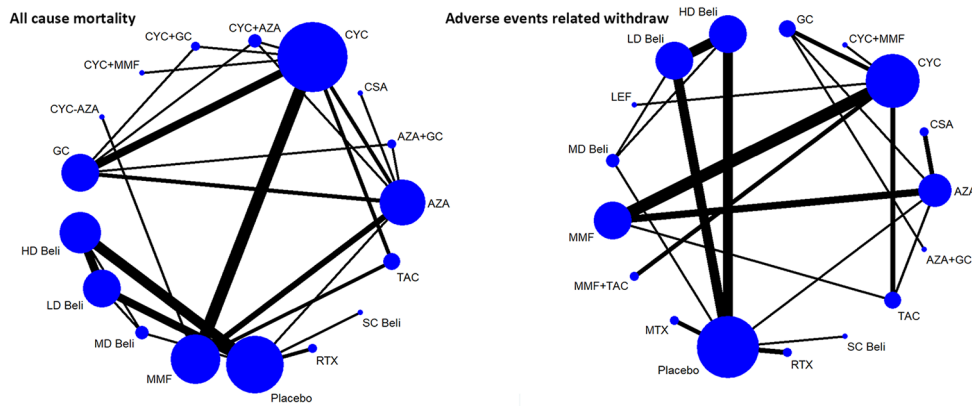


Figure 2 Networks of treatment comparisons for primary outcomes of SLE agents in patients with SLE. The size of the nodes (blue circles) corresponds to the number of trials of the treatments. Comparisons are linked with a line, the thickness of which corresponds to the number of trials that assessed the comparison. +, combined with; AZA, azathioprine; Bel, belimumab; CSA, cyclosporine; CYC-AZA, CYC followed by AZA; CYC, cyclophosphamide; GC, glucocorticoid; HD, high dose; LD, low dose; LEF, leflunomide; MD, moderate dose; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; SC, subcutaneous; TAC, tacrolimus.

low in most networks, moderate in networks for serious gastrointestinal events and ovarian failure and substantial in networks for AEs and new-onset hypertension. Treatment estimates from direct and indirect evidence in general did not show evidence of statistical inconsistency except for one loop of evidence for AEs (CYC–MMF–TAC). Global inconsistency was not noted within any network except for AEs (online supplementary appendix 6).

Outcomes

Data for direct comparisons and network estimates for statistically significant outcomes are shown in table 1, and complete outcomes are listed in online supplementary appendix 5 and 7.

Primary outcomes

For primary outcomes, all-cause mortality was reported in 29 studies (8762 participants), but because data were scant for some treatments, the results of both the pairwise and network estimates were not significant. Compared with CYC alone (the most commonly used drug), the ORs ranged from 0.44 (95% CI 0.84 to 2.31) for the highest ranked treatment strategy (TAC) to 5.76 (95% CI 0.24 to 137.52) for the lowest ranked agent (CYC followed by azathioprine (AZA)). AE-related withdrawal was reported in 29 studies (8371 participants). AZA was significantly less safe compared with CYC, TAC and MMF (ORs 3.04, 95% CI (1.44 to 6.42), 3.63 (1.05 to 12.61) and 2.08 (1.29 to 3.36), respectively), and CSA was also significantly less secure compared with CYC (3.28 (1.04 to 10.35)). AZA combined with GC, CYC combined with MMF and moderate dose (MD) belimumab were also ranked highly, indicating high safety, while GC with the lowest rank was considered to lead to a higher withdrawal rate (online supplementary appendix 7).

SECONDARY OUTCOMES

Adverse events

Chloroquine ranked highest in all treatments for the risk of AEs and was significantly safer than methotrexate (MTX), placebo, RTX, low dose (LD) belimumab, MD belimumab and high dose belimumab (OR 0.09, 95% CI (0.02 to 0.44), 0.16 (0.03 to 0.96), 0.10 (0.02 to 0.68), 0.15 (0.02 to 0.92), 0.08 (0.01 to 0.62), 0.16 (0.03 to 0.98), respectively). TAC was safer compared with CYC (0.03 (0.00 to 0.56)), and AZA was safer compared with GC (0.06 (0.01 to 0.61)). CYC followed by AZA ranked the lowest and increased the risk of AEs (online supplementary appendix 7).

SAEs

For SAEs, subcutaneous (SC) belimumab was significantly better than placebo and LD belimumab (0.65 (0.43 to 0.99) and 0.57 (0.36 to 0.91), respectively). MD belimumab ranked the lowest and increased the risk of SAEs (online supplementary appendix 7).

Serious infection

TAC was superior to CYC, AZA, MMF combined with TAC and CYC followed by AZA for prevention of serious infection (0.32 (0.12 to 0.83), 0.34 (0.12 to 0.96), 0.16 (0.04 to 0.62), and 0.22 (0.05 to 0.95), respectively), whereas the effects of other drugs were not significant or were very imprecise. Additionally, CYC combined with AZA, CYC combined with MMF, and TAC alone ranked highest and indicated a lower possibility of suffering serious infection, while MMF combined with TAC ranked lowest (online supplementary appendix 7).

Serious gastrointestinal events

RTX and placebo ranked high in all treatments and both had significant reductions in serious gastrointestinal events compared with AZA (0.04 (0.00 to 0.49) and 0.07 (0.01 to 0.60), respectively), MMF (0.09

Table 1 Results from pairwise meta-analysis and network meta-analysis ORs (and 95% CI) for statistically significant outcomes

Comparisons		Direct drug comparisons/ participants (n/N)	Pairwise meta-analysis	Network meta-analysis
Adverse events-related withdraw				
AZA versus	MMF	3/572	2.13 (1.30 to 3.47)	2.08 (1.29 to 3.36)
	CYC			3.04 (1.44 to 6.42)
	TAC			3.63 (1.05 to 12.61)
CSA versus	CYC			3.28 (1.04 to 10.35)
Adverse events				
TAC versus	CYC	1/40	0.03 (0.00 to 0.56)	
AZA versus	GC	1/28	0.06 (0.01 to 0.61)	
Chloroquine versus	MTX	1/37	0.09 (0.02 to 0.44)	0.09 (0.02 to 0.44)
	Placebo			0.16 (0.03 to 0.96)
	RTX			0.10 (0.02 to 0.68)
	LD belimumab			0.15 (0.02 to 0.92)
	MD belimumab			0.08 (0.01 to 0.62)
	HD belimumab			0.16 (0.03 to 0.98)
Serious adverse events				
SC belimumab versus	Placebo	1/836	0.65 (0.43 to 0.99)	0.65 (0.43 to 0.99)
	LD belimumab			0.57 (0.36 to 0.91)
Serious infection				
TAC versus	CYC	2/113	0.23 (0.06 to 0.91)	0.32 (0.12 to 0.83)
	AZA			0.34 (0.12 to 0.96)
	MMF+TAC			0.16 (0.04 to 0.62)
	CYC-AZA			0.22 (0.05 to 0.95)
Serious gastrointestinal events				
RTX versus	AZA			0.04 (0.00 to 0.49)
	MMF			0.09 (0.01 to 0.70)
	CSA			0.02 (0.00 to 0.26)
Placebo versus	AZA			0.07 (0.01 to 0.60)
	MMF	2/127	0.10 (0.02 to 0.57)	0.15 (0.03 to 0.80)
	CSA			0.03 (0.00 to 0.33)
Serious leucopenia				
MMF versus	CYC	2/87	0.14 (0.03 to 0.63)	0.12 (0.03 to 0.49)
	AZA	2/226	0.19 (0.04 to 0.86)	0.22 (0.05 to 0.91)
TAC versus	CYC			0.06 (0.01 to 0.29)
	AZA	1/70	0.11 (0.03 to 0.42)	0.11 (0.03 to 0.39)
Leucopenia				
AZA versus	MMF	2/345	7.68 (1.94 to 30.40)	5.81 (2.10 to 16.06)
	TAC	1/70	9.25 (2.39 to 35.80)	7.74 (2.31 to 25.92)
	CYC			3.20 (1.13 to 9.06)
	GC			12.30 (1.35 to 112.26)
	CSA	2/158	4.00 (1.85 to 8.33)	4.55 (2.22 to 9.09)
	MMF+TAC			15.51 (2.79 to 86.12)
CYC versus	MMF+TAC			4.84 (1.24 to 18.93)
	MMF			1.81 (1.05 to 3.14)

Continued

Table 1 Continued

Comparisons		Direct drug comparisons/ participants (n/N)	Pairwise meta-analysis	Network meta-analysis
Ovarian failure				
CYC versus	AZA	1/39	15.00 (3.17 to 71.00)	
GC versus	CYC	3/149	0.12 (0.03 to 0.46)	0.13 (0.02 to 0.71)
	CYC+GC	1/55	0.11 (0.02 to 0.54)	0.11 (0.01 to 0.95)
	CYC-AZA			0.07 (0.01 to 0.92)
Menstrual disorder				
CYC versus	MMF+TAC	2/402	3.94 (1.07 to 14.50)	3.94 (1.07 to 14.49)
	MMF			2.15 (1.00 to 4.60)
New-onset hypertension				
AZA versus	GC	1/28	0.10 (0.01 to 0.93)	
CSA versus	GC	1/27	84.14 (3.90 to 1814.89)	
HD belimumab versus	Placebo	1/577	0.53 (0.29 to 0.99)	

+, combined with; AZA, azathioprine; CSA, cyclosporine; CYC, cyclophosphamide; CYC-AZA, CYC followed by AZA; GC, glucocorticoid; HD, high dose; IV, intravenous infusion; LD, low dose; MD, moderate dose; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; SC, subcutaneous; TAC, tacrolimus.

(0.01 to 0.70) and 0.15 (0.03 to 0.80), respectively), and CSA (0.02 (0.00 to 0.26) and 0.03 (0.00 to 0.33), respectively). TAC alone also showed great benefit of serious gastrointestinal events. Compared with CSA alone, the combination with AZA could reduce the risk of serious gastrointestinal events (online supplementary appendix 7).

Serious leucopenia

TAC and MMF showed significantly rates of serious leucopenia compared with CYC (0.12 (0.03 to 0.49) and 0.06 (0.01 to 0.29), respectively) and AZA (0.22 (0.05 to 0.91) and 0.11 (0.03 to 0.39), respectively). Belimumab also had beneficial effects, while CYC alone, CYC followed by AZA and AZA alone demonstrated a higher possibility of suffering serious leucopenia (online supplementary appendix 7).

Leucopenia

Similar to the result of serious leucopenia, CYC and AZA increased the risk of suffering leucopenia compared with MMF, TAC, GC, CSA and MMF combined with TAC (table 1), and AZA was considered the worst (compared with CYC: 3.20 (1.13 to 9.06)). The combination of AZA and CYC also ranked low, as did LEF. GC and MMF combined with TAC, on the contrary, played an important role in reducing leucopenia events (online supplementary appendix 7).

Ovarian failure

TAC, AZA and GC ranked high in ovarian failure, and GC showed significant reductions compared with CYC, CYC combined with GC and CYC followed by AZA (0.13 (0.02 to 0.71), 0.11 (0.01 to 0.95) and 0.07 (0.01 to 0.92), respectively). CYC alone and in

combination increased the risk of ovarian failure (online supplementary appendix 7).

Menstrual disorder

Similar to the result of ovarian failure, TAC and AZA ranked high and reduced the risk of menstrual disorders. CYC ranked the lowest, and CSA also showed an increased tendency to cause menstrual disorders (online supplementary appendix 7).

New-onset hypertension

Different from pairwise analyses, the network results of new-onset hypertension were not significant. However, CSA was ranked lowest, which was also confirmed by direct comparison (compared with GC 84.14 (3.90 to 1814.89), while AZA compared with GC 0.10 (0.01 to 0.93)) indicated an increased risk of hypertension (online supplementary appendix 7).

Outcomes with no statistically significant

There was no evidence that any of these drugs had significantly different odds of CVEs, bone toxicity, malignant transformation and hyperglycaemia related to the limited data and follow-up duration. The rank results required cautious interpretation for the conflicting sort of these drugs alone or in combination (online supplementary appendix 7).

Sensitivity analyses

Results for serious infection were generally robust in sensitivity analyses restricted to lupus nephritis patients only and excluding biological agents, but it was imprecise when restricted to trials with follow-up of longer than 24 months (online supplementary appendix 8).

DISCUSSION

Our network meta-analysis provides unified hierarchies of evidence for all available effective agents in patients who have SLE, overcoming the absence of comparative data in head-to-head trials. Overall, no significant difference was observed in all cause mortality. However, GC ranked the lowest as the least effective agent for prevention of AE-related withdrawal, and AZA and CSA, which also ranked low, were significantly less secure compared with CYC. As for the result of all AEs, chloroquine ranked highest in all treatments and was significantly less safe than MTX and most biologicals; TAC compared with CYC and AZA compared with GC also had better safety. For SAEs, SC belimumab was significantly better than placebo and LD belimumab. These results provide us a comprehensive understanding of the agents' safety and, compared with CYC, TAC and chloroquine, may have better safety, while GC is believed to be less safe.

Compared with the general population, patients with SLE have more than a sixfold higher risk of developing atherosclerotic lesions and much a higher risk of cardiovascular morbidity and mortality,^{60 61} and the multiple SLE therapies play important roles in the disease progression.^{62 63} Subsequent studies have confirmed it and have indicated that corticosteroids were linked to increased CVE risk, whereas antimalarial medications were protective.^{64 65} Moreover, a similar study found that corticosteroids and non-steroidal anti-inflammatory drugs were associated with an increased risk of CVEs in rheumatoid arthritis.⁶⁶ However, limited to the simple size, we did not find significant results, and to exclude the effects of other factors, long-term follow-up is also required.

Serious infection is always a key concern for patients with SLE, since immunosuppressive drugs and GCs both suppress the immune system.^{67 68} Similar to Singh *et al*'s study,⁵ TAC was found to have a large advantage compared with several other agents for the prevention of serious infection. It also appears that the benefit of TAC was evident in lupus nephritis patients and in patients with SLE.

Bone toxicity, especially avascular necrosis, is a serious comorbidity in SLE patients, and strategies to minimise GC use are necessary to prevent this serious complication.^{69 70} Recent research has found that the use of immunosuppressive agents is also a significant risk factor, while antimalarial treatments played a protective role.⁷¹ However, since the incidence of bone toxicity in patients with SLE was affected by disease activity, a higher disease activity score is significantly associated with an accelerated incidence of bone toxicity; the influence of immunosuppressive agents should be cautiously estimated, since compared with the patients who do not use immunosuppressive agents, user conditions can be much worse and they are likely to have higher disease activity scores.

In the previous study, researchers found that compared with CYC, MMF incurred lower risks of nausea and vomiting, but it was more likely to cause diarrhoea.⁴ Although gastrointestinal events are quite common in

treatments for SLE, few studies focus on it. Our results indicated that RTX, TAC and placebo, as well as CSA combined with AZA could reduce the risk of serious gastrointestinal events, while CSA was associated with a higher risk of suffering serious gastrointestinal events. The combination of these agents may indicate lower levels of gastrointestinal toxicity, an effect similar to those shown in the previous outcomes. The combination of two low-rank agents became safer, and whether it is just a coincidence or a feasible process for toxicity reduction, more studies will be needed to draw a conclusion.

GC, MMF, TAC and their combinations showed benefits in the reduction of all leucopenia events. AZA and CYC, on the contrary, increased the risk of all leucopenia events. The result from both serious leucopenia and leucopenia were consistent, similar to the results for ovarian failure and menstrual disorders. Previous studies have already confirmed that patients who used CYC had a higher occurrence of transient amenorrhea and premature menopause.^{72–74} Apart from these findings, our results found that TAC, GC and AZA had low ovarian toxicity and may be good alternative therapies for women of childbearing age, while the risk of ovarian toxicity with CSA use should be considered.

Our study has potential limitations. First, because of scant primary data, the effects of agents on CVEs, bone toxicity, malignant transformation, new-onset hypertension and hyperglycaemia were very uncertain, leading to a pivotal weakness in our understanding of these drugs. The present debate about optimum treatments in SLE would be assisted greatly by the collection of robust data for these outcomes in future trials. Second, data for the outcome of SAEs were only reported in some of the studies, and most of them used biologicals; thus, we cannot directly determine the incidence rate of SAEs for all these agents. Third, haemorrhagic cystitis was poorly defined, and scant evidence relating to this outcome does not allow us to make proper estimates of the risk benefit ratio of agents in SLE. Fourth, we did not restrict patients to only adults, as if we had done so, the studies included would have been insufficient to run the analyses. Fifth, due to lack of original data, we are not sure whether the influence of other factors, including the organs involved, underlying disease and demographics, affect the outcomes.

In summary, our analysis showed that TAC is the safest strategy and has benefits for nearly all the SAEs, while the benefits of other agents are not very substantial in different types of SAEs. Therefore, we must consider the potential harms of these treatments in individual patients and even in one patient in different conditions. So that, the status of specific AEs can be evaluated, and appropriate treatments with improved safety should be adopted. Surveillance for treatment-related AEs is important, as is better recording these different types of SAEs and an improved understanding of their outcomes, particularly in the context of future trials.

Contributors JT contributed to design of the study, performed the systematic review and meta-analysis and drafted the manuscript. YL contributed to screen relevant studies, extract the data and drafted the manuscript. HW, HL and MZ contributed to screen relevant studies and extract the data. QL contributed to interpretation of the results and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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REFERENCES

- Murphy G, Lisnevskaja L, Isenberg D. Systemic lupus erythematosus and other autoimmune rheumatic diseases: challenges to treatment. *Lancet* 2013;382:809–18.
- Gordon C, Amisshah-Arthur M-B, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology* 2017;358.
- Lisnevskaja L, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet* 2014;384:1878–88.
- Palmer SC, Tunnicliffe DJ, Singh-Grewal D, et al. Induction and maintenance immunosuppression treatment of proliferative lupus nephritis: a network meta-analysis of randomized trials. *Am J Kidney Dis* 2017;70:324–36.
- Singh JA, Hossain A, Kotb A, et al. Risk of serious infections with immunosuppressive drugs and glucocorticoids for lupus nephritis: a systematic review and network meta-analysis. *BMC Med* 2016;14:137.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–41.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151:W–94.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
- Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3:80–97.
- Turner RM, Davey J, Clarke MJ, et al. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41:818–27.
- Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol* 2009;62:857–64.
- Veroniki AA, Vasilidis HS, Higgins JP, et al. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013;42:332–45.
- Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98–110.
- White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3:111–25.
- White IR. Multivariate random-effects meta-regression: updates to mvmeta. 2011.
- Stohl W, Schwarting A, Okada M, et al. Efficacy and Safety of Subcutaneous Belimumab in Systemic Lupus Erythematosus: A Fifty-Two-Week Randomized, Double-Blind, Placebo-Controlled Study. *Arthritis Rheumatol* 2017;69:1016–27.
- Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, et al. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: a randomised clinical trial. *Ann Rheum Dis* 2017;76:1575–82.
- Zhang F, Bae SC, Bass D, et al. Arthritis and rheumatology Conference: american college of rheumatology/association of rheumatology health professionals annual scientific meeting, ACR/ARHP. *A pivotal phase III, randomized, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan, and South Korea*. The Netherlands: John Wiley and Sons Inc, 2016:68.
- Rathi M, Goyal A, Jaryal A, et al. Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. *Kidney Int* 2016;89:235–42.
- Mok CC, Ying KY, Yim CW, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. *Ann Rheum Dis* 2016;75:30–6.
- Sun J, Zhang H, Ji Y, et al. Efficacy and safety of cyclophosphamide combined with mycophenolate mofetil for induction treatment of class IV lupus nephritis. *Int J Clin Exp Med* 2015;8:21572–8.
- Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. *Ann Intern Med* 2015;162:18–26.
- Wallace DJ, Navarra S, Petri MA, et al. Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus. *Lupus* 2013;22:144–54.
- van Vollenhoven RF, Petri MA, Cervera R, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. *Ann Rheum Dis* 2012;71:1343–9.
- Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 2012;64:1215–26.
- Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. *Nephrology Dialysis Transplantation* 2012;27:1467–72.
- Islam MN, Hossain M, Haq SA, et al. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. *Int J Rheum Dis* 2012;15:62–8.
- Chen W, Liu Q, Chen W, et al. Outcomes of maintenance therapy with tacrolimus versus azathioprine for active lupus nephritis: a multicenter randomized clinical trial. *Lupus* 2012;21:944–52.
- Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377:721–31.
- Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63:3918–30.
- 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.
- Chen W, Tang X, Liu Q, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: A multicenter randomized clinical trial. *Am J Kidney Dis* 2011;57:235–44.
- Zavada J, Pesickova S, Rysava R, et al. Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study. *Lupus* 2010;19:1281–9.
- Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010;62:222–33.
- 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.
- Griffiths B, Emery P, Ryan V, et al. The BILAG multi-centre open randomized controlled trial comparing ciclosporin vs azathioprine in patients with severe SLE. *Rheumatology* 2010;49:723–32.
- El-Shafey EM, Abdou SH, Shareef MM. Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferative lupus nephritis in Egyptian patients? *Clin Exp Nephrol* 2010;14:214–21.

38. Austin HA, Illei GG, Braun MJ, *et al.* Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. *J Am Soc Nephrol* 2009;20:901–11.
39. 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.
40. Wang HY, Cui TG, Hou FF, *et al.* Induction treatment of proliferative lupus nephritis with leflunomide combined with prednisone: a prospective multi-centre observational study. *Lupus* 2008;17:638–44.
41. Fortin PR, Abrahamowicz M, Ferland D, *et al.* Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2008;59:1796–804.
42. Bao H, Liu ZH, Xie HL, *et al.* Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 2008;19:2001–10.
43. Moroni G, Doria A, Mosca M, *et al.* A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. *Clin J Am Soc Nephrol* 2006;1:925–32.
44. Grootsholten C, Ligtenberg G, Hagen EC, *et al.* Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. *Kidney Int* 2006;70:732–42.
45. El-Sehemy MS, Al-Saaran AM, Baddour NM, *et al.* Comparative clinical prospective therapeutic study between cyclophosphamide, cyclosporine and azathioprine in the treatment of lupus nephritis. *Egypt J Immunol* 2006;13:39–52.
46. Ong LM, Hooi LS, Lim TO, *et al.* Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrology* 2005;10:504–10.
47. Ginzler EM, Dooley MA, Aranow C, *et al.* Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis. *N Engl J Med Overseas Ed* 2005;353:2219–28.
48. Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, *et al.* Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. *Ann Rheum Dis* 2005;64:620–5.
49. Contreras G, Pardo V, Leclercq B, *et al.* Sequential therapies for proliferative lupus nephritis. *N Engl J Med Overseas Ed* 2004;350:971–80.
50. Mok CC, Ho CT, Siu YP, *et al.* Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. *Am J Kidney Dis* 2001;38:256–64.
51. Chan TM, Li FK, Tang CS, *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med* 2000;343:1156–62.
52. Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. *J Rheumatol* 1999;26:1275–9.
53. Gourley MF, Austin HA, Scott D, *et al.* Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med* 1996;125:549.
54. Sesso R, Monteiro M, Sato E, *et al.* A controlled trial of pulse cyclophosphamide versus pulse methylprednisolone in severe lupus nephritis. *Lupus* 1994;3:107–12.
55. Boumpas DT, Austin HA, Vaughn EM, *et al.* Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992;340:741–5.
56. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. *Arthritis Rheum* 1991;34:945–50.
57. Donadio JV, Holley KE, Ferguson RH, *et al.* Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. *N Engl J Med* 1978;299:1151–5.
58. Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus. Report of a prospective controlled trial in 24 patients. *Ann Intern Med* 1975;83:597–605.
59. Cade R, Spooner G, Schlein E, *et al.* Comparison of azathioprine, prednisone, and heparin alone or combined in treating lupus nephritis. *Nephron* 1973;10:37–56.
60. Bartels CM, Buhr KA, Goldberg JW, *et al.* Mortality and cardiovascular burden of systemic lupus erythematosus in a US population-based cohort. *J Rheumatol* 2014;41:680–7.
61. Björnådal L, Yin L, Granath F, *et al.* Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964–95. *J Rheumatol* 2004;31:713–9.
62. Skaggs BJ, Hahn BH, McMahon M. Accelerated atherosclerosis in patients with SLE—mechanisms and management. *Nat Rev Rheumatol* 2012;8:214–23.
63. Ahmad Y, Shelmerdine J, Bodill H, *et al.* Subclinical atherosclerosis in systemic lupus erythematosus (SLE): the relative contribution of classic risk factors and the lupus phenotype. *Rheumatology* 2007;46:983–8.
64. Tselios K, Sheane BJ, Gladman DD, *et al.* Optimal monitoring for coronary heart disease risk in patients with systemic lupus erythematosus: a systematic review. *J Rheumatol* 2016;43:54–65.
65. Wu GC, Liu HR, Leng RX, *et al.* Subclinical atherosclerosis in patients with systemic lupus erythematosus: a systemic review and meta-analysis. *Autoimmun Rev* 2016;15:22–37.
66. Roubille C, Richer V, Starnino T, *et al.* The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:480–9.
67. Garcia Popa-Lisseanu MG, Greisinger A, Richardson M, *et al.* Determinants of treatment adherence in ethnically diverse, economically disadvantaged patients with rheumatic disease. *J Rheumatol* 2005;32:913–9.
68. Chambers SA, Raine R, Rahman A, *et al.* Why do patients with systemic lupus erythematosus take or fail to take their prescribed medications? A qualitative study in a UK cohort. *Rheumatology* 2009;48:266–71.
69. Becker A, Fischer R, Scherbaum WA, *et al.* Osteoporosis screening in systemic lupus erythematosus: impact of disease duration and organ damage. *Lupus* 2001;10:809–14.
70. Dubois EL, COZEN L, Avascular CL. Avascular (aseptic) bone necrosis associated with systemic lupus erythematosus. *JAMA* 1960;174:966–71.
71. Zhang K, Zheng Y, Jia J, *et al.* Systemic lupus erythematosus patients with high disease activity are associated with accelerated incidence of osteonecrosis: a systematic review and meta-analysis. *Clin Rheumatol* 2018;37.
72. Singh G, Misra R, Aggarwal A. Ovarian insufficiency is major short-term toxicity in systemic lupus erythematosus patients treated with cyclophosphamide. *J Assoc Physicians India* 2016;64:28–31.
73. Mayorga J, Alpizar-Rodriguez D, Prieto-Padilla J, *et al.* Prevalence of premature ovarian failure in patients with systemic lupus erythematosus. *Lupus* 2016;25:675–83.
74. Akawatcharangura P, Taechakraichana N, Osiri M. Prevalence of premature ovarian failure in systemic lupus erythematosus patients treated with immunosuppressive agents in Thailand. *Lupus* 2016;25:436–44.