Induction and maintenance immunosuppression treatment of proliferative lupus nephritis: Network meta-analysis

Authors first and last names and highest degree:

Suetonia C. Palmer, PhD[1*]
David J. Tunnicliffe, MIPH[2,3*]
Davinder Singh-Grewal, PhD[4,5]
Dimitris Mavridis, PhD[6,7]
Marcello Tonelli, MD[8]
David W. Johnson, PhD[9,10]
Jonathan C. Craig, PhD[2,3]
Allison Tong, PhD[2,3]
Giovanni FM Strippoli, PhD[2,11,12]

*This analysis was conducted in the main by Suetonia C. Palmer and David J. Tunnicliffe, who contributed equally.

Institution for each author:

1 Department of Medicine, University of Otago Christchurch, New Zealand
2 Sydney School of Public Health, University of Sydney, NSW, Australia
3 Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW 2145
4 School of Paediatrics and Child Health, The University of Sydney, NSW, Australia
5 Department of Rheumatology, The Sydney Children's Hospitals Network Westmead and Randwick, NSW, Australia
6 Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece
7 Department of Primary Education, University of Ioannina, Greece
8 Cumming School of Medicine, University of Calgary, Canada
9 Department of Nephrology, Division of Medicine, University of Queensland at the Princess Alexandra Hospital, Brisbane, Australia
10 Translational Research Institute, Brisbane, Australia
11 Diaverum Medical Scientific Office, Lund, Sweden and Diaverum Academy
12 Department of Emergency and Organ Transplantation, University of Bari, Italy

Corresponding author (address for reprints):

Professor Giovanni Strippoli,
Department of Emergency and Organ Transplantation
University of Bari,
Piazza Giulio Cesare
70124 Bari
Italy

gfmstrippoli@gmail.com
Phone: +39 3358756828

Manuscript word count: 4059

Abstract word count: 289

Abstract

Intravenous cyclophosphamide has been first line treatment for inducing disease remission in lupus nephritis. Newer agents such as mycophenolate mofetil and calcineurin inhibitors are available, but their comparative efficacy and toxicity are unclear. A network meta-analysis was conducted using a frequentist model to assess the comparative efficacy and safety of all immunosuppressive drug classes in adults and children with proliferative lupus nephritis. Cochrane databases, MEDLINE, and Embase were searched for randomized trials published through September 29, 2015. Primary outcomes were induction of disease remission and all-cause mortality. Secondary outcomes were end-stage kidney disease, disease relapse, and adverse events. Treatment estimates were calculated as odds ratios (OR) with 95% CI, using intravenous cyclophosphamide as the referent treatment for induction and azathioprine for maintenance of disease remission. Immunosuppression strategies were ranked using surface under the cumulative ranking (SUCRA) probabilities. 47 eligible studies involving 3645 adults and children aged 10 years or over were eligible. Induction and maintenance treatments were given for a median of 12 (IQR 6−84) months and 25 (IQR 12−48) months, respectively. Calcineurin inhibitors (odds ratio 1.86, 95% CI 1.05–3.30) and mycophenolate mofetil (1.54, 1.04–2.30) were the most effective treatments to induce disease remission. Immunosuppressive regimens did not have differing effects on all-cause mortality. Mycophenolate mofetil and calcineurin inhibitors were much less likely than intravenous cyclophosphamide to cause alopecia, while regimens had statistically similar effects on end-stage kidney disease, major infection, and ovarian failure. Mycophenolate mofetil was most effective for maintaining disease remission (0.53, 95% CI 0.31 to 0.90) compared with azathioprine. Thus, mycophenolate mofetil and calcineurin inhibitors were more effective to induce remission of lupus nephritis than intravenous cyclophosphamide, while conferring

similar or lower treatment toxicity. Mycophenolate mofetil was the most effective maintenance treatment to prevent disease relapse.

Introduction

Systematic lupus erythematosus (SLE) affects principally women of child-bearing age. Although clinical manifestations are highly variable, kidney involvement affects between 20% and 75% of patients in the first 10 years.[1] While survival for patients with SLE was less than 50% at 5 years in the 1950's, this has improved to greater than 90%, attributed to improved immunosuppression and other medical therapies (blood pressure lowering, dialysis and transplantation) and a better understanding of disease biology. Therapies have transformed lupus nephritis from an acute to chronic illness, in which the longer term efficacy and adverse effects of treatments may assume greater importance in medical decision-making.

Intravenous cyclophosphamide combined with corticosteroids has been first-line therapy to induce remission from lupus nephritis, but causes considerable toxicity including infertility, hair loss, and malignancy.[2] Newer immunosuppressive agents including calcineurin inhibitors and mycophenolate mofetil may have a more favorable side-effect profile, but whether these drugs are equivalent or superior to intravenous cyclophosphamide for induction of disease remission in lupus nephritis is uncertain.[3]

Existing conventional meta-analyses suggest similar efficacy for mycophenolate mofetil and cyclophosphamide on disease remission with lower toxicity than cyclophosphamide.[3 4] However, standard pairwise meta-analysis can only compare two drug classes that have already been evaluated in head to head trials. In a complex condition with several treatment options, not all of which have been directly compared in trials, a network meta-analysis offers the potential to compare all therapeutic strategies within a single framework and rank treatments according to their efficacy and safety. Additional potential treatments including rituximab and abatacept indicate that a network meta-analysis including all treatment options within coherent analyses might assist clinical decision-making. Existing network analyses

have evaluated induction therapy in lupus nephritis, but have been inconclusive due to relatively few included studies[5 6] or have reported only drug harms.[7]

A network meta-analysis of randomized controlled trials reporting immunosuppression treatments for lupus nephritis was therefore conducted to determine the most effective agent for inducing and maintaining disease remission of lupus nephritis.

Results

The trial selection process is shown in Figure 1. Overall, 38 trials in 146 publications were included from a previous Cochrane [3] review and 9 trials in 27 publications were identified through electronic database searching. In total, 47 randomized trials in 173 publications evaluating two or more treatment approaches for immunosuppression to induce or maintain disease remission of proliferative lupus nephritis were included involving 3645 adults and children (aged 10 years or older). Induction therapy was evaluated in 42 trials (n=3358 participants) and maintenance treatment was evaluated in 10 trials (n=737 participants). One trial reported outcomes for induction and maintenance therapy in two separate publications.[8 9]

Details of the characteristics of the included trials are reported in Supplemental Table 1 and definitions of trial endpoints are shown in Supplemental Table 2. All trials were reported between 1973 and 2015. The median number of participants was 47 (range 6 to 378), while the mean age was 29.9 years (standard deviation 5.0; range 10.2 to 40.3 years). Induction treatment was continued for a median follow-up of 12 months (range 5.5 to 84 months), while the median duration of follow-up for maintenance therapy was 25 months (range 12 to 48 months).

In the early trials between 1973 and 1984, the interventions were oral azathioprine, oral cyclophosphamide, prednisone alone, or plasma exchange. The first trial of intravenous

cyclophosphamide was reported in 1986 and trials evaluating calcineurin inhibitors emerged in 1992. The earliest study assessing mycophenolate mofetil appeared in 2005 and rituximab has been evaluated in trials since 2009. From 2012 onward, a range of other immunomodulatory drugs including atacicept, abatacept, and laquinimod have been included as induction therapies. Seventeen induction therapy trials (781 participants) contained an intravenous cyclophosphamide arm (500-1000 mg/m^2/body surface area monthly),[9-25], six trials (361 participants) included mycophenolate mofetil (2000-3000 mg daily),[9 15 16 20 23 24] five trials (102 participants) included oral cyclophosphamide (1.5-4 mg/kg daily),[11 26-29] six trials (104 participants) included calcineurin inhibitors (cyclosporine 1-3 mg/kg daily or tacrolimus 0.05-0.1 mg/kg daily),[10 14 19 20 29 30] and 2 (81 participants) included rituximab (commencing at 1000 mg on days 1 and 15).[31 32]

Risks of bias

The risks of bias in individual trials and overall are provided in Supplemental Figure 1 and 2. Generation of the randomization sequence and methods used to conceal allocation were unclearly reported in 35 (72%) and 33 (68%) trials, respectively. 35 (72%) trials did not report masking of participants and investigators to allocated treatment and there was uncertainty about whether endpoint assessment was masked in 43 (89%) trials. 40 trials (83%) had reported outcomes for most participants and with similar missing rates in all treatment arms, and 29 (60%) had reported relevant outcomes of interest. Fifteen trials (32%) had other potential sources of bias including differing baseline characteristics between treatment arms,[10 24 25 33 34] sponsor involvement in data analysis and reporting,[9 32 33 35-38] early trial termination,[33 39] pooling of several trials within a study report without meta-analytical techniques,[11] and crossover of participants between arms during follow-up.[28]

Exploration of network structure, heterogeneity and consistency

When the participant characteristics (age, gender, kidney function, disease definition, racial origin), interventions (doses and duration) and study design (duration of follow up) in the included trials were evaluated according to treatment class, the trials were deemed sufficiently similar for the key interventions that a network analysis was reasonable (Supplemental Figure 3). As expected, trials evaluating azathioprine, oral cyclophosphamide or prednisone were predominantly published in the 1970s to 1990s while intravenous cyclophosphamide, mycophenolate mofetil, and calcineurin inhibitors were evaluated in trials published generally since the year 2000.

Pairwise and network meta-analysis estimates were similar in magnitude (Supplemental Table 3 and 4) and testing did not reveal evidence of inconsistency between direct and indirect treatment effects, although confidence intervals were frequently wide (Supplemental Table 5). There was no evidence of global inconsistency between studies in any network (Supplemental Table 6).

Outcomes

The results of pairwise meta-analysis are shown in Supplemental Table 3 and network analysis odds ratios are summarized in Table 1 and 2 and Supplemental Figure 4**.** The confidence in treatment estimates for primary outcomes is provided in Table 3. Comparative effects of rituximab could not be estimated in network analyses due to insufficient trials comparing this treatment with other immunosuppressive agents. For the outcome of complete remission, 18 trials involving 1119 participants (337 events) assessed six immunosuppression strategies. For the outcome of all-cause mortality, 15 trials involving 1291 participants (94 deaths) assessed nine immunosuppression strategies. The treatment networks for primary outcomes are shown in Figure 2 and for secondary outcomes are shown in Supplemental Figure 5.

Primary outcomes

In network analysis, mycophenolate mofetil (OR 1.54 [95% CI 1.04 to 2.30]) and calcineurin inhibitors (OR 1.86 [95% CI 1.05 to 3.30]) were superior to intravenous cyclophosphamide for inducing disease remission (moderate confidence). Figure 3 shows the distribution of probabilities of each class being ranked at each of the possible positions from "best" to "worst". The probability of being ranked most efficacious was 54% for calcineurin inhibitors, 43% for mycophenolate mofetil and 0.4% for intravenous cyclophosphamide. There was no evidence of different effects of immunosuppression strategies on all-cause mortality (Table 1) and treatment rankings were characterized by marked uncertainty (Figure 3) (low confidence).

Secondary outcomes

Networks for secondary outcomes are shown in Supplemental Figure 4. For induction therapy, there was no evidence that mycophenolate mofetil or calcineurin inhibitors had different effects on end-stage kidney disease or doubling of serum creatinine when compared to intravenous cyclophosphamide or each other (Table 1). Intravenous cyclophosphamide had higher odds of failing to induce disease remission than mycophenolate mofetil (OR 2.04 [95% CI 1.15 to 03.57]) and calcineurin inhibitors (OR 3.03 [1.19 to 7.14]) (Table 1).

Mycophenolate mofetil had higher odds of major infection than calcineurin inhibitors (OR 2.17 [1.05 to 4.49]), although neither drug class had significantly different odds of major infection compared to intravenous cyclophosphamide (Table 2). Mycophenolate mofetil had lower odds of alopecia than intravenous cyclophosphamide (OR 0.22 [95% CI 0.13 to 0.39]), while the odds of alopecia with calcineurin inhibitors did not significantly differ from intravenous cyclophosphamide, although confidence intervals were wide (OR 0.19 [95% CI 0.02 to 1.72]) and calcineurin inhibitors were ranked similarly to mycophenolate mofetil. Compared to oral cyclophosphamide, intravenous cyclophosphamide (OR 0.15 [95% CI 0.01

to 1.79]), mycophenolate mofetil (OR 0.08 [95% CI 0.01 to 0.85]) and calcineurin inhibitors (OR 0.05 [95% 0.00 to 0.47]) conferred similarly lower odds of ovarian failure, although the result for intravenous cyclophosphamide did not reach statistical significance. Oral cyclophosphamide had a 92% probability of ranking worst for causing alopecia and a 93% probability of ranking worst for ovarian failure (Figure 3).

There was no evidence that mycophenolate mofetil, calcineurin inhibitors and intravenous cyclophosphamide had significantly different odds of leukopenia and herpes infection (Table 2). Mycophenolate was more likely to cause diarrhea than intravenous cyclophosphamide (OR 2.70 [95% 1.60-4.53]), while there were insufficient comparative data for calcineurin inhibitors. Treatment networks could not be generated for the outcomes of bladder toxicity, nausea and vomiting. In pairwise meta-analyses, mycophenolate appeared superior to intravenous cyclophosphamide for odds of nausea (OR 0.21 [95% CI 0.12 to 0.34]) and vomiting (OR 0.26 [0.15 to 0.44]). There was no evidence of different odds of bladder toxicity for oral compared with intravenous cyclophosphamide (OR 0.11 [95% CI 0.01-2.25]).

When considering maintenance therapy to prevent disease relapse, mycophenolate mofetil was superior to azathioprine (OR 0.53 [95% CI 0.31 to 0.90]) and had a 66% probability of being the best treatment, while treatment effects of calcineurin inhibitors did not differ significantly from mycophenolate mofetil (OR 0.70 [95% CI 0.20 to 2.48]) but were not significantly better than azathioprine (OR 0.75 [95% CI 0.24 to 2.37]) (Table 4 and Figure 4).

Sensitivity analysis

Pre-specified sensitivity analyses for the outcome of complete remission with induction treatment were conducted to test the robustness of the results. Treatment effects were imprecise in sensitivity analyses restricted to trials with follow up of 24 months or longer and

in trials in which allocation was adequately concealed (Supplemental Table 7). There were insufficient observations to perform reliable meta-regression analyses accounting for year of publication, race, or age.

Discussion

Considering benefits and harms of therapy, this network meta-analysis indicates that added to corticosteroids, mycophenolate mofetil or calcineurin inhibitors are superior induction therapy for proliferative lupus nephritis compared with intravenous cyclophosphamide. Mycophenolate mofetil was the only treatment with statistically lower risks of side-effects compared with cyclophosphamide, including hair loss, nausea, and vomiting. Calcineurin inhibitors posed lower risks of major infection than mycophenolate mofetil. Both mycophenolate mofetil and calcineurin inhibitors had considerably lower average odds of ovarian failure than intravenous cyclophosphamide, but this did not reach statistical significance for either therapy. Mycophenolate mofetil is superior to azathioprine for maintaining disease remission. However, despite 42 trials, the longer term effects of immunosuppression on risks of mortality or end-stage kidney disease following induction or maintenance therapy remain uncertain in part due to the relative rarity of these events and the short duration of existing studies. Based on these results and weighing the balance of benefits and harms, mycophenolate mofetil would be a reasonable first-line agent for inducing and maintaining disease remission in patients with proliferative lupus nephritis, although calcineurin inhibitors might be preferred in patients for whom major infection would be especially hazardous.

The finding that mycophenolate mofetil and calcineurin inhibitors have a higher probability of inducing disease remission than intravenous cyclophosphamide contrasts with a 2012 updated Cochrane review which found no differences between these two treatments for complete remission of proteinuria,[3] although with similar uncertainty as the current analysis

is for treatment effects on death and kidney function. Similarly, a 2009 meta-analysis observed similar efficacy between mycophenolate mofetil and intravenous cyclophosphamide for inducing renal remission, with comparable risks of death and end-stage kidney disease.[4] A Bayesian network meta-analysis published in 2014 concluded there was insufficient evidence to determine whether mycophenolate or tacrolimus were superior to cyclophosphamide for inducing proteinuric remission or normal serum creatinine at 6 months.[5] A network analysis involving 9 trials in 972 patients concluded that tacrolimus was superior to cyclophosphamide for inducing complete or partial disease remission but that mycophenolate mofetil was comparable to cyclophosphamide treatment.[6] The different conclusions drawn by these previous meta-analyses and the present study are likely due to the larger amount of information available in the present review to permit more precise inferences about competing treatments for lupus nephritis. This study integrated both direct and indirect drug comparisons from18 studies within highly coherent networks to compare and rank the best available treatments for complete remission and potentially had greater statistical power than existing reviews.

The findings of this network meta-analysis are consistent with a recent randomized trial comparing combined therapy with tacrolimus and mycophenolate versus intravenous cyclophosphamide in biopsy-proven lupus nephritis showing that patients who received combined therapy had a higher probability of complete or partial disease remission at 6 months (hazard ratio 1.72; 95% CI 1.34 to 2.21), although there were more serious adverse events and greater withdrawal from tacrolimus plus mycophenolate therapy driven primarily by infection-related events.[21] This raises the possibility that dual therapy might incur greater toxicity than each individual treatment class alone. Although there has been no previous head to head trials of dual versus monotherapy, when the two trials[12 21] evaluating combined mycophenolate mofetil plus tacrolimus versus cyclophosphamide as

induction therapy were included in the network for complete remission in this study, dual mycophenolate mofetil plus tacrolimus therapy was not significantly better than mycophenolate mofetil alone (1.74, 95% CI 0.97 to 3.14) or tacrolimus alone (1.45, 95% CI 0.70 to 2.98). Based on these promising but inconclusive results and to test the balance of benefits and harms of dual therapy further, a trial comparing mycophenolate mofetil or tacrolimus against combined mycophenolate mofetil plus tacrolimus might be considered a priority, including careful documentation of efficacy and patient-centered treatment harms.

This network analysis is consistent with the findings of a 2015 study evaluating comparative effects of cyclophosphamide, azathioprine, mycophenolate mofetil and prednisone alone on maintenance of disease remission in lupus nephritis.[40] In that meta-analysis, mycophenolate mofetil was ranked as the best therapy for preventing kidney failure during maintenance treatment, although due to a small number of events, the estimated treatment effects were very imprecise. The similar findings between this previous review and the present study despite differing statistical approaches and endpoints strengthens the conclusions of both studies that mycophenolate mofetil might be the best treatment for maintaining remission of lupus nephritis.

While the strengths of this systematic review include a comprehensive literature search without language or date restriction, evaluation of the assumptions of consistency among included trials before generating treatment estimates, and including standardized approaches to assessing the confidence that might be held in the results, the meta-analysis has some limitations that might be considered when interpreting the findings.

First, the analysis is limited by the data in the primary trials and the methods of reporting data. For example, complete remission was a heterogeneous outcome with variable definitions in existing studies. Notwithstanding the differences in endpoint definitions among

trials, there was evidence of low heterogeneity in the pooled analysis indicating that a network meta-analysis was appropriate. Second, there were few deaths (n=94) and patients progressing to end-stage kidney disease (n=151) during trial follow up leading to considerable uncertainty in treatment effects on these patient-relevant outcomes. It remains uncertain whether biochemical remission of disease based on proteinuria and/or serum creatinine is a valid predictor of longer term outcomes in lupus nephritis, particularly end-stage kidney disease, as existing trials generally do not follow patients for long enough to detect this treatment outcome. Similarly, there was insufficient precision in treatment effects on doubling of serum creatinine, although azathioprine or corticosteroids alone were clearly inferior to intravenous cyclophosphamide. Third, while the treatment classes were derived from similar study populations (age, gender, serum creatinine), there were secular trends in the publication era for differing treatments. As expected, azathioprine, oral cyclophosphamide and prednisone alone were principally evaluated in earlier decades while intravenous cyclophosphamide, mycophenolate mofetil and calcineurin inhibitors were assessed in more recent trials. While this difference might threaten the assumed consistency required to generate a single analytical network and confound treatment comparisons due to differing epidemiological patterns of disease and treatments over time, notably there was low heterogeneity observed in networks for the primary outcomes, and the key treatment comparisons (cyclophosphamide, mycophenolate mofetil and calcineurin inhibitors) were drawn from trials all published more recently. Fourth, different outcomes and responses to treatment are observed among people of different racial origins in lupus nephritis and therefore, it might be hypothesized that treatment effects might be different based on ethnicity. However, there were insufficient data for racial origin in the original trial reports to perform meta-regression analyses to explore this possibility. Fifth, combinations of treatment classes were not included in this study as these trials could not be connected sufficiently

within analytical networks to calculate treatment estimates. Similarly, evidence for rituximab was sparse and disconnected from networks as trials compared rituximab with combination therapy or placebo. Finally, the inconsistent endpoint definitions and imprecision in treatment estimates for mortality and end-stage kidney disease has implications for future trial design. In future studies, longer term endpoints and larger study populations might be achieved through more efficient study design – for example, registry-based randomized trials[41] – in which important patient-centered outcomes such as death and end-stage kidney disease are captured automatically during long-term routine follow up within registry databases. Standardization of both safety and short term and long term efficacy outcomes in trials evaluating therapies for lupus nephritis, as has been generated in rheumatology, might facilitate better understanding about the benefits and harms of therapy.[42] Based on the potential benefits of calcineurin inhibitors and mycophenolate mofetil on short term outcomes in this analysis, future head to head trials comparing the benefits and harms of these treatments alone or in combination might be prioritized.

Mycophenolate mofetil is superior to intravenous cyclophosphamide for short-term disease remission and lower treatment-related toxicity as induction therapy in proliferative lupus nephritis. Calcineurin inhibitors display greater efficacy than intravenous cyclophosphamide, when added to corticosteroids. Mycophenolate mofetil is superior to azathioprine for sustaining disease remission. Longer term benefits of treatment on mortality and end-stage kidney disease remain uncertain.

Concise Methods

A network meta-analysis was performed using a frequentist framework. The meta-analysis was conducted and reported according to a pre-specified protocol and the PRISMA Extension Statement for Reporting of Systematic Reviews incorporating network meta-analyses of health care interventions.[43]

Data sources and searches

Randomized controlled trials that were publically available on September 30, 2015 in which people with lupus nephritis were allocated to immunosuppression for induction or maintenance of disease remission were identified. The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase were searched using a highly-sensitive search strategy for each database developed by an experienced trials search coordinator. Searches were conducted without date or language restriction. The search terms are shown in the appendix. A previous published Cochrane meta-analysis was screened for eligible randomized trials.[3]

Study selection

Parallel-group randomized trials that involved adults or children with proliferative lupus nephritis (defined by trial investigators) and who received the following immunosuppression treatment for induction and/or maintenance of disease remission (in addition to corticosteroids) were included: intravenous cyclophosphamide, oral cyclophosphamide, mycophenolate mofetil, calcineurin inhibitor, rituximab or azathioprine. Included trials were those that reported a comparison between at least two different classes of immunosuppression or between a medication and a placebo or usual care. Trials were excluded if they were a crossover study design. Trials which used combination drug therapies for lupus nephritis or other classes of intervention (such as plasma exchange) were included to provide indirect

evidence for the principal treatment classes of interest. Abstracts of articles in non-English languages were reviewed and the full-text was translated when the citation was considered potentially eligible before assessment and data extraction. Two reviewers (SP, DT) working independently screened the titles and abstracts of the retrieved search records to determine potential eligibility. Any citation report that was considered potentially eligible was reviewed in full-text by the same two reviewers who resolved discrepancies through consensus.

Data extraction

Two investigators (SP, DT) abstracted data independently into an electronic database. The authors crosschecked the data and reached consensus for any discrepancies through discussion.

Risk of bias

Two independent reviewers (SP, DT) assessed risks of bias in the included trials using the Cochrane Collaboration assessment tool.[44]

Data synthesis and analysis

The primary outcomes of interest for induction therapy were complete remission of disease and all-cause mortality. Secondary outcomes were end-stage kidney disease, doubling of serum creatinine, failure of therapy to induce remission, major infection, alopecia, ovarian failure, malignancy, nausea, vomiting, bone toxicity, bladder toxicity, leukopenia, and herpes infection. In maintenance therapy, relapse of disease was the primary outcome. Outcome data were extracted for the longest reported follow up in studies. Studies reporting zero events in all arms had those outcomes excluded from analyses. The outcomes were used as defined in the individual trials. Data from trials principally evaluating induction treatment were analyzed separately from trials evaluating treatment for maintenance of disease remission.

In meta-analysis, first the clinical setting and participant characteristics were evaluated to consider whether the trials were sufficiently similar that a network meta-analysis approach was appropriate – that is, the trials did not differ for the distribution of potential effect modifiers. This is the assumption of consistency in study design and purpose that is necessary to assume the validity of a network meta-analysis, and considers the assumption that the direct evidence (from head to head trials) and the indirect evidence (derived from network analysis) estimate the same underlying treatment effect.[45] Box plots were generated according to treatment class to explore distributions of key effect modifiers including study age, gender, serum creatinine, and date of publication. We intended to explore distributions of treatment classes by ethnicity or race, but these assessments were precluded by insufficient data.

Second, random-effects pairwise meta-analysis was done for all head to head comparisons of drug classes. Heterogeneity of treatment estimates between trials in pairwise meta-analysis was assessed using the χ^2 test and corresponding I^2 statistic. The I^2 thresholds of 0% to 40%, 30% to 60%, 50% to 90% and 75% to 100% were considered to represent heterogeneity that might not be important, moderate, substantial and that was considerable, considering also the magnitude and direction of treatment effects.[46]

Third, using a frequentist framework, random-effects network meta-analysis was used to simultaneously compare all classes of immunosuppression for each pre-specified outcome.[45 47] Comparative treatment effects in all meta-analyses were calculated as odds ratios and corresponding 95% confidence intervals. The extent of heterogeneity in each network analysis was evaluated using the restricted maximum likelihood method to generate a common heterogeneity variance for the network (tau [τ]), which was then compared with an empirical distribution of heterogeneity variances, considering the range of odds ratios

expected. Values from 0.1 to 0.5 were considered low, 0.5 to 1.0 were considered fairly high, and above 1.0 represented fairly extreme heterogeneity.[48]

To explore for evidence of inconsistency between direct and indirect treatment estimates for a specific drug comparison, a loop-specific approach that compares direct and indirect treatment effects generated from closed evidence loops in the network (triangular or quadratic loops, connecting three or four different treatments, respectively) was used. The ratio of odds ratios (direct treatment estimate: indirect treatment estimate) was calculated together with the 95% confidence interval. A ratio of odds ratios with a confidence interval including 1 is consistent with no evidence of inconsistency. To check the assumption of consistency in the entire analytical network, the 'design-by-treatment' interaction approach was used.[49]

Drug classes were then ranked to generate a hierarchy of treatments for a given clinical endpoint. The relative ranking probability of each treatment being among the "best" treatment was obtained using surface under the cumulative ranking (SUCRA) curves and displayed using rankograms. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess confidence in estimates of effect associated with specific drug comparisons in network analyses was used.[50] The assessment addressed considerations of risk of bias, consistency, imprecision, indirectness and publication bias. The starting point for indirect estimates was "high" and downgraded considering these characteristics. GRADE was used to assess confidence in the primary outcomes of complete remission from disease and all-cause mortality.

Pairwise and network meta-analysis were done in Stata version 13 (www.stata.com) using the network command[51] and self-programmed Stata routines.[52]

References

1. Cervera R, Khamashta MA, Hughes G. The Euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. *Lupus* 18:869-74, 2009

2. Flanc RS, Roberts MA, Strippoli GFM, Chadban S, Kerr P, Atkins R. Treatment for lupus nephritis (Review). *Cochrane Database Syst Rev*: Issue 1. Art. No.:CD002922.pub2, 2004

3. Henderson L, Masson P, Craig JC, Flanc RS, Roberts MA, Strippoli GF, Webster AC. Treatment for lupus nephritis. *Cochrane Database Syst Rev* 12:CD002922, 2012

4. Mak A, Cheak AA, Tan JY, Su HC, Ho RC, Lau CS. Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: a meta-analysis and meta-regression. *Rheumatology* 48:944-52, 2009

5. Tian SY, Feldman BM, Beyene J, Brown PE, Uleryk EM, Silverman ED. Immunosuppressive therapies for the induction treatment of proliferative lupus nephritis: a systematic review and network metaanalysis. *J Rheumatol* 41:1998-2007, 2014

6. Lee YH, Song GG. Relative efficacy and safety of tacrolimus, mycophenolate mofetil, and cyclophosphamide as induction therapy for lupus nephritis: a Bayesian network meta-analysis of randomized controlled trials. *Lupus* 24:1520-8, 2015

7. Singh J, Kotb A, Hossain A, Wells G. A systematic review and network meta-analysis of cyclophosphamide and mycophenolate mofetil in lupus nephritis. Abstract number 1660. 2014 ACR/ARHP Annual Meeting. November 14-19, 2014. Boston MA. 2014

8. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, Eitner F, Appel GB, Contreras G, Lisk L, Solomons N, Group A. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 365:1886-95, 2011

9. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, Li LS, Mysler E, Sanchez-Guerrero J, Solomons N, Wofsy D, Aspreva Lupus Management Study Group. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 20:1103-12, 2009

10. El-Sehemy MS, Al-Saaran AM, Baddour NM, Adam AG, Moez PE. Comparative clinical prospective therapeutic study between cyclophosphamide, cyclosporine and azathioprine in the treatment of lupus nephritis. *Egypt J Immunol* 13:39-52, 2006

11. Austin HA, 3rd, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, Decker JL. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 314:614-9, 1986

12. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 19:2001-10, 2008

13. Boumpas DT, Austin H, Vaughn EM, Klippel J, Steinberg A, Yarboro C. Controlled Trial of Pulse Methylprednisolone Versus Two Regimens of Pulse Cyclophosphamide in Severe Lupus Nephritis. *Lancet* 340:741-5, 1992

14. Chen W, Tang X, Liu Q, Chen W, Fu P, Liu F, Liao Y, Yang Z, Zhang J, Chen J, Lou T, Fu J, Kong Y, Liu Z, Fan A, Rao S, Li Z, Yu X. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: A multicenter randomized clinical trial. *Am J Kidney Dis* 57:235-44, 2011

15. 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* 14:214-21, 2010

16. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, Petri M, Gilkeson GS, Wallace DJ, Weisman MH, Appel GB. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 353:2219-28, 2005

17. Gourley MF, Austin HA, 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, Boumpas DT, Klippel JH, Balow JE, Steinberg AD. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med* 125:549-57, 1996

18. Grootscholten C, Ligtenberg G, Hagen EC, van den Wall Bake AW, de Glas-Vos JW, Bijl M, Assmann KJ, Bruijn JA, Weening JJ, van Houwelingen HC, Derksen RH, Berden JH, Dutch Working Party on Systemic Lupus E. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. *Kidney Int* 70:732-42, 2006

19. Hong R, Haijin Y, Xianglin W, Cuilan H, Nan C. A preliminary study of tacrolimus versus cyclophosphamide in patients with diffuse proliferative lupus nephritis. *Nephrol Dial Transplant* 22:vi276, 2007

20. Li X, Ren H, Zhang Q, Zhang W, Wu X, Xu Y, Shen P, Chen N. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. *Nephrol Dial Transplant* 27:1467-72, 2012

21. Liu Z, Zhang H, Xing C, Fu P, Ni Z, Chen J, Lin H, Liu F, He Y, Miao L, Chen N, Li Y, Gu Y, Shi W, Hu W, Liu Z, Bao H, Zeng C, Zhou M. Multitarget therapy for induction treatment of lupus nephritis: A randomized trial. *Ann Intern Med* 162:18-26, 2015

22. Nakamura T, Ushiyama C, Hara M, Osada S, Ugai K, Shimada N, Hayashi K, Ebihara I, Koide H. Comparative effects of plasmapheresis and intravenous cyclophosphamide on urinary podocyte excretion in patients with proliferative Lupus nephritis. *Clin Nephrol* 57:108-13, 2002

23. Ong LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, Teo SM, Wong HS, Tan SY, Shaariah W, Tan CC, Morad Z. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrology* 10:504-10, 2005

24. Rathi M, Goyal A, Gupta PK, Jaryal A, Sharma A, Jha V, Ramachandran R, Kumar V, Kohli HS, Lal Gupta K, Sakhuja V. Randomized controlled trial of low-dose intravenous cyclophosphamide versus oral mycophenolate mofetil in treatment of lupus nephritis. *Nephrol Dial Transplant* 29:iii28-iii29, 2014

25. Sesso R, Monteiro M, Sato E, Kirsztajn G, Silva L, Ajzen H. A controlled trial of pulse cyclophosphamide versus pulse methylprednisolone in severe lupus nephritis. *Lupus* 3:107-12, 1994

26. Donadio JV, Jr., Holley KE, Ferguson RH, Ilstrup DM. Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. *N Engl J Med* 299:1151-5, 1978

27. Dyadyk O, Vasilenko I, Bagriy A, Kholopov L, Dyadyk O, Yarovaya N. Azathioprine and cyclophosphamide in diffuse proliferative lupus nephritis treatment - a randomized controlled study [abstract]. *Ann Rheum Dis* 66:467, 2007

28. Fries JF, Sharp GC, McDevitt HO, Holman HR. Cyclophosphamide therapy in systemic lupus erythematosus and polymyositis. *Arthritis Rheumatol* 16:154-62, 1973

29. Lui S, Cheng I, Tong K, Li C, Wong K, Chan T. Treatment of type iv lupus nephritis (LN) - comparison of 2 triple therapy regimens: cyclosporin a (CSA), prednisolone (PRED), azathioprine (AZA) vs. oral cyclophosphamide (POCP), prednisolone, azathioprine [abstract]. *Nephrology* 3:S476, 1997

30. Balletta M, Sabella D, Magri P, Sepe V, Stanziale P, Di Luccio R, Colucci G, Fuiano G. Cyclosporin plus steroids versus steroids alone in the treatment of lupus nephritis. *Contributions to Nephrology* 99:129-30, 1992

31. Li EK, Tam LS, Zhu TY, Li M, Kwok CL, Li TK, Leung YY, Wong KC, Szeto CC. Is combination rituximab with cyclophosphamide better than rituximab alone in the treatment of lupus nephritis? *Rheumatology* 48:892-8, 2009

32. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, Maciuca R, Zhang D, Garg JP, Brunetta P, Appel G, Lunar Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 64:1215-26, 2012

33. Ginzler EM, Wax S, Rajeswaran A, Copt S, Hillson J, Ramos E, Singer NG. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. *Arthritis Res Ther* 14:R33, 2012

34. 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* 83:597-605, 1975

35. The ACCESS Trial Group. Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. *Arthritis Rheumatol* 66:3096-104, 2014

36. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, Houssiau FA, Drappa J, Close D, Maciuca R, Rao K, Shahdad S, Brunetta P. Efficacy and safety of

ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. *Arthritis Rheum* 65:2368-79, 2013

37. Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R, Chen SL, Hillson JL, Meadows-Shropshire S, Kinaszczuk M, Merrill JT. Efficacy and safety of abatacept in lupus nephritis: A twelve-month, randomized, double-blind study. *Arthritis Rheumatol* 66:379-89, 2014

38. Moroni G, Doria A, Mosca M, Alberighi OD, Ferraccioli G, Todesco S, Manno C, Altieri P, Ferrara R, Greco S, Ponticelli C. A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. *Clin J Am Soc Nephrol* 1:925-32, 2006

39. Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. *N Engl J Med* 326:1373-9, 1992

40. Tian SY, Feldman BM, Beyene J, Brown PE, Uleryk EM, Silverman ED. Immunosuppressive Therapies for the Maintenance Treatment of Proliferative Lupus Nephritis: A Systematic Review and Network Metaanalysis. *J Rheumatol* 42:1392-400, 2015

41. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angeras O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Karegren A, Nilsson J, Robertson L, Sandhall L, Sjogren I, Ostlund O, Harnek J, James SK. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 369:1587-97, 2013

42. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: An International Initiative to Improve Outcome Measurement in Rheumatology. *Trials* 8:38, 2007

43. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catala-Lopez F, Gotzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Ann Intern Med* 162:777-84, 2015

44. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928, 2011

45. 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* 3:80-97, 2012

46. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. *BMJ* 2003:7414, 2003

47. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 331:897-900, 2005

48. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 41:818-27, 2012

49. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 3:98-110, 2012

50. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 9:e99682, 2014

51. White IR. Network meta-analysis. *Stata J* 15:951-85, 2015

52. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PloS One* 8:e76654, 2013

Contributors

SCP and GFMS had the idea for and designed the study.

SCP and DJT identified and acquired reports of trials and extracted data.

DM provided statistical advice and input.

SCP did all data analyses, checked for statistical inconsistency, and interpreted data.

DJT, DS-G, DM, MT, DWJ, JCC, AT, and GFMS contributed to data interpretation.

SCP drafted the report and DJT, DS-G, DM, MT, DWJ, JCC, AT, and GFMS critically reviewed the report.

GFMS had the final responsibility for submission of the paper.

Declaration of interests

SCP received a research grant from the Royal Society of New Zealand during the study and has received a research grant from Amgen Dompé outside the submitted work. DJ has received consultancy fees from Baxter, Fresenius, Gambro, Amgen, Janssen-Cilag, Roche, Genzyme, Shire, Sigma, Sanofi-Aventis, Boehringer-Ingelheim, Lilley, Merck Sharpe & Dohme, Bristol-Myers Squibb, and Novartis; speaker's honoraria from Baxter, Fresenius, Gambro, Amgen, Janssen-Cilag, Roche, Servier, Shire, Merck Sharpe & Dohme, Boehringer-Ingelheim, and Bristol Myers Squibb; research grants from Baxter Extramural, Fresenius, Roche Foundation for Anaemia Research (RoFar), Amgen, Janssen-Cilaz, Pfizer, and Abbott; and, travel sponsorships from Baxter, Fresenius, Gambro, Amgen, Janssen-Cilag, Roche, and Shire outside the submitted work. MT has received honoraria for a lecture series on management of dyslipidaemia of chronic kidney disease from Merck outside the submitted work; all honoraria were donated to charity. GFMS received a research grant from Agenzia

Italiana del Farmaco during the study and has received personal fees for consultancy from Servier Laboratories outside the submitted work.

Acknowledgements

SCP is supported by a Rutherford Discovery Fellowship. DJT is funded by a postgraduate scholarship from the Sydney Medical School, The University of Sydney. DM is supported by the European Research Council (IMMA 260559). MT received funding from Alberta Innovates Health Solutions.

Figure legends

Figure 1: Summary of evidence search and selection

Figure 2: Graphic representation of treatment comparison for efficacy and safety of induction immunosuppression treatment for proliferative lupus nephritis.

Lines represent trials comparing two classes of drug or drugs for A) complete remission of lupus nephritis and B) all-cause mortality. Lines indicate trials comparing two classes of drug. Numbers on connecting lines represent the number of studies/number of participants in trials directly comparing the two treatments. The nodes indicate the drug treatments assessed in existing trials. The size of the node is proportional to the number of studies evaluating the treatment. For example, the most commonly evaluated treatment for complete remission of lupus nephritis is intravenous cyclophosphamide. There were 18 studies involving 1119 patients in the network for complete remission and 15 studies involving 1291 patients in the network for all-cause mortality.

Figure 3: Rankings for efficacy and safety of immunosuppression treatment to induce disease remission in lupus nephritis

The graphs display the distribution of probabilities of treatment ranking from best through worst for each outcome. Ranking indicates the probability that drug class is first "best", second "best", etc. For example, the ranking suggests oral cyclophosphamide treatment posed the highest risk of incurring ovarian failure (worst), while calcineurin inhibitors incurred the lowest probability of ovarian failure (best). Mycophenolate mofetil and calcineurin inhibitors were among the best treatments for inducing disease remission while intravenous cyclophosphamide and prednisone alone provided the lowest probability of disease remission (worst).

Figure 4: Rankings for efficacy of immunosuppression as maintenance therapy to prevent disease relapse in lupus nephritis

Graph displays distribution of probabilities for each outcome. Ranking indicates probability that drug class is first "best", "second" best," etc. For example, mycophenolate mofetil is among the best for preventing disease relapse during maintenance therapy, while intravenous cyclophosphamide is among the worst.

Table 1: Summary efficacy of immunosuppression for proliferative lupus nephritis compared with intravenous cyclophosphamide

Drug class	Complete remission‡	All-cause mortality*	End-stage kidney disease*	Doubling creatinine*	Treatment failure*
Intravenous cyclophosphamide (reference)	1.00	1.00	1.00	1.00	1.00
Mycophenolate mofetil	1.54 (1.04-2.30)	1.08 (0.42-2.74)	2.61 (0.36-18.7)	1.35 (0.08-24.3)	0.49 (0.28-0.87)
Oral cyclophosphamide	0.64 (0.18-2.32)	2.73 (0.71-10.5)	1.34 (0.31-5.88)	1.83 (0.47-7.19)	1.79 (0.24-13.2)
Calcineurin inhibitor	1.86 (1.05-3.30)	0.48 (0.11-2.03)	2.73 (0.16-45.4)	3.67 (0.19-71.0)	0.33 (0.14-0.84)
Azathioprine	--	1.53 (0.50-4.69)	1.79 (0.56-5.70)	3.35 (1.17-9.68)	4.14 (0.16-105)
Rituximab	--	--	--	--	--
Prednisone	0.57 (0.23-1.40)	2.01 (0.69-5.86)	2.40 (1.05-5.47)	2.94 (1.44-6.00)	4.03 (1.30-12.5)
Number of studies/number of participants in network	*18/1119*	*15/1291*	*9/592*	*7/472*	*12/684*

Values are odds ratios and 95% confidence intervals derived from network meta-analysis. ‡Odds ratio >1 favors active drug class. *Odds ratio <1 favors active drug class. For example, an odds ratio of 1.54 for mycophenolate mofetil versus intravenous cyclophosphamide for the outcome of complete remission indicates the odds of complete disease remission is 1.54 (higher) with mycophenolate mofetil compared with intravenous cyclophosphamide. There were insufficient observations to calculate estimated treatment effects from network analysis for rituximab for any outcome and for intravenous cyclophosphamide versus azathioprine for the outcome of complete remission. The heterogeneity tau (τ) values in the network analyses were: complete remission $\tau<0.001$ (low heterogeneity); all-cause mortality $\tau=0.18$ (low heterogeneity); end-stage kidney disease $\tau<0.001$ (low heterogeneity); doubling of serum creatinine $\tau<0.001$ (low heterogeneity); treatment failure $\tau<0.001$ (low heterogeneity).

Table 2: Summary adverse effects of immunosuppression for proliferative lupus nephritis compared with intravenous cyclophosphamide

Drug class	Major infection	Alopecia	Ovarian failure	Malignancy	Nausea	Vomiting	Leukopenia	Herpes infection
Intravenous cyclophosphamide	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Mycophenolate mofetil	1.23 (0.84-1.77)	0.13 (0.22-0.39)	0.48 (0.11-2.08)	--	0.21 (0.12-0.34)	0.26 (0.15-0.44)	0.76 (0.31-1.86)	1.70 (0.92-3.15)
Oral cyclophosphamide	1.11 (0.43-2.93)	0.41 (0.02-8.50)	6.39 (0.56-7.30)	7.77 (0.81-74.9)	--	--	--	2.25 (0.77-6.57)
Calcineurin inhibitor	0.57 (0.27-1.16)	0.19 (0.02-1.73)	0.29 (0.08-1.06)	--	--	--	0.38 (0.10-1.49)	1.07 (0.30-3.93)
Azathioprine	0.34 (0.10-1.12)	--	0.44 (0.11-1.77)	4.76 (0.61-37.7)	--	--	--	0.46 (0.09-2.33)
Rituximab	--	--	--	--	--	--	--	--
Prednisone	0.81 (0.34-1.94)	--	0.11 (0.03-0.44)	0.56 (0.05-6.18)	--	--	--	0.54 (0.19-1.53)
Number of studies/number of participants in network	*18/1230*	*4/519*	*10/489*	*3/259*	*2/508*	*1/364*	*7/340*	*12/932*

Values are odds ratios and 95% confidence intervals derived from network meta-analysis. Odds ratio <1 favors active drug class. For example, an odds ratio of 0.13 for mycophenolate mofetil versus intravenous cyclophosphamide for the outcome of alopecia indicates the odds of alopecia is 0.13 (lower) compared with intravenous cyclophosphamide. – indicates insufficient observations to calculate treatment effects. The heterogeneity tau (τ) values in the network analyses were: major infection $\tau<0.001$ (low heterogeneity); alopecia $\tau<0.001$ (low heterogeneity); ovarian failure $\tau<0.001$ (low heterogeneity); malignancy τ not estimable (no source of heterogeneity); nausea τ=not estimable (no source of heterogeneity); vomiting τ=not estimable (no source of heterogeneity); leukopenia $\tau<0.001$ (low heterogeneity); herpes infection $\tau<0.001$ (low heterogeneity).

Table 3: Summary of confidence in network treatment estimates for the primary outcomes (complete disease remission and all-cause mortality) of immunosuppression treatments versus intravenous cyclophosphamide in people with lupus nephritis

Intervention	Confidence in the evidence	Reasons for downgrading confidence in the evidence*	Network treatment estimate OR (95% CI)
Complete remission			
Mycophenolate mofetil	Moderate ●●●○	Some study limitations	1.54 (1.04-2.30)
Oral cyclophosphamide	Low ●●○○	Some study limitations Imprecision	0.64 (0.18-2.32)
Calcineurin inhibitor	Moderate ●●●○	Some study limitations	1.86 (1.05-3.30)
Azathioprine	--	--	--
Rituximab	--	--	--
Prednisone	Low ●●○○	Some study limitations Imprecision	0.57 (0.23-1.40)
All-cause mortality			
Mycophenolate mofetil	Low ●●○○	Some study limitations Imprecision	1.08 (0.42-2.74)
Oral cyclophosphamide	Low ●●○○	Some study limitations Imprecision	2.73 (0.71-10.5)
Calcineurin inhibitor	Low ●●○○	Some study limitations Imprecision	0.48 (0.11-2.03)
Azathioprine	Low ●●○○	Some study limitations Imprecision	1.53 (0.50-4.69)
Rituximab	--	--	--
Prednisone	Low ●●○○	Some study limitations Imprecision	2.01 (0.69-5.86)

The confidence in the evidence is based on considerations of study limitations (methodological reporting), consistency in treatment effects between studies, directness of the evidence to likely clinical questions, evidence of small study effects (smaller studies with systematically different results from larger studies) and precision of the estimate (width of confidence interval when including 1 [null effect]) according to GRADE criteria.[50] Moderate confidence means that additional studies are likely to have an important impact on our confidence in treatment effects and may change the estimate. Low confidence means that additional studies are very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Table 4: Summary pairwise and network estimates of drug regimens as maintenance treatment on disease relapse compared to azathioprine

Drug(s) comparison	Network meta-analysis
Relapse	
Azathioprine (reference)	1.00
Mycophenolate mofetil	0.53 (0.31-0.90)
Calcineurin inhibitor	0.75 (0.24-2.37)
Intravenous cyclophosphamide	1.63 (0.50-5.39)
Number of studies/number of participants in network	*4/460*

Values are odds ratios and 95% confidence intervals derived from network meta-analysis. Odds ratio <1 favors active drug class. The heterogeneity tau (τ) values in the network analysis for treatment relapse was: $\tau<0.001$ (low heterogeneity).

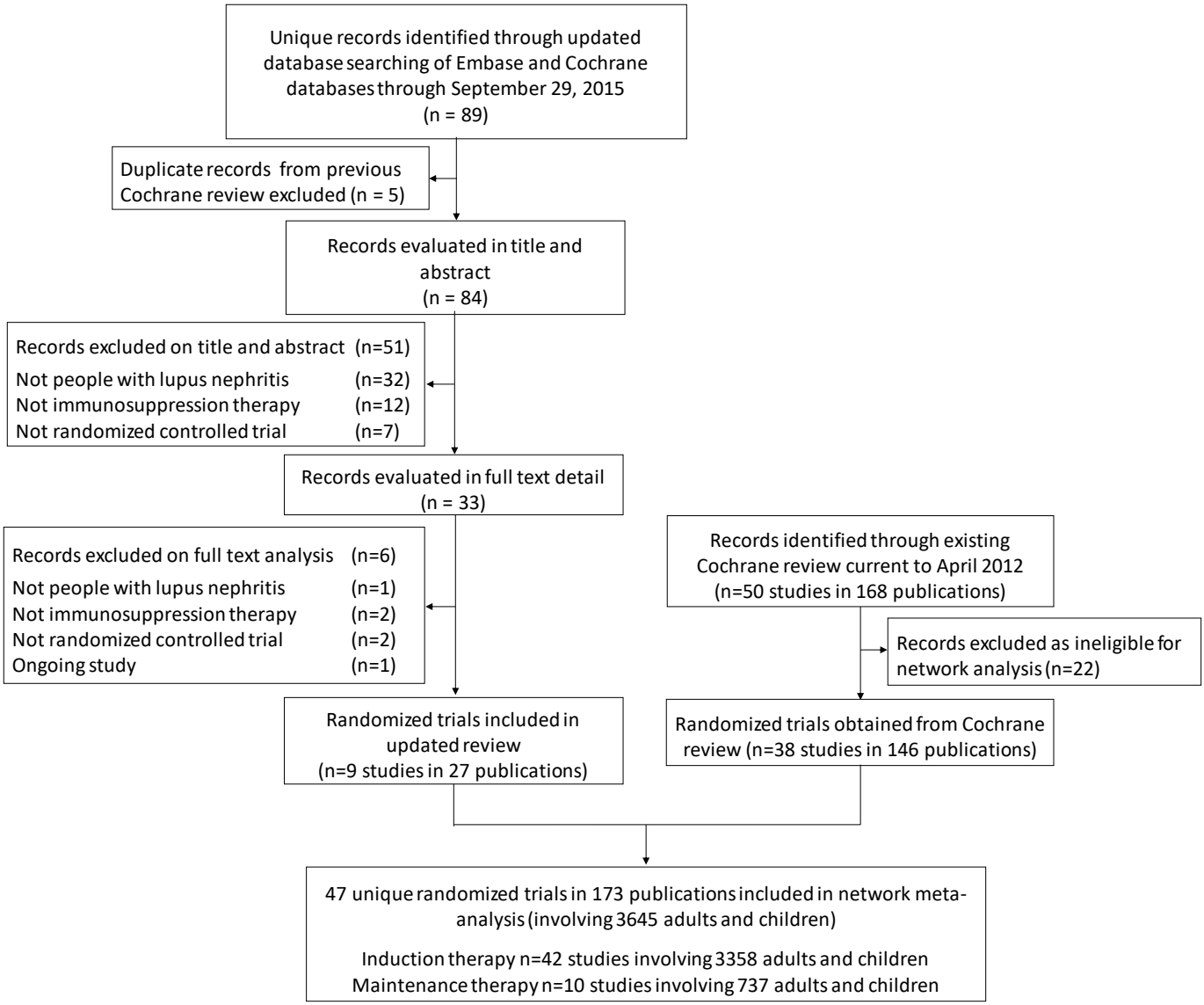
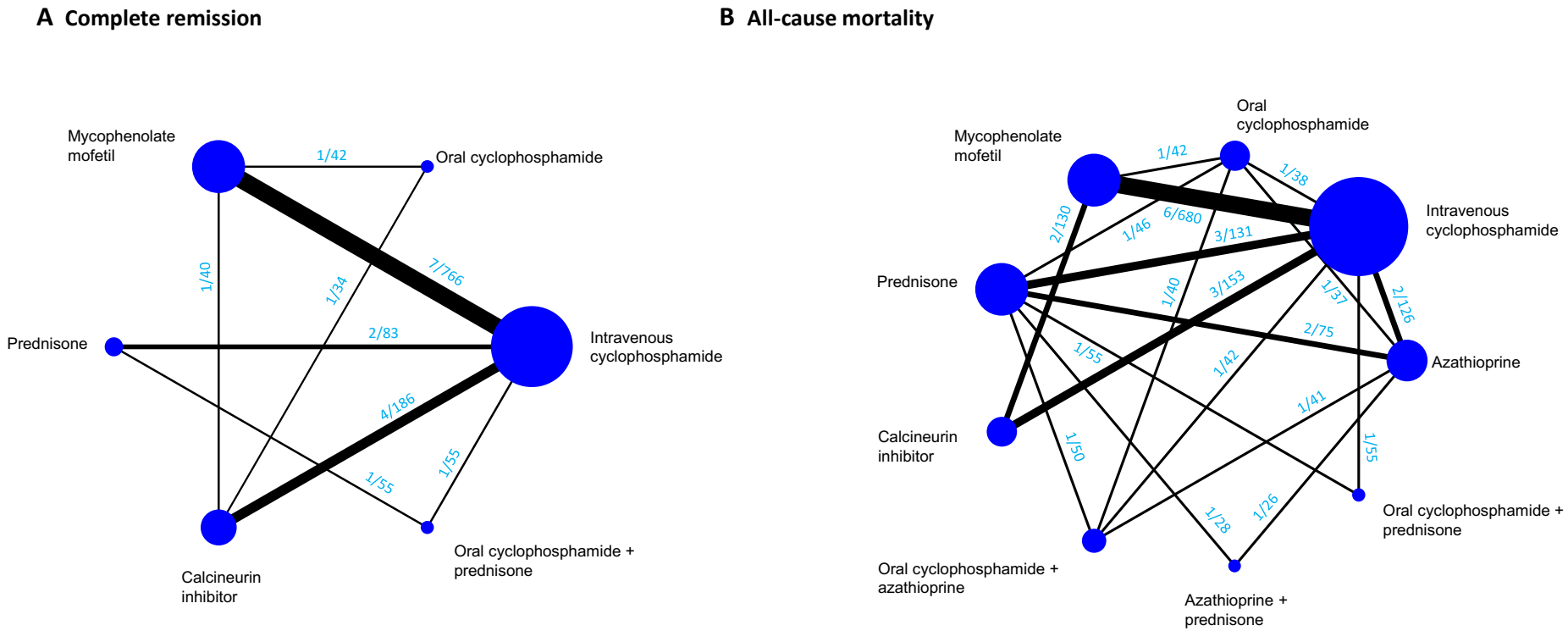


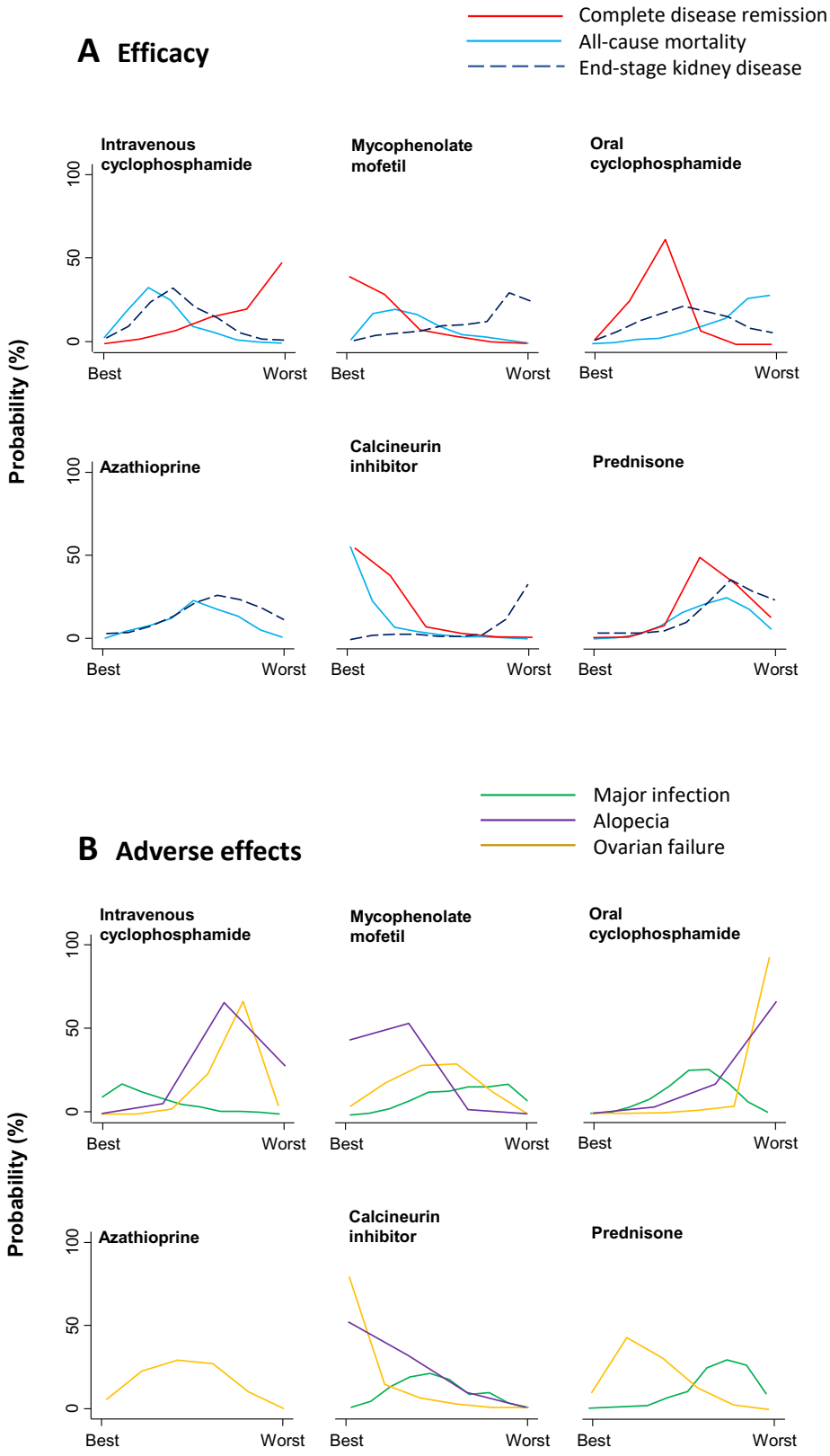
Figure 1: Summary of evidence search and selection

Figure 2: Graphic representation of treatment comparisons for efficacy and safety of induction immunosuppression treatment for proliferative lupus nephritis



Lines represent trials comparing two classes of drug or drugs for A) complete remission of lupus nephritis and B) all-cause mortality. Lines indicate trials comparing two classes of drug. Numbers on connecting lines represent the number of studies/number of participants in trials directly comparing the two treatments. The nodes indicate the drug treatments assessed in existing trials. The size of the node is proportional to the number of studies evaluating the treatment. For example, the most commonly evaluated treatment for complete remission of lupus nephritis is intravenous cyclophosphamide. There were 18 studies involving 1119 patients in the network for complete remission and 15 studies involving 1291 patients in the network for all-cause mortality.

Figure 3: Rankings for efficacy and safety of immunosuppression treatment to induce

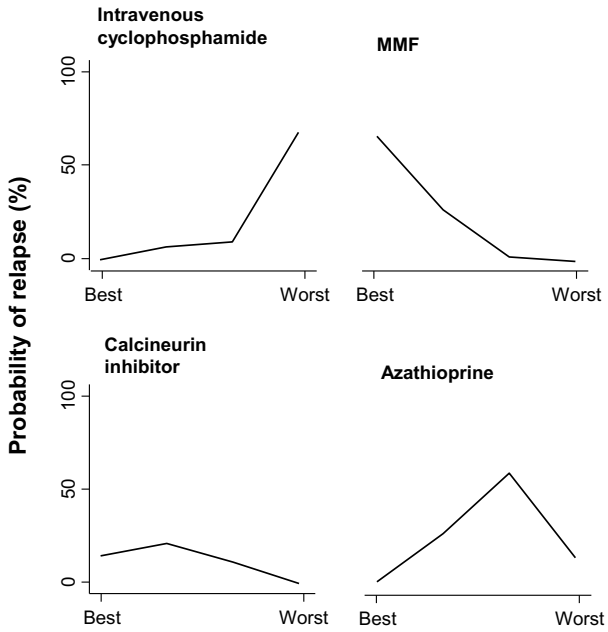


disease remission in lupus nephritis

The graphs display the distribution of probabilities of treatment ranking from best through worst for each outcome. Ranking indicates the probability that drug class is first "best", second "best", etc. For example, the ranking suggests oral cyclophosphamide treatment posed the highest risk of incurring ovarian failure (worst), while calcineurin inhibitors incurred the lowest probability of ovarian failure (best). Mycophenolate mofetil and

calcineurin inhibitors were among the best treatments for inducing disease remission while intravenous cyclophosphamide and prednisone alone provided the lowest probability of disease remission (worst).

Figure 4: Rankings for efficacy of immunosuppression as maintenance therapy to prevent disease relapse in lupus nephritis



Graph displays distribution of probabilities for each outcome. Ranking indicates probability that drug class is first "best", "second" best," etc. For example, mycophenolate mofetil is among the best for preventing disease relapse during maintenance therapy, while intravenous cyclophosphamide is among the worst.

Supplementary appendix

This appendix provides additional information for:

Palmer SC, Tunnicliffe D, Mavridis D, Tonelli M, Johnson DW, Craig JC, Tong A, Strippoli GFM. Induction and maintenance immunosuppression treatment of proliferative lupus nephritis. 2016

Supplemental Table 1: Characteristics of included studies

Study	Inclusion criteria	GN (WHO/ISN class-ification)	Maintenance and/or induction treatment	Active treatment	Control	Non-randomised immune-suppression	Duration follow up (months)	Number of patients	Female, n (%)	Age, years (mean)
Cade et al (1973)[1]	SLE based on history and physical findings; biopsy-proven active proliferative GN	IV	Induction	Azathioprine 1-2 mg/kg/day	Azathioprine 1-2 mg/kg/day + heparin *or* azathioprine 1-2 mg/kg/day + prednisone 60-100 mg/day or prednisone 60-100 mg/day	Conventional treatment	72	54	41 (76%)	30.5 24.8 26.1 22.4
Fries et al (1973)[2]	SLE with antinuclear antibodies; involvement of 2 or more organs	--	Induction	Oral cyclophosphamide (average 125 mg/day for 16 weeks)	Oral prednisone 1 mg/kg/day	Conventional treatment	24	10	--	--
Donadio et al (1974)[3]	Histological evidence of lupus nephritis	III, IV	Induction	Azathioprine 2 mg/kg/day (6 months)	Conventional treatment	Oral prednisone	6	16	14 (88%)	Range 17-68
Hahn et al (1975)[4]	SLE; active life-threatening disease	III, IV	Induction	Azathioprine 3-4 mg/kg/day (24 months)	Conventional treatment	Oral prednisone	24	24	20 (83%)	33.5 31.7
Donadio et al (1978)[5]	SLE; serological evidence; creatinine clearance <80 ml/min/1.73 m^2 or reduction of 25%; renal biopsy showing DPLN	IV	Induction	Oral cyclophosphamide 2 mg/kg/day (6 months)	Conventional treatment	Oral prednisone	24	30	21 (70%)	30.7 32.3
Clark et al (1981)[6]	SLE; serological evidence; biopsy-proven DPLN; creatinine clearance >30 ml/min	IV	Induction	Plasma exchange 4L monthly (3-24 months)	Conventional treatment	Oral prednisone; oral azathioprine	24	12	--	--
Clark et al (1984)[7]	SLE; serological evidence; biopsy-proven DPLN	IV	Induction	Plasma exchange 4L 5 exchanges in first 2 weeks then 3-4 weekly	Conventional treatment	Oral prednisone; cytotoxic therapy	18	39	33 (85%)	26 25

Supplemental Table 1: Characteristics of included studies

Study	Inclusion criteria	GN (WHO/ISN class-ification)	Maintenance and/or induction treatment	Active treatment	Control	Non-randomised immune-suppression	Duration follow up (months)	Number of patients	Female, n (%)	Age, years (mean)
Austin et al (1986)[8]	SLE; clinical or histological evidence of active GN; creatinine clearance >20 ml/min	III, IV, V	Induction	Intravenous cyclophosphamide 0.5-1 g/m^2 every 3 months (48 months)	Oral cyclophosphamide (up to 4 mg/kg/day for 48 months) or oral azathioprine (up to 4 mg/kg/day for 84 months) or combined oral azathioprine and cyclophosphamide (up to 1 mg/kg/day for 52 months) or oral prednisone (1 mg/kg/day)	Oral prednisone	84	111	92 (83%)	27
Balletta et al (1992)[9]	Lupus nephritis on biopsy	III, IV, V	Induction	Cyclosporin 1.5 mg/kg twice daily (12 months)	Conventional treatment	Oral prednisone	12	10	9 (90%)	25.6 23.4
Boumpas et al (1992)[10]	Severe lupus nephritis (impaired kidney function, active urine sediment or active GN on histology)	III, IV, V	Induction	Intravenous cyclophosphamide 0.5-1 g/m^2 monthly (6 months) then every 3 months (2 years)	Intravenous cyclophosphamide 0.5-1 g/m^2 monthly (6 months) or intravenous methylprednisolone 1.0 g/m^2 daily (3 days) then monthly (6 months)	Oral corticosteroids	60	65	60 (92%)	29
Lewis et al (1992)[11]	Lupus nephritis	III, IV	Induction	Plasma exchange 3-4 L three times weekly (4 weeks)	Conventional treatment	Oral prednisone; cyclophosphamide	31	86	53 (62%)	31 33
Doria et al (1994)[12]	Lupus nephritis; serum creatinine <106 µmol/l	IV	Induction	Plasma exchange (50% plasma volume) twice a week (2 weeks), weekly (2 months) fortnightly (3 months)	Intravenous methylprednisolone 500 mg daily (3 days) or conventional treatment	Oral corticosteroids	24 months	18	16 (89%)	27

Supplemental Table 1: Characteristics of included studies

Study	Inclusion criteria	GN (WHO/ISN class-ification)	Maintenance and/or induction treatment	Active treatment	Control	Non-randomised immune-suppression	Duration follow up (months)	Number of patients	Female, n (%)	Age, years (mean)
Sesso et al (1994)[13]	Lupus nephritis (active urine sediment; urine protein>3.0 g/day; impaired kidney function (creatinine clearance <80 ml/min or recent reduction of at least 30%)	II, III, IV	Induction	Intravenous cyclophosphamide 0.5-1 g/m^2 monthly (4 months), bimonthly (4 months), 3 monthly (6 months)	Intravenous methylprednisolone 10-20 mg/kg daily (3 days), monthly (3 months), bimonthly (4 months), 3 months (6 months)	Oral corticosteroids	14.4-15.4	29	25 (86%)	30.0 24.3
Belmont et al (1995)[14]	Active renal disease (active urine sediment, proteinuria and/or low C3 and or C4)	II, III, IV, V	Induction	Misoprostol 200 µg four times daily (8 weeks)	Placebo	Oral corticosteroids	18	14	11 (79%)	35
Gourley et al (1996)[15]	Glomerulonephritis (active urinary sediment and/or biopsy-proven disease)	III, IV	Induction	Intravenous cyclophosphamide 0.75-1 g/m^2 monthly (6 monthly), 3 monthly (2 years)	Intravenous cyclophosphamide 0.75-1 g/m^2 monthly (6 monthly), 3 monthly (2 years) and intravenous methylprednisolone (1 g/m^2 daily (3 days), monthly (12 months), 3 monthly (2 years) or intravenous methylprednisolone (1 g/m^2 daily (3 days), monthly (12 months), 3 monthly (2 years)	Oral corticosteroids	59.6	82	68 (83%)	30 31 31
Lui et al (1997)[16]	Lupus nephritis	IV	Induction	Oral cyclophosphamide 1 mg/kg/day (12 months)	Cyclosporin 5 mg/kg/day (12 months)	Oral corticosteroids; oral azathioprine	12	34	--	--
Fu et al (1998)[17]	Lupus nephritis; normal creatinine clearance	III, IV	Maintenance	Oral cyclophosphamide 2 mg/kg/day and oral prednisolone 2 mg/kg/day (12 months)	Cyclosporin 5 mg/kg/day (12 months)	Conventional care	12	40	--	10.4 10.2

Supplemental Table 1: Characteristics of included studies

Study	Inclusion criteria	GN (WHO/ISN class-ification)	Maintenance and/or induction treatment	Active treatment	Control	Non-randomised immune-suppression	Duration follow up (months)	Number of patients	Female, n (%)	Age, years (mean)
Wallace et al (1998)[18]	Lupus nephritis; chronicity index<6	III, IV	Induction	Plasma exchange 60 mL/kg on three consecutive days every month (6 months)	Conventional care	IV cyclo-phosphamide	24	18	19 (95%)	33 32
Boletis et al (1999)[19]	Lupus nephritis; response to cyclophosphamide therapy (6 months); inactive or improved urinary sediment	III, IV	Maintenance	IV cyclophosphamide 1 g/m^2 every 2 months (6 months) then every 3 months (12 months)	IV immunoglobulin 400 mg/kg monthly (18 months)	Oral corticosteroids	18	14	9 (64%)	31
Chan et al (2000)[20]	Lupus nephritis; urinary protein excretion >1g/24 hours; serum albumin<3.5g/dL; serum creatinine <300 µmol/L	IV	Induction and maintenance	Mycophenolate mofetil oral 1 g twice daily (6 months) then 500 mg twice daily (6 months)	Oral cyclophosphamide 2.5 mg/kg/day (6 months) replaced by azathioprine 1.5 mg/kg/day	Oral corticosteroids	12	42	39 (93%)	36 39
Nakamura et al (2002)[21]	Lupus nephritis; oral corticosteroid with or without cytotoxic medications for at least 6 months	IV	Induction	IV cyclophosphamide 0.75-1.0 g/m^2 monthly (6 months)	Plasmapheresis 1-2 times weekly (average 8.4 treatments)	Oral corticosteroids	6	20	29.5 30.5 (80%)	16
Contreras et al (2002)[22]	Lupus nephritis; creatinine clearance >20 mL/min	III, IV, Vb	Maintenance	IV cyclophosphamide 0.5-1.0 g/m^2 every 3 months (25 months)	Mycophenolate mofetil 500-3000 mg per day (29 months) or azathioprine 1-3 mg per day (30 months)	Oral corticosteroids	25-30	59	55 (93%)	33 32 33

Supplemental Table 1: Characteristics of included studies

Study	Inclusion criteria	GN (WHO/ISN class-ification)	Maintenance and/or induction treatment	Active treatment	Control	Non-randomised immune-suppression	Duration follow up (months)	Number of patients	Female, n (%)	Age, years (mean)
Ginzler et al (2005)[23]	Lupus nephritis; incident decrease in kidney function (serum creatinine >88.4 µmol/l), proteinuria >500 mg/24 hours, microscopic haematuria or cellular casts; increasing proteinuria with rising serum creatinine; active urine sediment, or serological abnormality	III, IV, V	Induction	IV cyclophosphamide monthly according to National Institutes of Health protocol (24 weeks)	Mycophenolate mofetil 500 mg twice daily increased to 750 mg twice daily (at week 2) and increased weekly to 1000 mg three times daily (24 weeks)	Oral corticosteroids	24 weeks (wit extension phase of 36.2-37.2 months)	140	156 (92%)	31 32.5
Ong et al (2005)[24]	Lupus nephritis; serum creatinine <200 µmol/L	III, IV	Induction	IV cyclophosphamide 0.75-1 g/m^2 monthly (6 months)	Mycophenolate mofetil 1 g twice daily (6 months)	Oral corticosteroids	6 months (with additional analysis for survival (range 24.2-47.7 months)	44	37 (84%)	30.5 31.3
El-Sehemy et al (2006)[25]	SLE; kidney disease (proteinuria and/or haematuria with urinary casts)	III, IV, V	Induction	IV cyclophosphamide 0.75 g/m^2 monthly (6 months)	Cyclosporine 1-2 mg/kg in two divided doses daily tapered to 2.5 mg/kg/day (6 months) or oral azathioprine 1-2 mg/kg/day	IV and oral corticosteroids	6	23	23 (100%)	25.6 22 21.4
Grootscholten et al (2006)[26]	Lupus nephritis; creatinine clearance >25 mL/min	III, IV, Vc, Vd	Induction	IV cyclophosphamide 0.75 g/m^2 every 4 weeks (6 pulses) then every 12 weeks (7 pulses)	Azathioprine 2 mg/kg/day	IV or oral corticosteroids (azathioprine group) or oral corticosteroids (cyclophospham ide group)	66.0-75.6	87	75 (86%)	30 33

Supplemental Table 1: Characteristics of included studies

Study	Inclusion criteria	GN (WHO/ISN class-ification)	Maintenance and/or induction treatment	Active treatment	Control	Non-randomised immune-suppression	Duration follow up (months)	Number of patients	Female, n (%)	Age, years (mean)
Moroni et al (2006)[27]	Lupus nephritis; serum creatinine <352 µmol/L	IV, Vc, Vd	Maintenance	Cyclosporin 4 mg/kg/day reduced every 2 weeks to maintenance dose 2.5-3.0 mg/kg/day (24 months)	Azathioprine 2 mg/kg/day	Oral corticosteroids	24	69	62 (90%)	31.7 31.2
Dyadyk et al (2007)[28]	Lupus nephritis	IV	Induction	Oral cyclophosphamide 1.5-3.5 mg/kg daily (mean 21.7 months)	Azathioprine 1.5-2.0 mg/kg/day (mean 18.9 months)	Not reported	21.7 18.9	59	50 (85%)	36
Hong et al (2007)[29]	Diffuse proliferative lupus nephritis, urine protein excretion >2 g; serum creatinine 265 µmol/L	IV	Induction	IV cyclophosphamide 0.5-0.75 g/m^2 monthly (6 months)	Tacrolimus 0.1 mg/kg daily	Corticosteroids	6	25	23 (92%)	30.7
Bao et al (2008)[30]	Lupus nephritis; Disease Activity Index ≥12; proteinuria ≥1.5 g/day with or without active urinary sediment; serum creatinine >265.2 µmol/L	V+IV	Induction	IV cyclophosphamide 0.5-1.0 g/m^2 monthly (6 months)	Mycophenolate mofetil 1.0 g daily and tacrolimus 4 mg/day (6 months)	IV and oral corticosteroids	6	40	36 (90%)	30.6 27.2
Mulic-Bacic et al (2008)[31]	Lupus nephritis	III, IV, V	Induction and maintenance	IV cyclophosphamide 0.5 g/m^2 monthly (24 weeks)	Mycophenolate mofetil 2000 mg daily (6 months) then 1000 mg daily (18 months)	Corticosteroids	5.5	45	--	--
Aspreva Lupus Management Study (2009)[32]	Lupus nephritis; if III or V, then proteinuria >2 g/day	III, IV-S, IV-G, V, III+V, IV+V	Induction	IV cyclophosphamide 0.5-1.0 g/m^2 monthly (24 weeks)	Mycophenolate mofetil 500 mg twice daily (1 week) then 1000 mg twice daily (1 week), then 1500 mg twice daily (22 weeks)	Oral corticosteroids	5.5	370	313 (84.6)	31.3 32.4
Li et al (2009)[33]	Lupus nephritis; clinical activity index ≥6/24; urinary protein ≥1.5 g/24 hours; serum albumin ≤35 g/l	III, IV	Induction	IV cyclophosphamide 750 mg plus rituximab 1000 mg (day 1 and day 15)	Rituximab 1000 mg (day 1 and 15)	IV and oral corticosteroids	12	19	18 (95%)	39.6 40.3

Supplemental Table 1: Characteristics of included studies

Study	Inclusion criteria	GN (WHO/ISN class-ification)	Maintenance and/or induction treatment	Active treatment	Control	Non-randomised immune-suppression	Duration follow up (months)	Number of patients	Female, n (%)	Age, years (mean)
Mok et al (2009)[34]	Lupus nephritis	III, IV, IV	Induction and maintenance	Mycophenolate mofetil 2-3 g daily (6 months)	Tacrolimus 0.06-0.1 mg daily (6 months)	Oral corticosteroids. Oral cyclo-phosphamide for poor response	6	96	-- (90%)	35.4
El-Shafey et al (2010)[35]	Lupus nephritis; estimated GFR>30 ml/min; serum creatinine <200 µmol/L	III, IV	Induction	Intravenous cyclophosphamide 0.5-1 g/m^2 (6 months)	Mycophenolate mofetil 1000 mg twice daily (6 months)	Oral corticosteroids	6	47	45 (96%)	22.8 23.8
MAINTAIN Nephritis Trial (2010)[36]	Lupus nephritis; proteinuria >0.5 g/day;	III, IV, Vc, Vd	Maintenance	Mycophenolate mofetil target dose 2 g/day (mean 48 months)	Azathioprine 2 mg/kg/day (mean 48 months)	Oral corticosteroids	48	105	96 (91%)	33 33
CYCLOFA-LUNE (2010)[37]	Lupus nephritis	III, IV	Induction and maintenance	IV cyclophosphamide 10 mg/kg (every 1.5, 2, then 3 weekly (24 weeks) then every 6-8 weeks (4-5 boluses)	Cyclosporin 4-5 mg/kg/day (9 months) then decreasing to 1.25 mg/kg/day (18 months)	Oral corticosteroids	18	40	29 (73%)	30 28
Chen et al (2012)[38]	Lupus nephritis	III, IV-S, IV-G, V+III, V+IV	Induction	IV cyclophosphamide 500-1000 mg/m^2 every 4 weeks (6 pulses)	Tacrolimus 0.05 mg/kg/day in divided doses twice daily	Oral corticosteroids	6	81	69 (85%)	31.9 32
Dooley et al (2011)[39] (extension of Aspreva Lupus Management Study (2009)[32])	Lupus nephritis; clinical response to mycophenolate mofetil or IV cyclophosphamide during induction	III, IV, V	Maintenance	Mycophenolate mofetil 1000 mg twice daily (36 months)	Oral azathioprine 2 mg/kg/day (36 months)	IV cyclophosphamide or mycophenolate mofetil induction (24 weeks) oral corticosteroids	36	227	195 (86%)	31.8 31.0

Supplemental Table 1: Characteristics of included studies

Study	Inclusion criteria	GN (WHO/ISN class-ification)	Maintenance and/or induction treatment	Active treatment	Control	Non-randomised immune-suppression	Duration follow up (months)	Number of patients	Female, n (%)	Age, years (mean)
Ginzler et al (2012)[40]	Lupus nephritis including urine protein: creatinine ratio >1.0 mg/mg and haematuria; estimated glomerular filtration rate >30 mL/min/1.73 m^2; stable disease	III, IV	Induction	Atacicept 150 mg subcutaneous twice weekly (4 weeks) then 150 mg weekly (total 48 weeks but trial terminated after 6 patients enrolled)	Placebo	Mycophenolate mofetil; oral corticosteroids	3	6	4 (66%)	18-54 (range)
Li et al, 2012[41]	Lupus nephritis; chronic index ≤3; urinary protein ≥1.0 g/day	III, IV-S; IV-G; V; V+III; V+IV	Induction	IV cyclophosphamide 0.5-0.75 g/m^2 monthly (6 months)	Mycophenolate mofetil 1.5-2.0 g daily (6 months) or tacrolimus 0.08-0.1 mg/kg/day (6 months)	Oral corticosteroids	6	60	52 (87%)	33 26.5 29
LUNAR (2012)[42]	Lupus nephritis; urine protein: creatinine ratio >1.0; estimated glomerular filtration rate ≥25 mL per minute/1.73 m^2; <50% glomerular sclerosis	III, IV, III+V, IV+V	Induction	Rituximab 1000 mg on days 1, 15, 168, and 182	Placebo	Mycophenolate mofetil; IV and oral corticosteroids	12	144	130 (90%)	31.8 29.4
Jayne et al (2013)[43]	Lupus nephritis	--	Induction	Laquinimod 0.5 mg/day (24 weeks) or laquinimod 1 mg/day	Placebo	Mycophenolate mofetil; corticosteroids	5.5	46	--	--
BELONG (2013)[44]	Lupus nephritis; urine protein: creatinine ratio ≥1.0; estimated glomerular filtration rate ≥25 mL per minute/1.73 m^2; <50% glomerular sclerosis	III, IV, III+V, IV+V	Induction	IV ocrelizumab 400 mg or 1000 mg (days 1 and 15 then week 16 and every 16 weeks)	Placebo	Mycophenolate mofetil or cyclo-phosphamide followed by azathioprine; IV or oral corticosteroids	12	378	329 (87%)	31.9 30.6 31.3

Supplemental Table 1: Characteristics of included studies

Study	Inclusion criteria	GN (WHO/ISN class-ification)	Maintenance and/or induction treatment	Active treatment	Control	Non-randomised immune-suppression	Duration follow up (months)	Number of patients	Female, n (%)	Age, years (mean)
ACCESS (2014)[45]	Lupus nephritis; urine protein: creatinine ratio ≥1.0	III, IV, III+V, IV+V	Induction	IV abatacept 500-1000 mg monthly (5.5 months)	Placebo	IV cyclo-phosphamide followed by azathioprine; oral corticosteroids	5.5	134	122 (91%)	32 32.7
Furie et al (2014)[46]	Lupus nephritis; if biopsy > 3 months previously then low complement levels or elevated anti-dsDNA, urine protein: creatinine ratio ≥0.44 mg/mmol; and active urine sediment; serum creatinine <265 µmol/L and <88.4 µmol increase within 1 month	III, IV, III+V, IV+V	Induction	IV abatacept 30 mg/kg or 10 mg/kg (days 1, 15, 29, 57) then 500-1000 mg on days 85, 113, 141, 169, 197, 225, 253, 281, 309, 337	Placebo	Mycophenolate mofetil; corticosteroids	12	198	170 (86%)	31.0 30.5 31.8
Rathi et al(2014)[47]	Lupus nephritis without crescentic glomerulonephritis; serum creatinine ≤265 µmol/L	III, IV, V	Induction	IV cyclophosphamide 500 mg fortnightly (6 infusions)	Mycophenolate mofetil 2-3 g daily (24 weeks)	IV and oral corticosteroids	5.5	81	--	--
Liu et al(2015)[48]	Biopsy-proven lupus nephritis within 6 months; proteinuria at least 1.5 g/day; serum creatinine <265.2 µmol/L	III, IV, III+V, IV+V	Induction	IV cyclophosphamide 0.75 g/m^2 body surface area then adjusted to 0.5 to 1.0 g/m^2 every 4 weeks for 6 doses	Mycophenolate mofetil 0.5 g twice daily plus tacrolimus 2 mg twice daily	IV and oral corticosteroids	5.5	362	329 (91%)	33.6 30.3

47 studies in 48 publications were included in this table. Dooley et al (2011) was an extension/maintenance phase of the Aspreva Lupus Management Study (2009).[32 39]
Abbreviations: GN = glomerulonephritis; DPLN = diffuse proliferative lupus nephritis; ISN = International Society of Nephrology; WHO = World Health Organization.

Supplemental Table 2: Definitions of primary and secondary endpoints in trials

Study	Endpoint definition
Complete remission	
Lewis et al (1992)[11]	Serum creatinine ≤106 µmol/L (1.2 mg/dl) and 24 hour urine protein ≤0.2 g/day
Sesso et al (1994)[13]	Improvement of serum creatinine and/or urine sediment or proteinuria
Gourley et al (1996)[15]	Not defined
Lui et al (1997)[16]	Full response, not otherwise defined
Wallace et al (1998)[18]	Serum creatinine <124 µmol/L (1.4 mg/dl), urine protein <0.5 g/day, absence of urinary casts; normal blood pressure and serum albumin >4.0 mg/dL
Chan et al (2000)[20]	Urinary protein excretion <0.3 g/24 hours; normal urinary sediment, serum albumin and serum creatinine; and creatinine clearance increase <15% above baseline
Ginzler et al (2005)[23]	Return to within 10% of normal serum creatinine level, proteinuria and urinary sediment
Ong et al (2005)[24]	Stabilisation or improvement in kidney function (serum creatinine <20% compared with the baseline and reduction in serum creatinine ≥20%), urinary red blood cells < 10 per HPF, and reduction of proteinuria to <0.3 g/day
Hong et al (2007)[29]	Urinary protein excretion <0.4g/24h, no active urinary sediment (urinary RBC<10×10^4/ml), serum albumin > 35g/L, serum creatinine normal
Bao et al (2008)[30]	Proteinuria <0.4 g/24 h, normal urinary sediment, serum albumin ≥3.5 g/dl and a normal serum creatinine or no more than >15% above baseline values
Mulic-Bacic et al (2008)[31]	Normalization and maintenance of abnormal renal measurements
Aspreva Lupus Management Study (2009)[32]	Return to normal serum creatinine; urine protein ≤0.5 g/day; inactive urinary sediment (≤5 white blood cells per high power field, ≤5 red blood cells per high power field, and cells < 1+ on dipstick and absence of red cell casts)
Li et al (2009)[33]	Proteinuria <0.5 g/day, no hematuria or pyuria
Cyclofa-Lune (2010)[37]	Serum creatinine within the normal range with stable or improved values as compared with baseline (no more than 15% above baseline), and inactive urinary sediment, and normal range proteinuria (<0.3 g/24 h)
El-Shafey et al (2010)[35]	Normal serum creatinine concentration, proteinuria <0.5 g/day; no hematuria
Chen et al (2011)[38]	Urinary protein excretion ≤0.3 g/24 h with normal urinary sediment, normal serum albumin concentration (serum albumin 3.5 g/dL), and stable kidney function (normal serum creatinine range or increase not 15% or more above baseline values)
LUNAR Study (2012)[42]	Serum creatinine level of ≤115% of baseline if it was normal at baseline; inactive urinary sediment (<5 red blood cells per high power field) and absence of red cell casts); and urine protein to creatinine ratio <0.5
BELONG Study (2013)[44]	Normal serum creatinine [25% increase from baseline] and improvement in urinary protein to urinary creatinine ratio to <0.5
Jayne et al (2013)[43]	Renal response not otherwise defined
ACCESS Study (2014)[45]	Urinary protein to creatinine ratio of 0.5 based on a 24-hour urine collection, serum creatinine level of 1.2 mg/dl or 125% of baseline, and adherence to the prednisone taper to 10 mg/day by week 12
Furie et al (2014)[46]	Complete response (estimated glomerular filtration rate (eGFR) 90% of screening level if normal at screening visit, or eGFR ≥90% of 6 months, pre-flare value if abnormal at screening, 2) urinary protein to creatinine ratio <0.26 gm/gm (30 mg/mmol), and 3) inactive urinary sediment (RBCs and WBCs per high power field within normal limits of central laboratory assessments; no red blood cell or white blood cell casts)
Rathi et al (2014)[47]	Normal serum creatinine; proteinuria <0.5 g/day; and inactive urine sediment
Liu et al(2015)[48]	24-hour urinary protein excretion of 0.4 g or less, the absence of active urine sediments, serum albumin level of 35 g/L or greater, and normal serum creatinine levels

Supplemental Table 2: Definitions of primary and secondary endpoints in trials

Study	Endpoint definition
End-stage kidney disease	
Cade et al (1973)[1]	Renal death
Donadio et al (1978)[5]	End-stage kidney disease on dialysis or died of kidney failure
Austin et al (1986)[8]	End-stage kidney failure
Boumpas et al 1992[10]	End-stage kidney disease
Lewis et al (1992)[11]	Renal failure defined as increase in the serum creatinine concentration that was at least 265 µmol/l (3 mg/dl) above baseline concentration or the requirement for dialysis
Sesso et al (1994)[13]	Kidney failure requiring dialysis
Belmont et al (1995)[14]	End-stage kidney disease requiring hemodialysis
Gourley et al (1996)[15]	End-stage kidney disease
Wallace et al (1998)[18]	End-stage kidney disease
Contreras et al (2002)[22]	End-stage kidney disease
Ong et al (2005)[24]	Commencement of permanent dialysis or kidney transplantation
Grootscholten et al 2006[26]	End-stage kidney disease
Mok et al (2009)[34]	End-stage kidney disease
El-Shafey et al (2010)[35]	Commencement of permanent dialysis or kidney transplantation
MAINTAIN Nephritis Trial (2010)[36]	End-stage kidney disease
Aspreva Lupus Management Study (2011)[39]	Long-term dialysis or kidney transplantation
Furie et al (2014)	Acute or chronic kidney failure
Treatment failure	
Donadio et al (1978)[5]	End-stage kidney disease or final creatinine clearance increased by 25% or more
Gourley et al (1996)[15]	Urine ≥10 erythrocytes per high-power field, cellular casts, proteinuria (>1 g protein excretion per day)
Lui et al (1997)[16]	Not described
Chan et al (2000)[20]	Urine protein excretion that remained at or above 3 g per 24 hours or a value of 0.3 to 2.9 g per 24 hours but with a serum albumin concentration < 3.0 g/dl and increase in the serum creatinine ≥0.6 mg/dl(50 µmol/l) or a value for creatinine clearance that was more than 15% above the baseline value or the discontinuation of treatment due to side effects
Ginzler et al (2005)[23]	Those without complete (return to within 10 percent of normal values of serum creatinine levels, proteinuria, and urine sediment) or partial remission (improvement of 50% in all abnormal renal measurements, without worsening (within 10 percent) of any measurement) at 24 weeks, plus those who stopped treatment for any reason
Grootscholten et al (2006)[26]	Doubling of serum creatinine at week 12
Li et al (2009)[33]	Worse disease activity
Mok et al (2009)[34]	Failure to respond
Cyclofa-Lune Study (2010)[37]	Not described
El-Shafey et al (2010)[35]	Not described
Chen et al 2011[38]	Failure to meet complete (urinary protein excretion ≤0.3 g/24 h with normal urinary sediment, normal serum albumin concentration (serum albumin 3.5 g/dL), and stable kidney function (normal serum creatinine range or increase not 15% or more above baseline values) or partial (urinary protein excretion range of 0.3-2.9 g/24 h and a decrease of at least 50% of baseline level, with serum albumin concentration of at least 3.0 g/dL and stable kidney function) remission
Aspreva Lupus Management Study (2011)[39]	Renal flare (either proteinuric or nephritic): Proteinuric flare: (doubling of the urinary protein to creatinine ratio and proteinuria ≥ 1 g/24 h in patients with urinary protein ≥ 0.5 g/24 h at the end of the induction phase or proteinuria ≥ 2 g/24 h in subjects with urinary protein ≥ 0.5 g/24 h at the end of the induction phase) Nephritic flare: 25% increase in serum creatinine level over the best value achieved from screening to end of induction. Increase in serum creatinine must be accompanied by one or more of the following: simultaneous doubling of proteinuria reaching a minimum of 2 g/24 h (or ratio equivalent); new/increased hematuria; appearance of cellular casts

Supplemental Table 2: Definitions of primary and secondary endpoints in trials

Study	Endpoint definition
LUNAR Study (2012)[42]	If criteria for complete remission (serum creatinine level of ≤115% of baseline if it was normal at baseline; inactive urinary sediment (<5 red blood cells per high power field) and absence of red cell casts); and urine protein to creatinine ratio <0.5) or partial remission (serum creatinine level ≤ 115% of baseline; red blood cells per high power field ≤50% above baseline and no red cell casts; and at least a 50% decrease in the urine protein to creatinine ratio to <1.0 (if the baseline ratio was ≤ 3.0) or to ≤3.0 (if the baseline ratio was >3.0) were not met, for early termination from the study or inability to assess the end point due to missing data, or for initiation of a new immunosuppressant agent prior to week 52
Disease relapse	
Fu et al (1998)[17]	Reactivation
Chan et al (2000)[20]	Urinary protein excretion increased by 1 g per 24 hours or more above baseline value or if there was an increase in the serum creatinine concentration irrespective of the value for serum anti-double stranded DNA antibody or C3 concentration. Renal relapse was confirmed by histological studies.
Contreras et al (2002)[22]	Doubling of urinary protein to creatinine ratio
Moroni et al (2004)[27]	Renal flare
Mok et al (2009)[34]	Renal flare
Cyclofa-Lune 2010[37]	In patients who had achieved a response to induction therapy, substantial impairment of renal function (defined as an increase in serum creatinine greater than 50 μmol/l), new or persistent nephrotic range proteinuria (>3.5 g/day), or new or persistent nephritic syndrome (defined as any combination of at least three items of the following: 33% increase in serum creatinine, active urinary sediment, proteinuria >0.5 g/day, low C3).
MAINTAIN Nephritis Trial (2010)[36]	(i) the recurrence or the development of nephrotic syndrome (serum albumin ≤3.5 g/dl and 24 h proteinuria ≥3 g; this type of renal flare is further referred to as 'nephrotic syndrome'), (ii) renal impairment (≥33% increase of serum creatinine within a 1-month period directly attributed to lupus and confirmed 1 week later; flare referred to as 'renal impairment') or (iii) a threefold increase of 24 h proteinuria within a 3-month period accompanied by microscopic hematuria (defined as a number of red blood cells (RBC) per high power field superior to upper normal limit for the local laboratory) and ≥33% reduction of serum C3 level within a 3-month period (this definition of renal flare was only applicable to those patients with low-baseline 24 h proteinuria (≥0.5 g and <1 g); this type of renal flare is further referred to as 'proteinuria increase')
Aspreva Lupus Management Study (2011)[39]	Renal flare (either proteinuric or nephritic): Proteinuric flare: (doubling of the urinary protein to creatinine ratio and proteinuria ≥ 1 g/24 h in patients with urinary protein ≥ 0.5 g/24 h at the end of the induction phase or proteinuria ≥ 2 g/24 h in subjects with urinary protein ≥ 0.5 g/24 h at the end of the induction phase) Nephritic flare: 25% increase in serum creatinine level over the best value achieved from screening to end of induction. Increase in serum creatinine must be accompanied by one or more of the following: simultaneous doubling of proteinuria reaching a minimum of 2 g/24 h (or ratio equivalent); new/increased hematuria; appearance of cellular casts

Supplemental Table 2: Definitions of primary and secondary endpoints in trials

Study	Endpoint definition
Ovarian failure	
Boumpas et al (1992)[10]	Premature ovarian failure in women <45 years of age
Gourley et al (1996)[15]	Amenorrhea
Lui et al (1997)[16]	Amenorrhea
Chan et al (2000)[20]	Not described
Adam et al (2004)[25]	Menstrual disturbance
Grootscholten et al (2006)[26]	Postmenopausal before 40 years of age, proven with high LH and FSH levels
Bao et al (2008)[30]	Irregular menstruation
Cyclofa-Lune Study (2010)[37]	Amenorrhea
El-Shafey et al (2010)[35]	Irregular menstruation
MAINTAIN Nephritis Trial (2010)[36]	Transient amenorrhea
Chen et al (2011)[38]	Amenorrhea
Li et al (2012)[41]	Not described
Liu et al(2015)[48]	Menstrual disorder
Leukopenia	
Donadio et al (1974)[3]	White cell count <3000 per cubic milliliter
Doria et al (1994)[12]	Not described
Lui et al (1997)[16]	Not described
Chan et al (2000)[20]	White cell count <2000 per cubic milliliter
Moroni et al (2004)[27]	Not described
Ong et al (2005)[24]	White cell count $<3.5 \times 10^9$ per liter
Bao et al (2008)[30]	Not described
Cyclofa-Lune Study (2010)[37]	Not described
El-Shafey et al (2010)[35]	White cell count $<3.5 \times 10^9$ per liter
Chen et al (2011)[38]	White cell count <2000 per cubic milliliter
Li et al (2012)[41]	Not described
Aspreva Lupus Management Study (2011)[39]	Not described
Liu et al(2015)[48]	Common terminology Criteria for Adverse Events

Supplemental Table 3: Summary pairwise and network estimates of efficacy end points associated with immunosuppression compared to intravenous cyclophosphamide (referent) for induction treatment of proliferative lupus nephritis

Drug(s) comparison	No. of direct drug comparisons (no. of participants)	Pairwise meta-analysis	Hetero-geneity in pairwise analysis, I^2	Network meta-analysis
Complete remission				
Intravenous cyclophosphamide (reference)				
Calcineurin inhibitor	4 (186)	1.74 (0.95-3.20)	0.0%	**1.86 (1.05-3.30)**
Mycophenolate mofetil	7 (766)	**1.60 (1.07-2.41)**	0.0%	**1.54 (1.04-2.30)**
Oral cyclophosphamide	0 (0)	--	--	0.64 (0.18-2.32)
Prednisone	2 (83)	0.59 (0.21-1.68)	23.8%	0.57 (0.23-1.40)
All-cause mortality				
Intravenous cyclophosphamide (reference)				
Calcineurin inhibitor	3 (153)	0.39 (0.06-2.81)	0.0%	0.48 (0.11-2.03)
Mycophenolate mofetil	6 (680)	1.14 (0.49-2.65)	0.0%	1.08 (0.42-2.74)
Azathioprine	2 (126)	2.63 (0.73-9.46)	0.0%	1.53 (0.50-4.69)
Prednisone	3 (131)	1.38 (0.41-4.65)	3.2%	2.01 (0.69-5.86)
Oral cyclophosphamide	1 (38)	3.46 (0.58-20.7)	NA	2.73 (0.71-10.5)
End-stage kidney disease				
Intravenous cyclophosphamide (reference)				
Oral cyclophosphamide	1 (38)	5.43 (0.55-54.0)	NA	1.34 (0.31-5.88)
Azathioprine	2 (126)	5.47 (0.89-33.9)	0.0%	1.79 (0.56-5.70)
Prednisone	4 (196)	2.29 (0.96-5.45)	0.0%	2.40 (1.05-5.47)
Mycophenolate mofetil	2 (91)	2.61 (0.36-18.7)	0.0%	2.61 (0.36-18.7)
Calcineurin inhibitor	0 (0)	--	NA	2.73 (0.16-45.4)
Doubling creatinine				
Intravenous cyclophosphamide (reference)				
Mycophenolate mofetil	0 (0)	--	NA	1.35 (0.08-24.3)
Oral cyclophosphamide	1 (38)	5.43 (0.55-54.0)	NA	1.83 (0.47-7.19)
Prednisone	4 (196)	**2.89 (1.34-6.20)**	0.0%	**2.94 (1.44-6.00)**
Azathioprine	2 (126)	**5.82 (1.54-22.1)**	0.0%	**3.35 (1.17-9.68)**
Calcineurin inhibitor	1 (40)	3.15 (0.12-82.2)	NA	3.67 (0.19-71.0)
Treatment failure				
Intravenous cyclophosphamide (reference)				
Calcineurin inhibitor	2 (121)	0.40 (0.11-1.45)	0.0%	**0.33 (0.14-0.84)**
Mycophenolate mofetil	2 (187)	**0.48 (0.26-0.87)**	0.0%	**0.49 (0.28-0.87)**
Oral cyclophosphamide	0 (0)	--	NA	1.79 (0.24-13.2)
Prednisone	1 (54)	**4.04 (1.30-12.6)**	NA	**4.03 (1.30-12.5)**
Azathioprine	1 (87)	4.15 (0.16-104.8)	NA	4.14 (0.16-105)

An odds ratio above 1 indicates the drug is more likely to cause the outcome compared with intravenous cyclophosphamide and an odds ratio below 1 indicates the drug is less likely to lead to the specified outcome compared with intravenous cyclophosphamide.

Supplemental Table 4: Summary pairwise and network estimates of safety end points associated with immunosuppression for induction treatment of proliferative lupus nephritis

Drug(s) comparison	No. of direct drug comparisons (no. of participants)	Pairwise meta-analysis	Hetero-geneity in pairwise analysis, I^2	Network meta-analysis
Major infection				
Intravenous cyclophosphamide (reference)				
Azathioprine	2 (54)	0.39 (0.05-3.13)	44.6%	0.34 (0.10-1.12)
Calcineurin inhibitor	4 (167)	0.46 (0.18-1.21)	3.1%	0.57 (0.27-1.16)
Prednisone	4 (196)	0.65 (0.18-2.32)	38.5%	0.81 (0.34-1.94)
Oral cyclophosphamide	1 (38)	1.80 (0.26-12.2)	NA	1.11 (0.43-2.93)
Mycophenolate mofetil	4 (495)	1.30 (0.88-1.92)	0.0%	1.23 (0.84-1.77)
Alopecia				
Intravenous cyclophosphamide (reference)				
Mycophenolate mofetil	1 (364)	0.22 (0.13-0.39)	NA	**0.13 (0.22-0.39)**
Calcineurin inhibitor	2 (113)	0.21 (0.02-1.92)	0.0%	0.19 (0.02-1.73)
Oral cyclophosphamide	0 (0)	--	--	0.41 (0.02-8.50)
Ovarian failure				
Intravenous cyclophosphamide (reference)				
Prednisone	2 (98)	0.11 (0.03-0.45)	0.0%	**0.11 (0.03-0.44)**
Calcineurin inhibitor	4 (167)	0.26 (0.07-1.06)	0.0%	0.29 (0.08-1.06)
Azathioprine	2 (102)	0.61 (0.11-3.33)	24.9%	0.44 (0.11-1.77)
Mycophenolate mofetil	2 (87)	0.30 (0.06-1.62)	0.0%	0.48 (0.11-2.08)
Oral cyclophosphamide	0 (0)	--	--	6.39 (0.56-73.0)
Malignancy				
Intravenous cyclophosphamide (reference)				
Prednisone	2 (113)	0.52 (0.02-13.2)	0.0%	0.56 (0.05-6.18)
Oral cyclophosphamide	1 (38)	9.26 (0.45-193)	NA	7.77 (0.81-74.9)
Azathioprine	2 (126)	4.97 (0.53-46.5)	0.0%	4.76 (0.61-37.7)
Nausea				
Intravenous cyclophosphamide (reference)				
Mycophenolate mofetil	1 (364)	**0.21 (0.12-0.34)**	NA	**0.21 (0.12-0.34)**
Vomiting				
Intravenous cyclophosphamide (reference)				
Mycophenolate mofetil	1 (364)	**0.26 (0.15-0.44)**	**NA**	**0.26 (0.15-0.44)**
Diarrhea				
Intravenous cyclophosphamide (reference)				
Oral cyclophosphamide	0 (0)	-	-	0.87 (0.03-23.2)
Mycophenolate mofetil	2 (411)	**2.70 (1.61-4.53)**	**0.0%**	**2.70 (1.61-4.53)**
Bladder toxicity				
Intravenous cyclophosphamide (reference)				
Oral cyclophosphamide	1 (38)	0.11 (0.01-2.25)	NA	NA

Supplemental Table 4: Summary pairwise and network estimates of safety end points associated with immunosuppression for induction treatment of proliferative lupus nephritis

Drug(s) comparison	No. of direct drug comparisons (no. of participants)	Pairwise meta-analysis	Hetero-geneity in pairwise analysis, I^2	Network meta-analysis
Bone toxicity				
Intravenous cyclophosphamide (reference)				
Prednisone	2 (101)	1.27 (0.40-4.03)	NA	1.27 (0.40-4.03)
Leukopenia				
Intravenous cyclophosphamide (reference)				
Calcineurin inhibitor	3 (153)	0.38 (0.10-1.49)	0.0%	0.38 (0.10-1.49)
Mycophenolate mofetil	3 (131)	0.77 (0.31-1.94)	0.0%	0.76 (0.31-1.86)
Herpes infection				
Intravenous cyclophosphamide (reference)				
Azathioprine	1 (39)	0.35 (0.06-2.09)	NA	0.46 (0.09-2.33)
Prednisone	3 (167)	0.48 (0.12-1.92)	38.1%	0.54 (0.19-1.53)
Calcineurin inhibitor	2 (113)	1.46 (0.36-5.95)	0.0%	1.07 (0.30-3.93)
Mycophenolate mofetil	3 (455)	1.66 (0.88-3.13)	0.0%	1.70 (0.92-3.15)
Oral cyclophosphamide	1 (38)	1.00 (0.13-7.85)	NA	2.25 (0.77-6.57)

An odds ratio above 1 indicates the drug is more likely to cause the outcome compared with intravenous cyclophosphamide and an odds ratio below 1 indicates the drug is less likely to lead to the specified outcome compared with intravenous cyclophosphamide. A network was not possible for the outcome of bladder toxicity as data were only available in a single trial.

Supplemental Table 5: Evaluation of loop-specific consistency in triangular and quadratic treatment loops for each binary outcome network

Closed loop of evidence	Ratio of odds ratios obtained by pairwise and network meta-analysis
Complete remission of disease	
Oral cyclophosphamide – MMF – CNI	8.43 (1.00-163)
IV cyclophosphamide – Prednisone – Cyclophosphamide + prednisone	2.99 (1.00-25.8)
IV cyclophosphamide – MMF – CNI	1.11 (1.00-4.71)
All-cause mortality	
IV cyclophosphamide – Prednisone – Cyclophosphamide + prednisone	10.7 (1.00-627)
AZA – Prednisone – Prednisone + AZA	6.55 (1.00-91.7)
AZA – Prednisone – Prednisone + cyclophosphamide	6.55 (1.00-85.1)
AZA – Oral cyclophosphamide – Prednisone	6.55 (1.00-87.4)
AZA – IV cyclophosphamide – Prednisone	6.06 (1.00-99.3)
IV cyclophosphamide – Oral cyclophosphamide – Prednisone	2.99 (1.00-48.9)
IV cyclophosphamide – Prednisone – AZA + cyclophosphamide	2.99 (1.00-47.7)
IV cyclophosphamide – Oral cyclophosphamide – MMF	1.81 (1.00-71.5)
AZA - IV cyclophosphamide - Oral cyclophosphamide	1.52 (1.00-28.9)
AZA - IV cyclophosphamide – AZA + cyclophosphamide	1.52 (1.00-28.3)
IV cyclophosphamide – MMF – CNI	1.37 (1.00-19.8)
End stage kidney disease	
AZA – IV cyclophosphamide – Prednisone	6.84 (1.00-66.9)
IV cyclophosphamide – Oral cyclophosphamide – Prednisone	6.32 (1.00-106)
IV cyclophosphamide – Prednisone – CNI	6.32 (1.00-143)
AZA – Oral cyclophosphamide – Prednisone	2.42 (1.00-32.2)
AZA – Prednisone – AZA + cyclophosphamide	2.42 (1.00-46.8)
AZA – Prednisone – CNI	2.42 (1.00-44.4)
AZA – IV cyclophosphamide – Oral cyclophosphamide	2.11 (1.00-145)
IV cyclophosphamide – Prednisone – AZA + Prednisone	1.17 (1.00-108)
AZA – Oral cyclophosphamide – CNI	Multi-arm trials only*
IV cyclophosphamide – Oral cyclophosphamide – CNI	Multi-arm trials only*
Oral cyclophosphamide – Prednisone – CNI	Multi-arm trials only*
Doubling of serum creatinine	
IV cyclophosphamide – Oral cyclophosphamide – MMF	5.43 (1.00-2329)
IV cyclophosphamide – Oral cyclophosphamide – Prednisone	4.52 (1.00-73.2)
IV cyclophosphamide – Prednisone – AZA + cyclophosphamide	4.52 (1.00-98.7)
AZA – IV cyclophosphamide – Prednisone	3.00 (1.00-21.9)
AZA – IV cyclophosphamide – Oral cyclophosphamide	1.89 (1.00-46.1)
AZA – IV cyclophosphamide – AZA + cyclophosphamide	1.89 (1.00-60.1)
IV cyclophosphamide – Prednisone – Cyclophosphamide + prednisone	1.25 (1.00-109)
IV cyclophosphamide – Oral cyclophosphamide – Cyclophosphamide + AZA	Multi-arm trials only*
AZA – Prednisone – Cyclophosphamide + AZA	Multi-arm trials only*
AZA – Oral cyclophosphamide – Cyclophosphamide + AZA	Multi-arm trials only*
AZA – Oral cyclophosphamide – Prednisone	Multi-arm trials only*
Oral cyclophosphamide – Prednisone – Cyclophosphamide + AZA	Multi-arm trials only*

Closed loop of evidence	Ratio of odds ratios obtained by pairwise and network meta-analysis
IV cyclophosphamide – MMF – CNI	Multi-arm trials only*
Treatment failure	
MMF – Prednisone - Cyclophosphamide + AZA	3.80 (1.00-222)
Oral cyclophosphamide – Prednisone - Cyclophosphamide + AZA	1.20 (1.00-7.57)
Oral cyclophosphamide – CNI – Cyclophosphamide + Prednisone	Multi-arm trials only*
Major infection	
AZA – IV cyclophosphamide – Cyclophosphamide + AZA	79.4 (1.07-5869)
AZA – IV cyclophosphamide – Oral cyclophosphamide	79.4 (1.06-5943)
AZA – Oral cyclophosphamide – CNI	18.6 (1.00-790)
IV cyclophosphamide – Oral cyclophosphamide – Prednisone	9.10 (1.00-136)
IV cyclophosphamide – Prednisone – Cyclophosphamide + AZA	9.10 (1.00-134)
AZA – Control – Oral cyclophosphamide	5.57 (1.00-157)
IV cyclophosphamide – Prednisone – Cyclophosphamide + prednisone	5.10 (1.00-52.8)
AZA – IV cyclophosphamide – CNI	2.75 (1.00-292)
AZA – IV cyclophosphamide – Prednisone	2.63 (1.00-63.0)
AZA – Prednisone – Cyclophosphamide + AZA	1.77 (1.00-92.0)
AZA – Prednisone – AZA + prednisone	1.77 (1.00-101.4)
AZA – Oral cyclophosphamide – Prednisone	1.77 (1.00-93.3)
IV cyclophosphamide + Oral cyclophosphamide – MMF	1.53 (1.00-17.1)
IV cyclophosphamide + Oral cyclophosphamide – CNI	1.26 (1.00-30.7)
IV cyclophosphamide – MMF – CNI	1.16 (1.00-4.84)
Oral cyclophosphamide – MMF – CNI	1.06 (1.00-19.0)
IV cyclophosphamide – Oral cyclophosphamide - Cyclophosphamide + AZA	Multi-arm trials only*
AZA – Oral cyclophosphamide – Cyclophosphamide + AZA	Multi-arm trials only*
Oral cyclophosphamide – Prednisone – Cyclophosphamide + AZA	Multi-arm trials only*
Ovarian failure	
AZA – IV cyclophosphamide – CNI	8.23 (1.00-185)
Oral cyclophosphamide – MMF – CNI	5.28 (1.00-1292)
IV cyclophosphamide – MMF – CNI	3.30 (1.00-168)
Malignancy	
AZA – IV cyclophosphamide – Oral cyclophosphamide	1.41 (1.00-166)
AZA – IV cyclophosphamide – Cyclophosphamide + AZA	1.41 (1.00-558)
IV cyclophosphamide – Prednisone - Cyclophosphamide + AZA	1.39 (1.00-901)
IV cyclophosphamide – Oral cyclophosphamide – Prednisone	1.39 (1.00-300)
AZA – IV cyclophosphamide – Prednisone	1.18 (1.00-176)
AZA – Oral cyclophosphamide – Prednisone	Multi-arm trials only*
Oral cyclophosphamide – Prednisone – Cyclophosphamide + AZA	Multi-arm trials only*
IV cyclophosphamide – Oral cyclophosphamide – Cyclophosphamide + AZA	Multi-arm trials only*
AZA – Prednisone – Cyclophosphamide + AZA	Multi-arm trials only*
AZA – Oral cyclophosphamide – Cyclophosphamide + AZA	Multi-arm trials only*
Bone toxicity	
IV cyclophosphamide – Prednisone – Cyclophosphamide + prednisone	3.25 (1.00-40.8)
Leukopenia	
Oral cyclophosphamide – MMF – CNI	5.68 (1.00-972)

Closed loop of evidence	Ratio of odds ratios obtained by pairwise and network meta-analysis
IV cyclophosphamide – MMF – CNI	2.69 (1.00-78.0)
Herpes infection	
IV cyclophosphamide – Oral cyclophosphamide – CNI	8.20 (1.00-312)
IV cyclophosphamide – Prednisone – Cyclophosphamide + AZA	3.53 (1.00-45.5)
IV cyclophosphamide – Oral cyclophosphamide – Prednisone	3.53 (1.00-48.3)
AZA – IV cyclophosphamide – Prednisone	3.53 (1.00-73.5)
AZA – Control – Prednisone	3.51 (1.00-995)
IV cyclophosphamide – Prednisone – Cyclophosphamide + Prednisone	2.94 (1.00-51.7)
IV cyclophosphamide – Oral cyclophosphamide – MMF	1.11 (1.00-14.6)
AZA – Prednisone – Cyclophosphamide + AZA	Multi-arm trials only*
Oral cyclophosphamide – Prednisone – Cyclophosphamide + AZA	Multi-arm trials only*
AZA – IV cyclophosphamide – Cyclophosphamide + AZA	Multi-arm trials only*
AZA – Oral cyclophosphamide – Cyclophosphamide + AZA	Multi-arm trials only*
Control – Plasma exchange – Prednisone	Multi-arm trials only*
AZA – Oral cyclophosphamide – Prednisone	Multi-arm trials only*
AZA – IV cyclophosphamide – Oral cyclophosphamide	Multi-arm trials only*
Relapse	
AZA – IV cyclophosphamide – MMF	1.45 (1.00-11.7)

Abbreviations; AZA, azathioprine; IV, intravenous; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor. *Consistent by definition. A ratio of odds ratios between treatment estimates obtained from pairwise meta-analysis and network meta-analysis provides information about evidence for consistency between direct and indirect treatment estimates. A ratio of odds ratios with a 95% confidence interval compatible with 1 indicates there is no evidence of inconsistency between estimates for direct treatment effects and those generated by network meta-analysis. A loop of evidence is when three or four treatments are directly compared in a closed loop of evidence in which direct treatment effects from different studies are joined. For example, a closed loop is formed for treatment estimates of complete remission by conjointly analyzing studies that directly compare oral cyclophosphamide and mycophenolate mofetil, mycophenolate mofetil and calcineurin inhibitor and calcineurin inhibitor with oral cyclophosphamide. A triangular loop is formed by direct comparisons for three treatments analyzed within a treatment network and a quadratic loop is formed for direct comparisons of four treatments analyzed within a treatment network. Data for inconsistency factors for the outcomes of alopecia, nausea, vomiting, diarrhea, and bladder toxicity are not shown as no closed loops were present in the networks of evidence for these endpoints.

Supplemental Table 6: Evidence of heterogeneity (global) within analyses

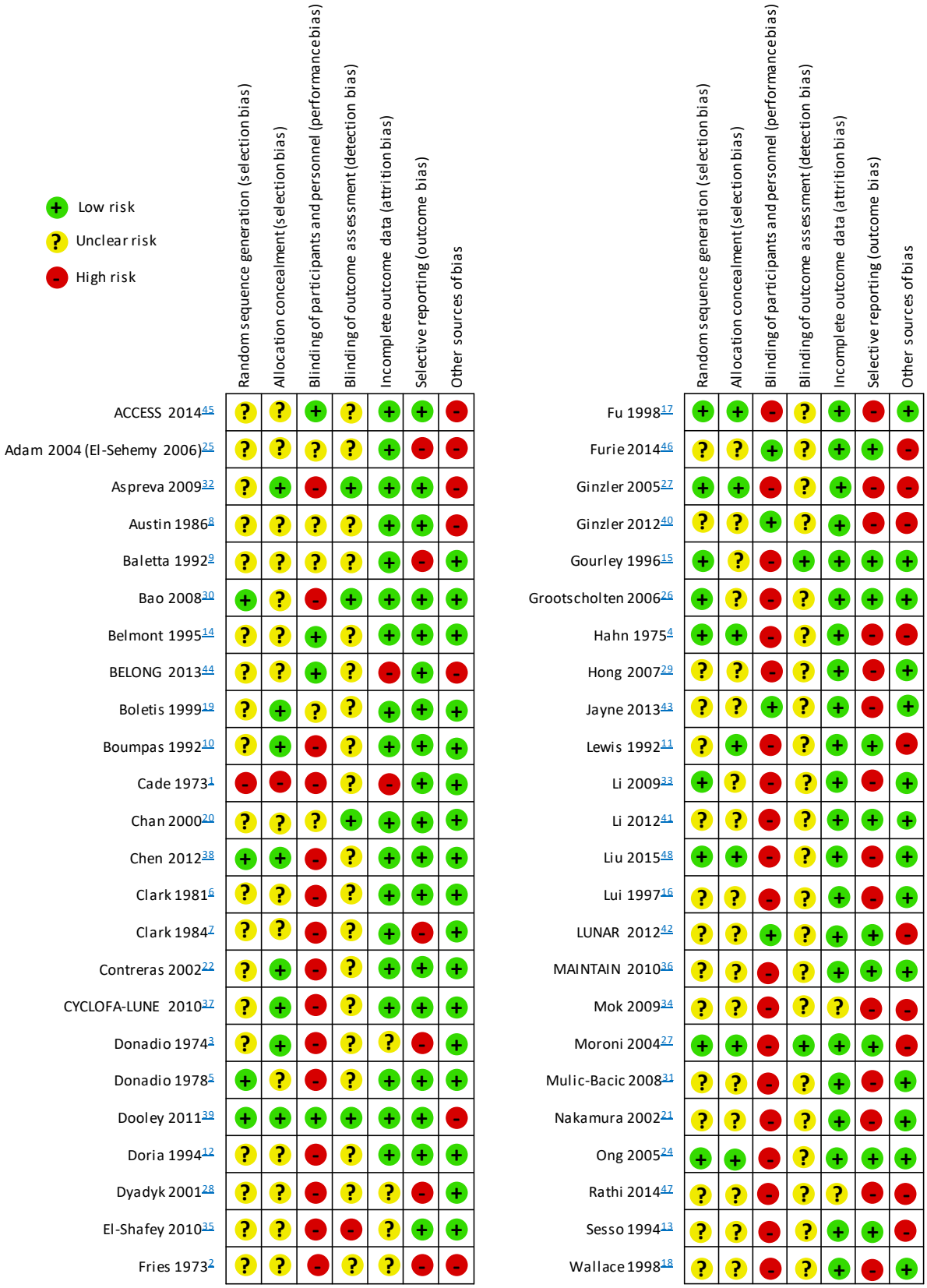
Endpoint	Chi square	P value
Complete remission	3.45	0.47
All-cause mortality	6.85	0.55
End-stage kidney disease	3.98	0.41
Doubling of serum creatinine	2.09	0.72
Treatment failure	0.51	0.77
Relapse	0.19	0.66
Major infection	15.1	0.13
Alopecia	Insufficient observations	
Ovarian failure	4.38	0.50
Malignancy	0.03	0.99
Nausea	Insufficient observations	
Vomiting	Insufficient observations	
Diarrhea	Insufficient observations	
Bladder toxicity	Insufficient observations	
Bone toxicity	Insufficient observations	
Leukopenia	0.84	0.82
Herpes infection	4.41	0.49

Supplemental Table 7: Pre-specified sensitivity analyses for the primary outcome of complete disease remission

Analysis to assess whether treatment effects were different among adults and children as planned were not possible as separate data for different age groups was not available in primary trials.

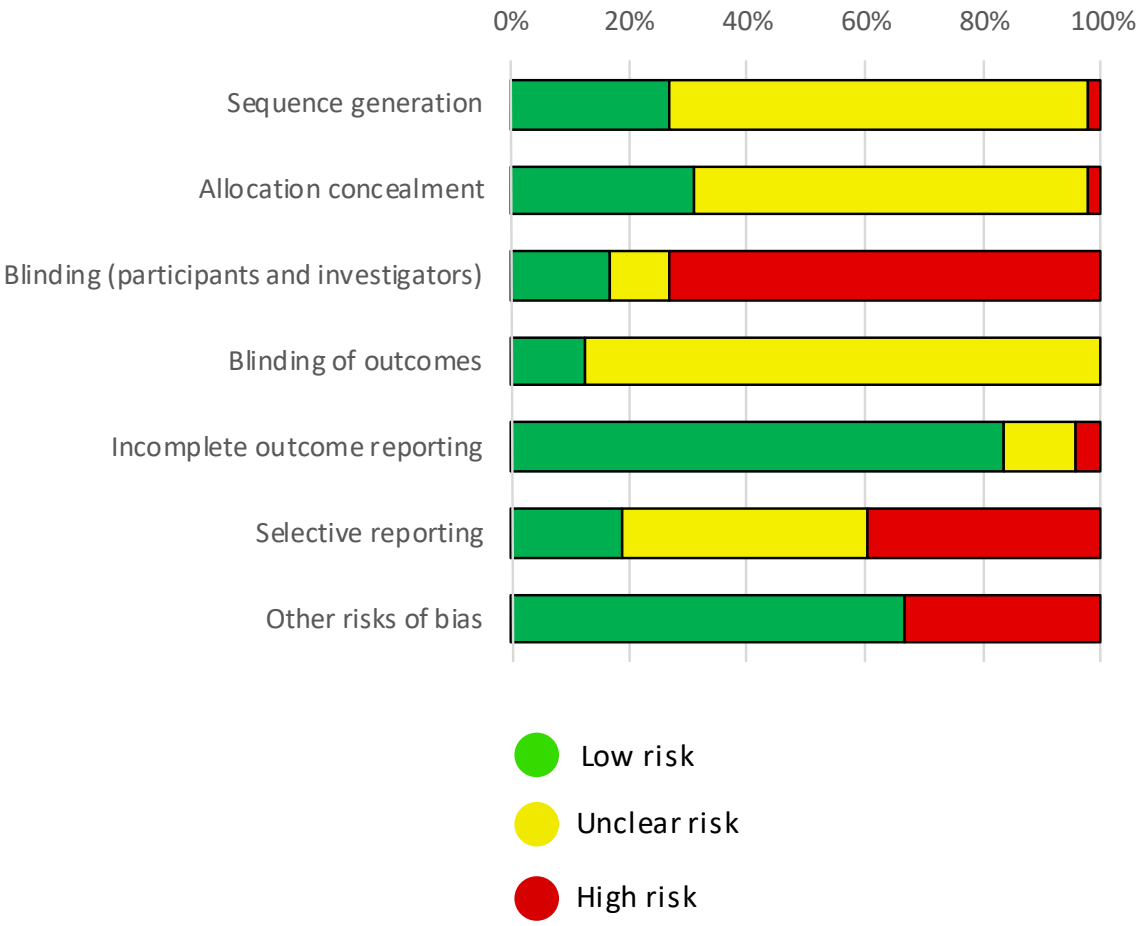
Drug class	Trials of 24 months follow up or longer	Trials with allocation concealment
Intravenous cyclophosphamide	1.00	1.00
Mycophenolate mofetil	0.14 (0.01 to 3.68)	2.04 (0.85 to 4.93)
Oral cyclophosphamide	0.10 (0.01 to 1.78)	--
Calcineurin inhibitor	1.14 (0.23 to 5.72)	1.50 (0.53 to 4.30)
Rituximab	--	--
Prednisone	0.59 (0.20 to 1.74)	--
Number of studies/number of participants in network	*11/227*	*5/674*

Supplemental Figure 1: Risks of bias in individual studies



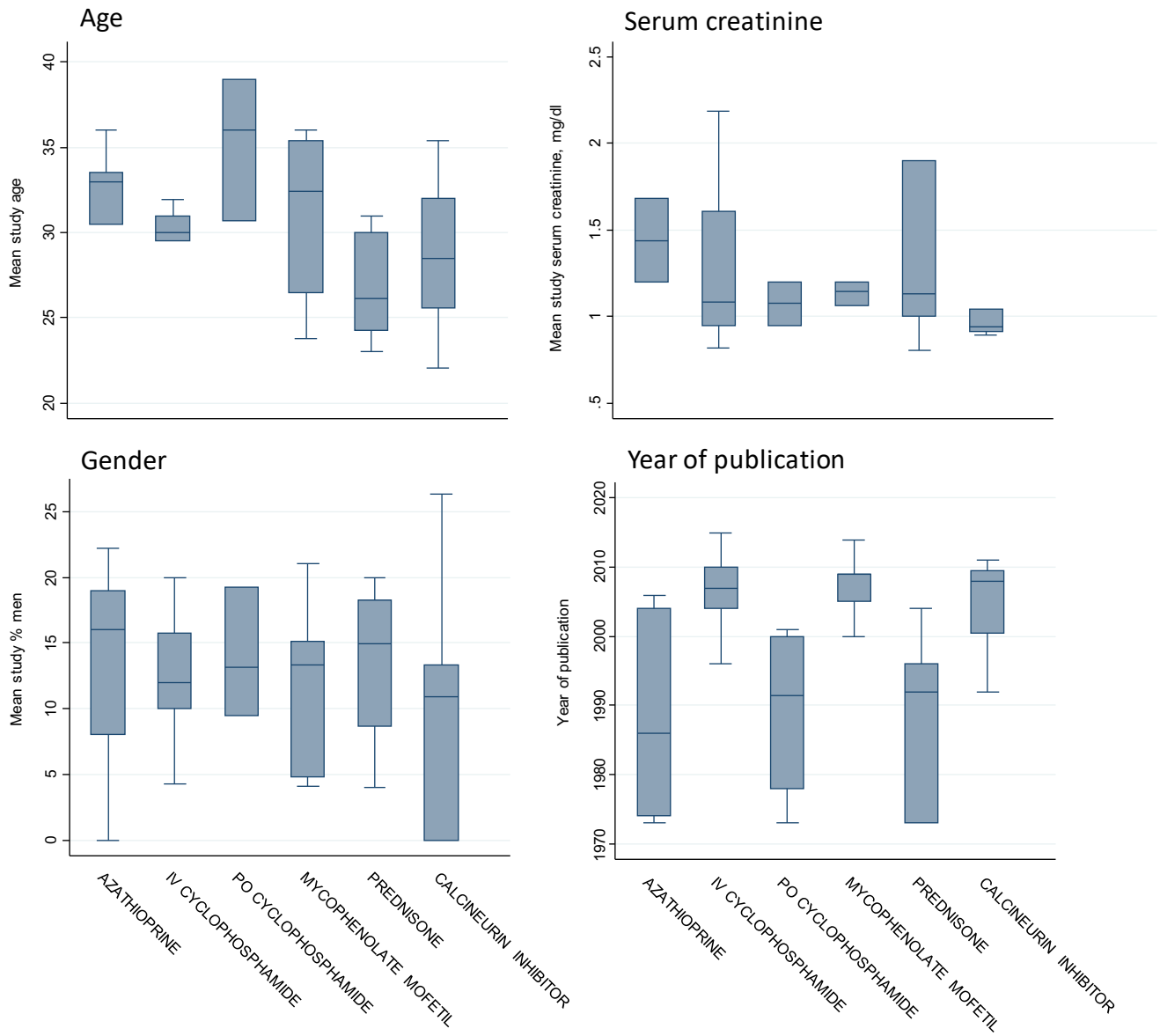
47 studies in 48 publications were included in this analysis. Dooley et al (2011) was an extension/maintenance phase of the Aspreva Lupus Management Study (2009).[32 39]

Supplemental Figure 2: Summary of risks of bias in included studies



47 studies in 48 publications were included in this analysis. Dooley et al (2011) was an extension/maintenance phase of the Aspreva Lupus Management Study (2009).[32 39]

Supplemental Figure 3: Summary study-level characteristics according to treatment class.



Box plots showing the distribution of study level characteristics according to treatment class. There were insufficient observations to provide box plots for ethnicity/racial origin.

Supplemental Figure 4: Summary odds ratios and 95% confidence intervals estimated by network meta-analysis for induction treatment of lupus nephritis.

The values below the drug class correspond to the odds of the clinical end point between the column treatment compared to the row treatment. An odds ratio >1 indicates the odds of the outcome was more likely with the column treatment. The values in bold are the estimated odds ratios that are statistically significant (excluding the likelihood of no effect).

Complete remission

MMF						
1.54 1.04-2.30	IV CYC					
2.40 0.69-8.39	1.55 0.43-5.61	Oral CYC				
0.83 0.43-1.60	**0.53 0.30-0.95**	0.35 0.09-1.29	CNI			
--	--	--	--	AZA		
2.72 1.01-7.31	1.76 0.71-4.36	1.13 0.24-5.45	**3.27 1.12-9.57**	--	PRED	
--	--	--	--	--	--	RITUX

There were 18 studies involving 1119 participants in this network reporting 337 people experiencing complete remission of lupus nephritis during treatment. The heterogeneity tau for the network was 0.00 indicative of low heterogeneity in treatment effects among studies.

All-cause mortality

MMF						
1.07 0.42-2.74	IV CYC					
0.39 0.08-1.86	0.37 0.10-1.40	Oral CYC				
2.25 0.52-9.84	2.09 0.49-8.88	5.71 0.82-39.8	CNI			
0.70 0.18-2.81	0.65 0.21-2.00	1.78 0.48-6.62	0.31 0.05-1.90	AZA		
0.54 0.14-2.06	0.50 0.17-1.44	1.36 0.38-4.82	0.24 0.04-1.40	0.76 0.28-2.05	PRED	
--	--	--	--	--	--	RITUX

There were 15 unique studies included in the network reporting 94 deaths in a total of 1346 randomized participants. The heterogeneity tau for the network estimating treatment effects on all-cause mortality was 0.18 indicative of low-level heterogeneity in treatment effects among studies.

End-stage kidney disease

MMF						
2.61 0.37-18.7	IV CYC					
1.94 0.17-22.8	0.75 0.17-3.27	Oral CYC				
0.95 0.13-7.09	0.37 0.02-6.08	0.49 0.02-11.8	CNI			
1.46 0.15-14.3	0.56 0.18-1.79	0.75 0.19-3.01	1.53 0.07-32.0	AZA		
1.08 0.13-9.18	**0.42** **0.18-0.95**	0.56 0.15-2.05	1.14 0.06-21.3	0.74 0.29-1.90	PRED	
--	--	--	--	--	--	RITUX

There were 9 studies reporting 151 participants experiencing end-stage kidney disease in a total of 1036 randomized participants. The heterogeneity tau for the network estimating treatment effects on end-stage kidney disease was <0.001 indicative of low heterogeneity in treatment effects among studies.

Doubling of serum creatinine

MMF						
1.35 0.08-24.3	IV CYC					
0.74 0.04-13.2	0.55 0.14-2.15	Oral CYC				
0.37 0.02-7.14	0.27 0.01-5.28	0.50 0.02-11.3	CNI			
0.40 0.02-7.93	**0.30** **0.10-0.85**	0.54 0.14-2.17	1.09 0.05-24.2	AZA		
0.46 0.03-8.44	**0.34** **0.17-0.69**	0.62 0.17-2.24	1.25 0.06-25.4	1.15 0.41-3.19	PRED	
--	--	--	--	--	--	RITUX

There were seven studies reporting 68 participants experiencing doubling of serum creatinine among a total of 472 randomized participants. The heterogeneity tau for the network estimating odds of doubling of serum creatinine was <0.001 indicative of low heterogeneity in treatment effects among studies.

Failure to induce disease remission (treatment failure)

MMF						
0.49 0.28-0.87	IV CYC					
0.28 0.04-1.94	0.56 0.08-4.13	Oral CYC				
1.46 0.61-3.50	**2.94 1.19-7.27**	5.26 0.72-38.2	CNI			
0.12 0.00-3.16	0.24 0.01-6.09	0.43 0.10-19.2	0.08 0.00-2.34	AZA		
0.12 0.03-0.43	**0.25 0.08-0.77**	0.44 0.04-4.41	**0.08 0.02-0.36**	8.38 0.32-221	PRED	
--	--	--	--	--	--	RITUX

There were 12 studies reporting 182 participants experiencing failure to induce remission events among a total of 684 randomized participants. The heterogeneity tau for the network estimating odds of failure to induce disease remission was <0.001, indicative of low heterogeneity in treatment effects among studies.

Major infection

MMF						
1.23 0.84-1.79	IV CYC					
1.10 0.42-2.87	0.89 0.34-2.35	Oral CYC				
2.17 **1.05-4.49**	1.77 0.86-3.64	1.98 0.67-5.82	CNI			
3.66 **1.07-12.6**	2.98 0.89-10.0	3.34 0.93-11.9	1.69 0.47-6.10	AZA		
1.52 0.60-3.85	1.24 0.52-2.98	1.38 0.47-4.10	0.70 0.24-2.06	**0.27** **0.08-0.94**	PRED	
--	--	--	--	--	--	RITUX

There were 18 studies reporting 380 participants experiencing one or more major infections among a total of 1230 randomized participants. The heterogeneity tau for the network estimating odds of major infection was <0.001, indicative of low heterogeneity in treatment effects among studies.

Alopecia

MMF						
0.22 0.13-0.39	IV CYC					
0.09 0.00-1.80	0.41 0.02-8.56	Oral CYC				
1.16 0.12-11.3	5.24 0.58-47.7	12.8 0.30-549	CNI			
--	--	--	--	AZA		
--	--	--	--	--	PRED	
--	--	--	--	--	--	RITUX

There were four studies reporting 92 participants experiencing alopecia among a total of 519 randomized participants. The heterogeneity tau for the network estimating odds of alopecia was <0.001, indicative of low heterogeneity in treatment effects among studies.

Ovarian failure

MMF						
0.48 0.11-2.08	IV CYC					
0.08 **0.01-0.85**	0.15 0.01-1.79	Oral CYC				
1.67 0.28-10.0	3.44 0.94-12.6	**22.0** **2.11-230**	CNI			
1.11 0.15-8.00	2.29 0.57-9.29	14.6 0.99-217	0.67 0.13-3.36	AZA		
4.53 0.59-34.7	**9.35** **2.25-38.9**	**59.7** **3.55-1004**	2.72 0.40-18.6	4.08 0.55-30.1	PRED	
--	--	--	--	--	--	RITUX

There were ten studies reporting 60 participants experiencing ovarian failure among a total of 489 randomized participants. The heterogeneity tau for the network estimating odds of ovarian failure was <0.001, indicative of low heterogeneity in treatment effects among studies.

Malignancy

MMF						
--	IV CYC					
--	0.13 0.01-1.24	Oral CYC				
--	--	--	CNI			
--	0.21 0.03-1.65	1.62 0.29-8.96	--	AZA		
--	1.77 0.16-19.4	**13.8** **1.07-177**	--	8.49 0.69-104	PRED	
--	--	--	--	--	--	RITUX

There were three studies reporting 13 participants experiencing one or more malignancies among a total of 259 randomized participants. The heterogeneity tau for the network estimating odds of malignancy was not estimable.

Diarrhea

MMF						
2.70 1.60-4.53	IV CYC					
3.15 0.12-81.7	1.17 0.04-31.6	Oral CYC				
--	--	--	CNI			
--	--	--	--	AZA		
--	--	--	--	--	PRED	
--	--	--	--	--	--	RITUX

There were four studies reporting 87 participants experiencing one or more episodes of diarrhea among a total of 597 randomized participants. The heterogeneity tau for the network estimating odds of failure to induce disease remission was <0.001, indicative of low heterogeneity in treatment effects among studies.

Bone toxicity

MMF						
--	IV CYC					
--	--	Oral CYC				
--	--	--	CNI			
--	--	--	--	AZA		
--	0.79 0.25-2.50	--	--	--	PRED	
--	--	--	--	--	--	RITUX

There were three studies reporting 25 participants experiencing bone toxicity among a total of 491 randomized participants. The heterogeneity tau for the network estimating odds of failure to induce disease remission was 0.32, indicative of moderate heterogeneity in treatment effects among studies.

Leukopenia

MMF						
0.76 0.31-1.86	IV CYC					
0.11 0.01-1.05	0.14 0.01-1.43	Oral CYC				
2.12 0.50-8.92	2.79 0.79-9.43	**19.5** **2.07-185**	CNI			
--	--	--	--	AZA		
--	--	--	--	--	PRED	
--	--	--	--	--	--	RITUX

There were seven studies reporting 51 participants experiencing one or more episodes of leukopenia among a total of 340 randomized participants. The heterogeneity tau for the network estimating odds of leukopenia was <0.001, indicative of low heterogeneity in treatment effects among studies.

Herpes infection

MMF						
1.72 0.92-3.15	IV CYC					
0.76 0.24-2.40	0.44 0.15-1.30	Oral CYC				
1.58 0.38-6.53	0.93 0.25-3.37	2.08 0.44-9.85	CNI			
3.69 0.67-20.3	2.16 0.43-10.9	4.87 0.92-25.7	2.33 0.31-17.8	AZA		
3.17 0.96-10.5	1.86 0.65-5.31	**4.18** **1.12-15.6**	2.01 0.39-10.3	0.86 0.15-4.80	PRED	
--	--	--	--	--	--	RITUX

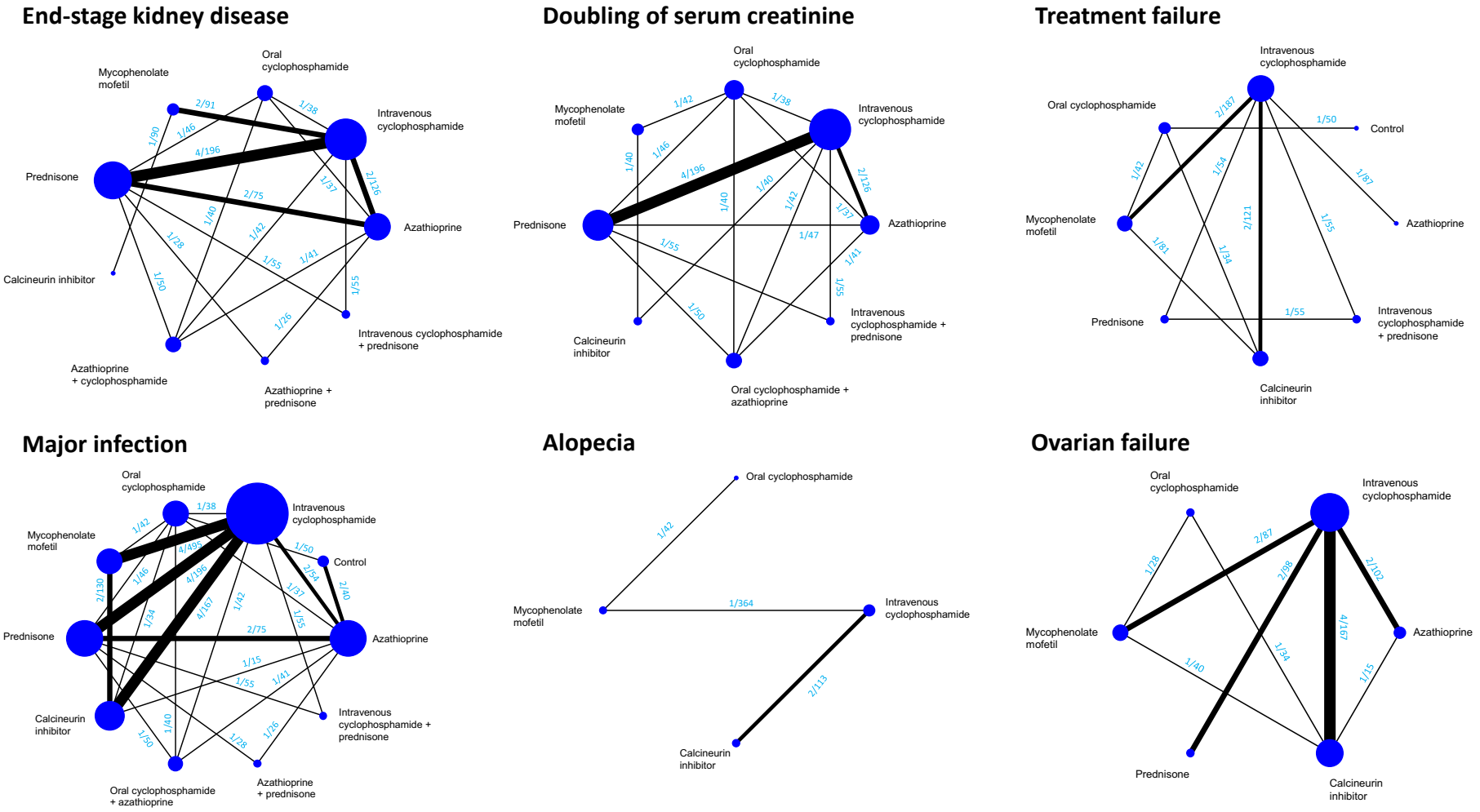
There were 12 studies reporting 104 participants experiencing one or more episodes of herpes infection events among a total of 932 randomized participants. The heterogeneity tau for the network estimating odds of failure to induce disease remission was <0.001, indicative of low heterogeneity in treatment effects among studies.

Disease relapse (during maintenance treatment)

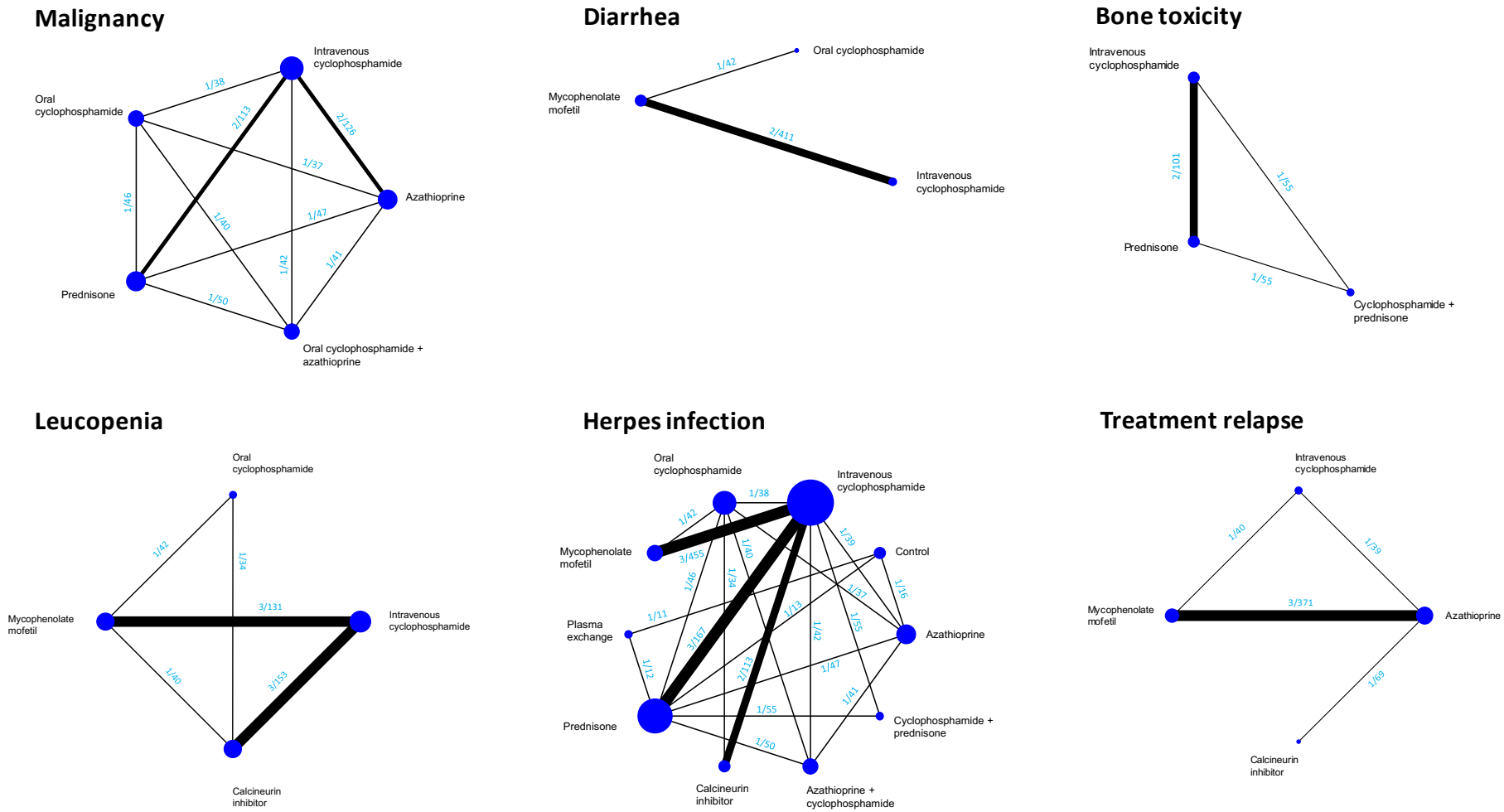
MMF					
0.32 0.10-1.09	IV CYC				
--	--	Oral CYC			
0.70 0.20-2.48	2.17 0.42-11.3	--	CNI		
0.53 **0.31-0.90**	1.64 0.50-5.39	--	0.75 0.24-2.37	AZA	
--	--	--	--	--	PRED

There were four studies reporting 96 participants experiencing disease relapse among a total of 460 randomized participants. The heterogeneity tau for the network estimating odds of relapse was <0.001, indicative of low heterogeneity in treatment effects among studies.

Supplemental Figure 5: Networks of treatment comparisons for efficacy and safety of immunosuppression as induction treatment for lupus nephritis (secondary outcomes)



Supplemental Figure 5 (continued): Networks of treatment comparisons for efficacy and safety of immunosuppression as induction



treatment for lupus nephritis (secondary outcomes)

Supplemental References

1. Cade R, Spooner G, Schlein E, Pickering M, DeQuesada A, Holcomb A, Juncos L, Richard G, Shires D, Levin D, Hackett R, Free J, Hunt R, Fregly M. Comparison of azathioprine, prednisone, and heparin alone or combined in treating lupus nephritis. *Nephron* 10:37-56, 1973

2. Fries JF, Sharp GC, McDevitt HO, Holman HR. Cyclophosphamide therapy in systemic lupus erythematosus and polymyositis. *Arthritis Rheumatol* 16:154-62, 1973

3. Donadio JV, Jr., Holley KE, Wagoner RD, Ferguson RH, McDuffie FC. Treatment of lupus nephritis with prednisone and combined prednisone and azathioprine. *Ann Intern Med* 77:829-35, 1972

4. 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* 83:597-605, 1975

5. Donadio JV, Jr., Holley KE, Ferguson RH, Ilstrup DM. Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. *N Engl J Med* 299:1151-5, 1978

6. Clark WF, Lindsay RM, Cattran DC, Chodirker WB, Barnes CC, Linton AL. Monthly plasmapheresis for systemic lupus erythematosus with diffuse proliferative glomerulonephritis: a pilot study. *Can Med Assoc J* 125:171-4, 1981

7. Clark WF, Balfe JW, Cattran DC. Long-term plasma exchange in patients with systemic lupus erythematosus and diffuse proliferative glomerulonephritis. *Plasma Therapy and Transfusion Technology* 5:353-60, 1984

8. Austin HA, 3rd, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, Decker JL. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 314:614-9, 1986

9. Balletta M, Sabella D, Magri P, Sepe V, Stanziale P, Di Luccio R, Colucci G, Fuiano G. Cyclosporin plus steroids versus steroids alone in the treatment of lupus nephritis. *Contributions to Nephrology* 99:129-30, 1992

10. Boumpas DT, Austin H, Vaughn EM, Klippel J, Steinberg A, Yarboro C. Controlled Trial of Pulse Methylprednisolone Versus Two Regimens of Pulse Cyclophosphamide in Severe Lupus Nephritis. *Lancet* 340:741-5, 1992

11. Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. *N Engl J Med* 326:1373-9, 1992

12. Doria A, Piccoli A, Vesco P, Vaccaro E, Marson P, De Silvestro G, Ossi E, Gambari P. Therapy of lupus nephritis. A two-year prospective study. *Ann Med Interne (Paris)* 145:307-11, 1994

13. Sesso R, Monteiro M, Sato E, Kirsztajn G, Silva L, Ajzen H. A controlled trial of pulse cyclophosphamide versus pulse methylprednisolone in severe lupus nephritis. *Lupus* 3:107-12, 1994

14. Belmont HM, Kitsis E, Skovron ML, Buyon J, McCullagh E, Abramson S. Misoprostol and prednisone treatment of lupus nephritis. *Am J Ther* 2:928-32, 1995

15. Gourley MF, Austin HA, 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, Boumpas DT, Klippel JH, Balow JE, Steinberg AD. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med* 125:549-57, 1996

16. Lui S, Cheng I, Tong K, Li C, Wong K, Chan T. Treatment of type iv lupus nephritis (LN) - comparison of 2 triple therapy regimens: cyclosporin a (CSA), prednisolone (PRED), azathioprine (AZA) vs. oral cyclophosphamide (POCP), prednisolone, azathioprine [abstract]. *Nephrology* 3:S476, 1997

17. Fu LW, Yang LY, Chen WP, Lin CY. Clinical efficacy of cyclosporin a neoral in the treatment of paediatric lupus nephritis with heavy proteinuria. *Br J Rheumatol* 37:217-21, 1998

18. Wallace DJ, Goldfinger D, Pepkowitz SH, Fichman M, Metzger AL, Schroeder JO, Euler HH. Randomized controlled trial of pulse/synchronization cyclophosphamide/apheresis for proliferative lupus nephritis. *J Clin Apheresis* 13:163-6, 1998

19. Boletis JN, Ioannidis JPA, Boki KA, Moutsopoulos HM. Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis. *Lancet* 354:569-70, 1999

20. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, Lau CS, Wong AK, Tong MK, Chan KW, Lai KN. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med* 343:1156-62, 2000

21. Nakamura T, Ushiyama C, Hara M, Osada S, Ugai K, Shimada N, Hayashi K, Ebihara I, Koide H. Comparative effects of plasmapheresis and intravenous cyclophosphamide on urinary podocyte excretion in patients with proliferative Lupus nephritis. *Clin Nephrol* 57:108-13, 2002

22. Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, Roth D. Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 350:971-80, 2004

23. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, Petri M, Gilkeson GS, Wallace DJ, Weisman MH, Appel GB. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 353:2219-28, 2005

24. Ong LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, Teo SM, Wong HS, Tan SY, Shaariah W, Tan CC, Morad Z. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrology* 10:504-10, 2005

25. El-Sehemy MS, Al-Saaran AM, Baddour NM, Adam AG, Moez PE. Comparative clinical prospective therapeutic study between cyclophosphamide, cyclosporine and azathioprine in the treatment of lupus nephritis. *Egypt J Immunol* 13:39-52, 2006

26. Grootscholten C, Ligtenberg G, Hagen EC, van den Wall Bake AW, de Glas-Vos JW, Bijl M, Assmann KJ, Bruijn JA, Weening JJ, van Houwelingen HC, Derksen RH, Berden JH, Dutch Working Party on Systemic Lupus E. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. *Kidney Int* 70:732-42, 2006

27. Moroni G, Doria A, Mosca M, Alberighi OD, Ferraccioli G, Todesco S, Manno C, Altieri P, Ferrara R, Greco S, Ponticelli C. A randomized pilot trial comparing cyclosporine and

azathioprine for maintenance therapy in diffuse lupus nephritis over four years. *Clin J Am Soc Nephrol* 1:925-32, 2006

28. Dyadyk O, Vasilenko I, Bagriy A, Kholopov L, Dyadyk O, Yarovaya N. Azathioprine and cyclophosphamide in diffuse proliferative lupus nephritis treatment - a randomized controlled study [abstract]. *Ann Rheum Dis* 66:467, 2007

29. Hong R, Haijin Y, Xianglin W, Cuilan H, Nan C. A preliminary study of tacrolimus versus cyclophosphamide in patients with diffuse proliferative lupus nephritis. *Nephrol Dial Transplant* 22:vi276, 2007

30. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 19:2001-10, 2008

31. Mulic-Bacic S, Antic D, Krizic M, Hajdarovic A, Mulic E. Mycophenolate mofetil or intravenous cyclophosphamide in treatment of lupus nephritis [abstract]. *Annals of the Rheumatic Disease* 67:349, 2008

32. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, Li LS, Mysler E, Sanchez-Guerrero J, Solomons N, Wofsy D, Aspreva Lupus Management Study Group. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 20:1103-12, 2009

33. Li EK, Tam LS, Zhu TY, Li M, Kwok CL, Li TK, Leung YY, Wong KC, Szeto CC. Is combination rituximab with cyclophosphamide better than rituximab alone in the treatment of lupus nephritis? *Rheumatology* 48:892-8, 2009

34. Mok C, Ying S, Tong K, Siu Y, To C, Yim C. Mycophenolate mofetil versus tacrolimus for active lupus nephritis: an extended observation of a randomized controlled trial [abstract]. *Annals of the Rheumatic Disease* 68:246, 2009

35. 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* 14:214-21, 2010

36. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, Fiehn C, de Ramon Garrido E, Gilboe IM, Tektonidou M, Blockmans D, Ravelingien I, le Guern V, Depresseux G, Guillevin L, Cervera R, Maintain Nephritis Trial Group. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Annals of the Rheumatic Diseases* 69:2083-9, 2010

37. Zavada J, Pesickova S, Rysava R, Olejarova M, Horak P, Hrncir Z, Rychlik I, Havrda M, Vitova J, Lukac J, Rovensky J, Tegzova D, Bohmova J, Zadrazil J, Hana J, Dostal C, Tesar V. Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study. *Lupus* 19:1281-9, 2010

38. Chen W, Tang X, Liu Q, Chen W, Fu P, Liu F, Liao Y, Yang Z, Zhang J, Chen J, Lou T, Fu J, Kong Y, Liu Z, Fan A, Rao S, Li Z, Yu X. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: A multicenter randomized clinical trial. *Am J Kidney Dis* 57:235-44, 2011

39. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, Eitner F, Appel GB, Contreras G, Lisk L, Solomons N, Group A. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 365:1886-95, 2011

40. Ginzler EM, Wax S, Rajeswaran A, Copt S, Hillson J, Ramos E, Singer NG. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. *Arthritis Res Ther* 14:R33, 2012

41. Li X, Ren H, Zhang Q, Zhang W, Wu X, Xu Y, Shen P, Chen N. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. *Nephrol Dial Transplant* 27:1467-72, 2012

42. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, Maciuca R, Zhang D, Garg JP, Brunetta P, Appel G, Lunar Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 64:1215-26, 2012

43. Jayne D, Appel G, Chan TM, Barkay H, Weiss R, Wofsy D. A randomized controlled study of laquinimod in active lupus nephritis patients in combination with standard of care [Abstract]. *Annals of the Rheumatic Diseases* 722013

44. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, Houssiau FA, Drappa J, Close D, Maciuca R, Rao K, Shahdad S, Brunetta P. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. *Arthritis Rheum* 65:2368-79, 2013

45. The ACCESS Trial Group. Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. *Arthritis Rheumatol* 66:3096-104, 2014

46. Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R, Chen SL, Hillson JL, Meadows-Shropshire S, Kinaszczuk M, Merrill JT. Efficacy and safety of abatacept in lupus nephritis: A twelve-month, randomized, double-blind study. *Arthritis Rheumatol* 66:379-89, 2014

47. Rathi M, Goyal A, Gupta PK, Jaryal A, Sharma A, Jha V, Ramachandran R, Kumar V, Kohli HS, Lal Gupta K, Sakhuja V. Randomized controlled trial of low-dose intravenous cyclophosphamide versus oral mycophenolate mofetil in treatment of lupus nephritis. *Nephrol Dial Transplant* 29:iii28-iii29, 2014

48. Liu Z, Zhang H, Xing C, Fu P, Ni Z, Chen J, Lin H, Liu F, He Y, Miao L, Chen N, Li Y, Gu Y, Shi W, Hu W, Liu Z, Bao H, Zeng C, Zhou M. Multitarget therapy for induction treatment of lupus nephritis: A randomized trial. *Ann Intern Med* 162:18-26, 2015