Efficacy and safety of immunosuppressive agent monotherapy for IgA nephropathy: a network meta-analysis

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Abstract

Background

The efficacy and safety of immunosuppressive agent monotherapy were evaluated for Immunoglobulin A nephropathy (IgAN) using a network meta-analysis approach based on randomised controlled trials (RCTs).

Methods

PubMed, Embase, the Cochrane library, and the Web of Science were systematically searched for RCTs published before October 2019 using immunosuppressive agents for treating IgAN. Quality assessments were performed according to the Cochrane Handbook. Pooled relative risks (RRs) or standard mean differences (SMDs) with corresponding 95% confidence intervals (CIs) were calculated for discrete or continuous variables, respectively. The primary outcomes were clinical remission, end-stage renal disease (ESRD), and serious adverse events (SAEs); the secondary outcomes were urinary protein excretion and serum creatinine. Data were synthesised by the random-effects model.

Results

Twenty-five RCTs with 2005 participants were deemed to be eligible, and six medications were evaluated: corticosteroids, mycophenolate mofetil (MMF), tacrolimus (TAC), cyclosporine (CsA), leflunomide (LEF), and hydroxychloroquine (HCQ). Compared to supportive care alone, steroids (RR 1.50, 95% CI 1.17–1.93), MMF (RR 2.05, 95% CI 1.15–3.65), TAC (RR 3.67, 95% CI 1.06–12.63), and HCQ (RR 3.25, 95% CI 1.05–10.09) each significantly improved clinical remission rates; only steroids reduced the risk of ESRD (RR 0.35, 95% CI 0.12–0.98), but the SAEs were significantly higher than those in the control group (RR 2.90, 95% CI 1.37–6.13). Furthermore, steroids, LEF, and HCQ showed lower proteinuria in the pairwise meta-analysis. There was no evidence of different effects of the therapies on serum creatinine levels. The effect of MMF, whereby it induced remission, was reversed when excluding studies with follow-up of fewer than two years in the sensitivity analysis (RR 1.41, 95% CI 0.40–4.92). The anti-proteinuric effect of TAC was reversed three months after discontinuing medication; the long-term effects of HCQ could not be evaluated due to the short follow-up.

Conclusions

Corticosteroids might induce remission and increase renal survival in IgAN; however, the adverse reactions should be considered. TAC, LEF, HCQ, and MMF, might improve remission of proteinuria when treating IgAN, but showed no superiority compared to steroids, and the long-term effects require further study.

1. Introduction

Immunoglobulin A nephropathy (IgAN) is one of the most common glomerular diseases and a leading cause of end-stage renal disease (ESRD) worldwide [1]. Approximately 20–40% of patients progress to ESRD within 10–20 years after diagnosis [2]. To date, renin-angiotensin system (RAS) blockade-based supportive care has been the preferred treatment for IgAN, and corticosteroids have been recommended for selected IgAN patients with proteinuria >1.0 g and an estimated glomerular filtration rate (eGFR) >50 ml/min/1.73 m^2 despite supportive therapies based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [3]. However, in light of the KDIGO Controversies Conference 2017, this recommendation may need to be revisited [4]. More recently, in the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study, steroids were shown to be potentially beneficial for clinical remission of IgAN; despite being associated with a significant increase in serious adverse events (SAE) [5]. Corticosteroid-based immunosuppressive treatments have also been reported as a potential treatment for remission in IgAN; however, they are also limited by their higher risks of adverse events [6]. Immunosuppressive agent monotherapy is an optional treatment for IgAN, such as calcineurin inhibitors, mycophenolate mofetil (MMF), and so on [7]. Previous pairwise meta-analyses indicated that either calcineurin inhibitors, MMF, or leflunomide (LEF) might be effective for IgAN [8,9,10], although, their independent effects are controversial, and, the relative effects between different immunosuppressive agents also are unknown. Given that network meta-analysis (NMA) can give a unified, coherent analysis of the direct and indirect evidence of these drug effects, as well as rank the probability of optimal treatment; we conducted this NMA of randomised controlled trials (RCTs) to

determine the efficacy and safety of monotherapy for IgAN using different immunosuppressive agents, and if possible, predict the best candidate for treatment.

2. Methods

2.1 Design and ethics

This work was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMA [11] and checklist (see Additional file 1). The data used in this study were obtained from previously published literature; therefore, ethical approval and informed consent were not applicable.

2.2 Search strategy

Eligible studies published prior to October 2019 were searched on PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Web of Science. Medical subject headings and free-text searches were applied by combining the following three domains without language restrictions: immunosuppressive agent (cyclophosphamide [CYC], azathioprine [AZA], cyclosporine [CsA], tacrolimus [TAC], LEF, hydroxychloroquine [HCQ], MMF, and steroid), IgAN, and RCT. The details of the search strategy are mentioned in Additional file 2.

2.3 Eligibility criteria

The inclusion criteria were identified by the Participants, Interventions, Comparisons, Outcomes, and Study design (PICOS) framework—(1) participants: patients with biopsy-proven IgAN; (2) intervention and comparison: different immunosuppressive agent monotherapy (CYC, AZA, MMF, CsA, TAC, LEF, HCQ, or steroid), were compared with each other or with non-immunosuppressive treatments. In addition, supportive therapies could be administrated for both groups; (3) outcomes: the primary outcomes were clinical remission, including complete remission (CR), or partial remission (PR), which were assessed according to the definition provided in each study, and the endpoint of ESRD and SAEs, including death, serious infection, new diabetes mellitus, and other SAEs defined by originating studies; secondary outcomes were urinary protein excretion and serum creatinine; and (4) study design: RCT.

The exclusion criteria were as follows: (1) secondary IgAN; or (2) no data available for analysis.

2.4 Study selection and data extraction

Study selection and data extraction were performed independently by two investigators each, and any disagreement was solved via discussion with a third reviewer. The process of study selection is summarised in the PRISMA flowchart. We extracted the following data from each of the studies included: first author, publication year, location, baseline information for all groups (sample size, age, gender), details of the intervention, duration of follow-up, and outcomes.

2.5 Risk of bias assessment

The Cochrane Handbook assessment tool for the risk of bias (version 5.1.0) was used to assess the methodological quality of each trial by two investigators independently. This tool consists of seven items, the assessments of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The results for each domain were divided into three levels: low risk of bias, high risk of bias, and unclear risk of bias [12].

2.6 Statistical analysis

All statistical analyses were performed by the STATA software (version 14.0). Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated for discrete data; continuous data were compared using standardised mean differences (SMDs) and corresponding 95% CIs because they might be detected at different follow-up times. Pairwise meta-analyses were performed for each outcome using a random-effects model for each direct contrast. Inconsistency test and loop-specific approach were used to evaluate inconsistency of the entire network and local inconsistency between direct and indirect comparisons. The

random-effects NMA was conducted to compare all classes of interventions for each prespecified outcome under the frequentist framework if there was no inconsistency [13]. The surface under the cumulative ranking curve (SUCRA) value was calculated to rank the interventions. A sensitivity analysis was conducted by excluding studies with follow-ups of fewer than two years. A comparison-adjusted funnel plot was conducted to assess the small-study effect.

3. Results

3.1 Characteristics of eligible studies

A total of 1251 publications were retrieved from the electronic databases after removing duplications. Twenty-five RCTs in twenty-nine publications were identified for meta-analyses [5,14–41]. Details of the literature selection process are shown in Figure 1. There were 2005 participants (1195 males and 810 females) enrolled in the 25 RCTs. In these studies, six immunosuppressive agents, including corticosteroids, MMF, TAC, CsA, LEF, and HCQ, were reported. A novel, oral, targeted-release formulation of the glucocorticoid (TRF-budesonide) was included; therefore, it was presented independently to differentiate from conventional formulations of steroids. Supportive therapies were administrated for both groups, comparisons were performed between immunosuppressive drugs and controls (placebo, 11; supportive care, 12; dipyridamole, 1), except one that compared MMF with prednisone [20]. The median duration of each drug was as follows: steroids, 8.5 (Range, 4–24) months; MMF, 12 (Range, 6–36) months; TAC, 16 weeks; CsA, 12 weeks; LEF, 6 (Range, 6–24) months; and HCQ, six months. Median follow-up was as follows: steroids, 35 (Range, 12–120) months; MMF, 24 (Range, 18–72) months; TAC, five years; CsA, 24 weeks; LEF, 7 (Range, 6–24) months; and HCQ, six months. Characteristics of the selected studies are depicted in Additional file 3. The network graphs for each outcome are presented in Figure 2.

3.2 Risk of bias assessment

Fifteen of the 25 (60%) trials described the methods for generating random sequences appropriately; thus, their selection bias risk was considered low. The remaining studies were classified as an unclear risk because they only mentioned ‘random’ selection. Eleven (44%) trials used placebo-controlled blinding, 13 (52%) trials reported the processes for allocation concealment, nine studies (36%) reported assessment of blinded outcome. All (100%) studies possessed complete data. Six (24%) studies were at low selective bias because of early registration. Three (12%) trials were terminated early, one (4%) study was a preliminary analysis, and their other biases were classified as high risk (Figure 3).

3.3 Primary outcomes

Seventeen studies reported CR or PR outcomes. NMA results indicated that steroids (RR 1.50, 95% CI 1.17–1.93), MMF (RR 2.05, 95% CI 1.15–3.65), TAC (RR 3.67, 95% CI 1.06–12.63), and HCQ (RR 3.25, 95% CI 1.05–10.09) each significantly improved the clinical remission rate in IgAN patients compared to the control group, as well as the results of the pairwise meta-analyses. However, there was no significant difference in the clinical remission rates between each of these immunosuppressive agents for patients with IgAN (Table 1).

Ten studies, involving LEF, MMF, steroids, and TRF-budesonide, reported the hard endpoint of ESRD. There were no significant differences in the incidences of ESRD between any of the groups, except the conventional steroids group (RR 0.35, 95% CI 0.12–0.98), showed better renal survival than the control group (Table 2).

SAEs were reported in twenty-two studies for all included medications for IgAN. The results showed that IgAN patients receiving steroids had higher risks of SAE than those in the control group (RR 2.90, 95% CI 1.37–6.13), the same results were found in the pairwise meta-analysis (RR 4.27, 95% CI 1.79–10.18), all the remaining immunosuppressive agents had no significant difference when compared to the control or each other (Table 3).

3.4 Secondary outcomes

Nineteen RCTs reported urinary protein excretion. There was some inconsistency in the data (P = 0.04, tau = 0.43); therefore, the results were analysed only using a pairwise meta-analysis. When compared to the control group, the IgAN patients receiving

steroids (SMD: -0.69, 95% CI: -0.98–-0.41), LEF (SMD: -0.58, 95% CI: -0.89–-0.27), and HCQ (SMD: -1.09, 95% CI: -1.64–-0.55) had significantly lower levels of urinary protein excretion. Patients in MMF groups showed lower urinary protein excretion than those in the steroid treatment groups (SMD: -0.77, 95% CI: -1.28–-0.25) (see Additional file 4).

Eleven RCTs, including five immunosuppressive agents (LEF, CsA, TAC, MMF, steroid), reported serum creatinine levels. There were no significant differences between serum creatinine levels in any of the groups in either the network or pairwise meta-analysis (see Additional file 5).

3.5 Sensitivity analysis and SUCRA

Considering that follow-up might influence the main outcomes, we further performed a sensitivity analysis to exclude studies with follow-ups of fewer than two years. The sensitivity analysis of clinical remission was conducted between MMF, steroids, and the control group. Steroids might improve clinical remission compared to non-immunosuppressive therapy (RR 1.47, 95% CI 1.10–1.96); however, MMF showed no improvement of remission in the sensitivity analysis compared with controls (RR 1.41, 95% CI 0.40–4.92). The results of the ESRD were stable in this sensitivity analysis between LEF, MMF, steroids, and the control group (see Additional file 6).

The comparison-adjusted funnel plot indicated that small-study effects might exist (Figure 4); therefore, we next performed a sensitivity analysis to compare the main outcomes after omitting studies with participants less than 100, the same results were documented (see Additional file 7).

Ranking of treatments between MMF, steroids, and controls indicated that MMF might be the best treatment to induce remission (SUCRA 91.7%), followed by steroids and controls (SUCRA 57.9% and 0.4%, respectively). Steroids ranked as the best intervention to prevent ESRD (SUCRA 91.4%), but the worst treatment when serious adverse reactions were considered (SUCRA 3.7%, MMF 76.2%) (Table 4).

4. Discussion

IgAN is a common glomerulonephritis and the cause of ESRD worldwide [42]. There are several clinical risk factors that have demonstrated consistent associations with renal outcome in IgAN, of which, proteinuria has been reported as the best evaluable marker for predicting treatment response prognosis, as well as deteriorated renal function [43]. Steroids and immunosuppressive regimens, are potential optimal therapies to reduce proteinuria and improve renal survival; however, adverse events, especially serious infections, are significant [44]. Another choice for IgAN might be the use of immunosuppressive agent monotherapy; nevertheless, the efficacy and adverse reactions have not been determined.

This NMA is an effort to compare the direct and indirect effects of single therapy with different immunosuppressive agents beside corticosteroid, with/without supportive care, in treating patients with IgAN. The study included twenty-five RCTs with 2005 subjects, involving corticosteroids, MMF, TAC, CsA, LEF, and HCQ. The results indicated that steroids, MMF, TAC, and HCQ might improve the clinical remission rates for IgAN; however, the beneficial effect of MMF for remission was not significant in studies with a follow-up time of more than two years, suggesting that the long-term efficacy of MMF for IgAN might be poor. While TAC showed a beneficial effect in inducing remission, the five-year follow-up of the same participants presented negative results [39]. The follow-up times of CsA or HCQ for IgAN in the included studies were less than one year, so the long-term effect was unknown. Only steroids decreased the risk of ESRD, but SAE was significantly increased. All immunosuppressants exhibited no superiority when compared to glucocorticoids, whether in terms of clinical efficacy or adverse reactions.

The findings of this meta-analysis were consistent with the recent TESTING study comparing oral methylprednisolone with placebo, which showed a higher rate of remission in proteinuria and lower occurrence of ESRD in the methylprednisolone group than in the placebo group (48.2 vs. 21.8%; 2.9% vs. 7.9%), but was discontinued because of excess SAEs (14.7% vs. 3.2%) [5]. Thus, corticosteroid regimens in IgAN should be reviewed with regard to safety.

To date, the use of MMF in IgAN is still controversial, this study suggested a higher clinical remission in MMF monotherapy groups, but no beneficial effect was found when the follow-up time was more than two years, in clinical remission, ESRD, or

serum creatinine level. These results were consistent with the work from Hogg et al. [36], which was terminated early because of the lack of benefit (PR, 14% vs. 9%). Conversely, a six-year study from Tang et al. [33] showed that patients receiving MMF had better renal survival than those receiving placebo (90% vs. 55%). The paradoxical results might be due to different follow-up times or races, since the trials were conducted in North America and Asia, respectively. Notably, the adverse reactions of MMF seem to be tolerable. The results also provided a possibility for combined therapy of MMF and low-dose glucocorticoid to reach clinical remission and lower adverse reactions. A recent trial comparing MMF 1.5 g/d with prednisolone 0.4–0.6 mg/kg/d against prednisolone 0.8–1.0 mg/kg/d alone in treating IgAN [45]. Although the CR rates showed no significant differences, the steroid-related adverse events were lower in the MMF group than in the prednisone group, but the follow-up time of this study was only 12 months. So, further studies are needed to determine the long-term efficacy of MMF for IgAN.

TAC might be an effective treatment to induce remission for IgAN patients in 16 weeks; however, the sample size was limited (20 in the TAC group and 20 in the placebo group), and the five-year follow-up of the same cohorts showed that the anti-proteinuria effect was promptly reversed three months after discontinuing the drug [39]. HCQ has been little studied in IgAN—a recent RCT examined the effect of a six-month regimen of HCQ compared with placebo in patients with IgAN who were receiving optimised RAS inhibitor therapy [41], and the results suggested that HCQ effectively reduced proteinuria and increased PR in proteinuria. In addition, HCQ was well tolerated, where no SAEs were reported. Since the study was an early-phase trial, the long-term renoprotective efficacy and safety still require confirmation. A recent systematic review included 44 studies and 1802 patients to assess the effect of LEF in treating IgAN [10], and the results showed significantly lower urine protein and serum creatinine in patients treated with LEF and corticosteroids or angiotensin-converting enzyme inhibitor (ACEI) compared with patients treated with corticosteroids or ACEI alone. Our results indicate that LEF monotherapy had no superiority in achieving remission of proteinuria or renal survival when compared with supportive care alone, although the direct comparison suggested that LEF might have lower proteinuria-causing activity.

This study has limitations that reduce the applicability of the findings to clinical practice, which relate to the extent and quality of the information in individual studies. First, the quality of the included trials varied, causing significant heterogeneity. Second, the lack of reporting of many outcomes in many studies was a potential limitation. Third, most contributing trials had small sample sizes, just like the results of the funnel plot, which might reduce the statistical efficiency.

5. Conclusions

In conclusion, steroids might be an effective intervention strategy for IgAN to induce remission and increase renal survival; however, the adverse reactions cannot be ignored. Calcineurin inhibitors, LEF, HCQ, and MMF, might improve remission of proteinuria in treating IgAN, but they showed no superiority compared to steroids, and the long-term effects, in particular, still require further study.

Abbreviations

AZA: Azathioprine; ACEI: Angiotensin-converting enzyme inhibitor; CENTRAL: Cochrane Central Register of Controlled Trials; CYC: Cyclophosphamide; CsA: Cyclosporine; CR: Complete remission; CI: Confidence interval; ESRD: End-stage renal disease; eGFR: estimated glomerular filtration rate; HCQ: Hydroxychloroquine; IgAN: Immunoglobulin A nephropathy; KDIGO: Kidney Disease Improving Global Outcomes; LEF: Leflunomide; MMF: Mycophenolate mofetil; NMA: Network meta-analysis; PICOS: Participants, Interventions, Comparisons, Outcomes, and Study design; PR: Partial remission; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RAS: Renin-angiotensin system; RCT: Randomised controlled trials; RR: Relative risk; SMD: Standard mean differences; SUCRA: Surface under the cumulative ranking curve; SAE: Serious adverse event; TRF: Targeted-release formulation; TESTING: Therapeutic Evaluation of Steroids in IgA Nephropathy Global study; TAC: Tacrolimus.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

SSH and TWY conducted the literature retrieval, data extraction, data analyses, and manuscript writing; YL and MC assessed the risk of bias; XQY and YW designed this study, participated in the literature retrieval, data extraction, and quality assessment. All authors read and approved the final manuscript.

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Tables

Table 1: Results of the meta-analysis for clinical remission

Hydroxychloroquine						**3.25 (1.19, 8.83), N = 1**
3.32 (0.89, 12.37)	Leflunomide					0.98 (0.65, 1.46), N = 1
0.42 (0.02, 9.37)	0.13 (0.01, 2.46)	Cyclosporine				7.70 (0.45, 131.36), N = 1
0.89 (0.17, 4.74)	0.27 (0.07, 1.09)	2.10 (0.09, 48.52)	Tacrolimus			**3.67 (1.20, 11.19), N = 1**
1.59 (0.44, 5.67)	0.48 (0.20, 1.16)	3.76 (0.20, 71.46)	1.79 (0.46, 7.02)	Mycophenolate mofetil	1.25 (0.57, 2.74), N = 1	**2.25 (1.23, 4.13), N = 3, *P* = 0.65**
2.16 (0.68, 6.90)	0.65 (0.32, 1.33)	5.13 (0.28, 92.89)	2.44 (0.69, 8.62)	1.36 (0.75, 2.48)	Steroids	**1.52 (1.16, 1.98), N = 9, *P* < 0.01**
3.25 (1.05, 10.09)	0.98 (0.50, 1.90)	7.70 (0.43, 138.03)	**3.67 (1.06, 12.63)**	**2.05 (1.15, 3.65)**	**1.50 (1.17, 1.93)**	Control

The results of network meta-analysis (bottom left) and pairwise meta-analysis (upper right) for clinical remission. Estimates are shown as relative risk (95% confidence interval [CI]). The risk estimate is for the column-defining treatment compared to the row-defining treatment. Statistical significance is defined as 95% CIs that do not overlap one (bold text). N = number of studies; *P* = p-value for heterogeneity of pairwise meta-analysis. The heterogeneity in the tau value in the network analysis was low (*P* = 0.83, tau = 0.28).

Table 2: Results of meta-analysis for end-stage renal disease

TRF-budesonide				NS
5.61 (0.03, 1061.66)	Leflunomide			0.09 (0.01, 1.62), N = 1
0.59 (0.01, 45.96)	0.11 (0.00, 3.36)	Mycophenolate mofetil		0.96 (0.16, 5.72), N=3, *P* = 0.05
1.47 (0.02, 106.16)	0.26 (0.01, 7.61)	2.50 (0.46, 13.67)	Steroids	**0.37 (0.18, 0.79), N = 5, *P* = 0.51**
0.51 (0.01, 32.36)	0.09 (0.00, 2.24)	0.86 (0.23, 3.25)	**0.35 (0.12, 0.98)**	Control

The results of network meta-analysis (bottom left) and pairwise meta-analysis (upper right) for clinical remission. Estimates are shown as relative risk (95% confidence interval [CI]). The risk estimate is for the column-defining treatment compared to the row-defining treatment. Statistical significance is defined as 95% CIs that do not overlap one (bold text). N = number of studies; *P* = p-value for heterogeneity of pairwise meta-analysis. NS: the event in both groups were zero.

Table 3: Results of meta-analysis for serious adverse events

TRF-udesonide							1.33 (0.37, 4.81), N = 1
1.33 (0.02, 80.00)	Hydroxychloroquine						NS
0.96 (0.20, 4.68)	0.72 (0.01, 39.14)	Leflunomide					1.42 (0.54, 3.74), N = 3, *P* = 0.68
1.21 (0.02, 68.51)	0.91 (0.00, 212.53)	1.27 (0.02, 65.07)	Cyclosporine				NS
0.44 (0.01, 13.25)	0.33 (0.00, 49.45)	0.46 (0.02, 12.35)	0.37 (0.00, 51.81)	Tacrolimus			3.00 (0.13, 69.51), N = 1
1.62 (0.22, 11.81)	1.22 (0.02, 78.95)	1.70 (0.29, 10.08)	1.34 (0.02, 81.90)	3.65 (0.11, 119.54)	Mycophenolate mofetil	NS	0.54 (0.07, 4.18), N = 4, *P* = 0.44
0.46 (0.10, 2.03)	0.35 (0.01, 18.10)	0.48 (0.14, 1.60)	0.38 (0.01, 18.72)	1.04 (0.04, 26.20)	0.28 (0.06, 1.46)	Steroids	**4.27 (1.79, 10.18)** N = 10, *P* = 0.87
1.33 (0.37, 4.81)	1.00 (0.02, 48.82)	1.39 (0.55, 3.56)	1.10 (0.02, 50.43)	3.00 (0.13, 69.52)	0.82 (0.18, 3.75)	**2.90 (1.37, 6.13)**	Control

The results of network meta-analysis (bottom left) and pairwise meta-analysis (upper right) for clinical remission. Estimates are shown as relative risk (95% confidence interval [CI]). The risk estimate is for the column-defining treatment compared to the row-defining treatment. Statistical significance is defined as 95% CIs that do not overlap one (bold text). N = number of studies; *P* = p-value for heterogeneity of pairwise meta-analysis. The heterogeneity in the tau value in the network analysis was low (*P* = 0.48, tau = 0.01). NS: the event in both groups were zero.

Table 4: SUCRA between steroids, mycophenolate mofetil, and control

	Clinical remission	ESRD	Adverse events
Steroids	57.9 (15.8%)	91.4 (84.5%)	3.7 (0.1%)
Mycophenolate mofetil	91.7 (84.2%)	36.5 (14.7%)	76.2 (59.5%)
Control	0.4 (0.0%)	22.0 (0.8%)	70.1 (40.4%)

Data are shown as percentage surface under the cumulative ranking curve (possibility to be the best treatment); SUCRA = surface under the cumulative ranking curve.

Figures

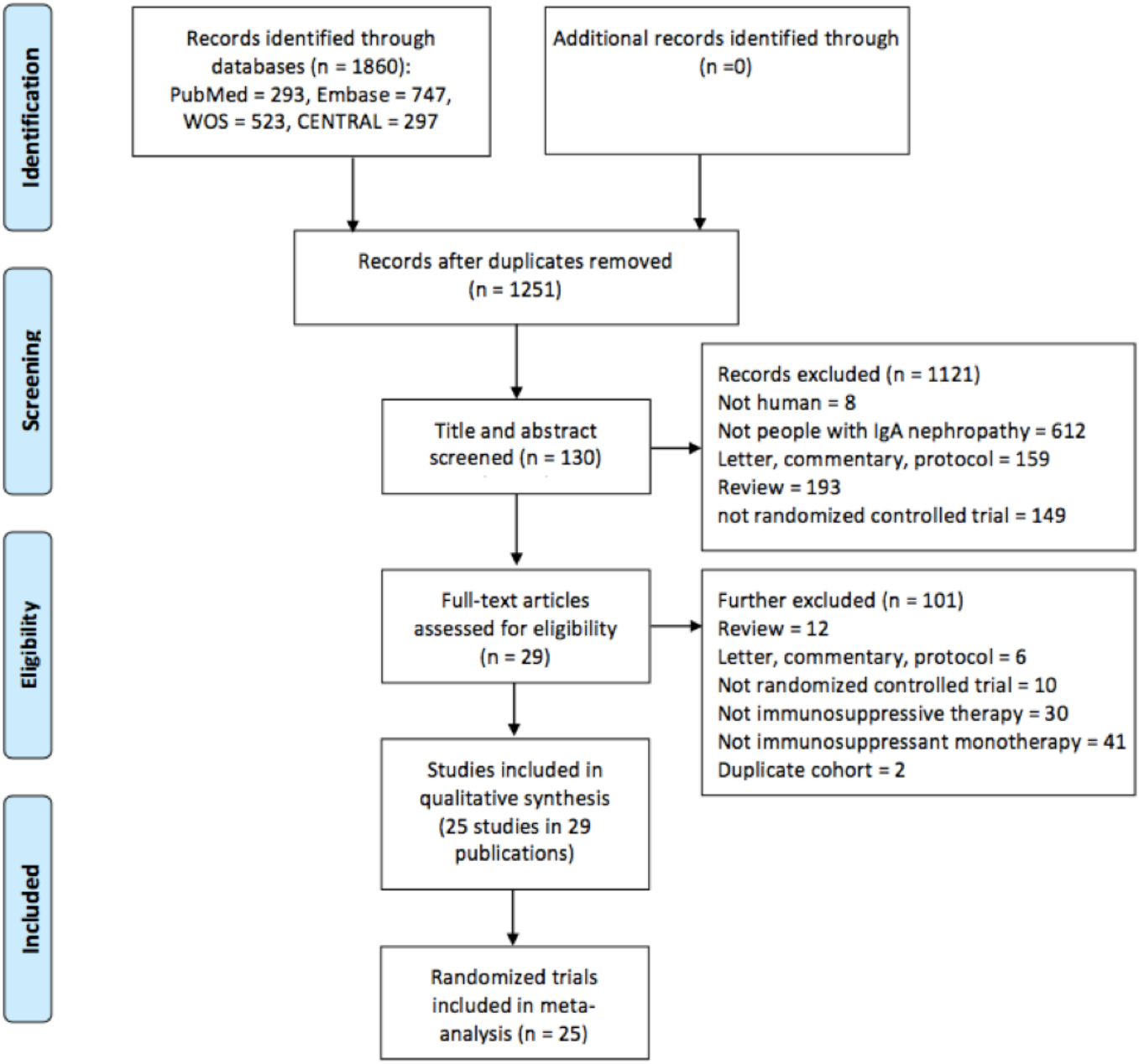

Figure 1

Flow chart of the study selection

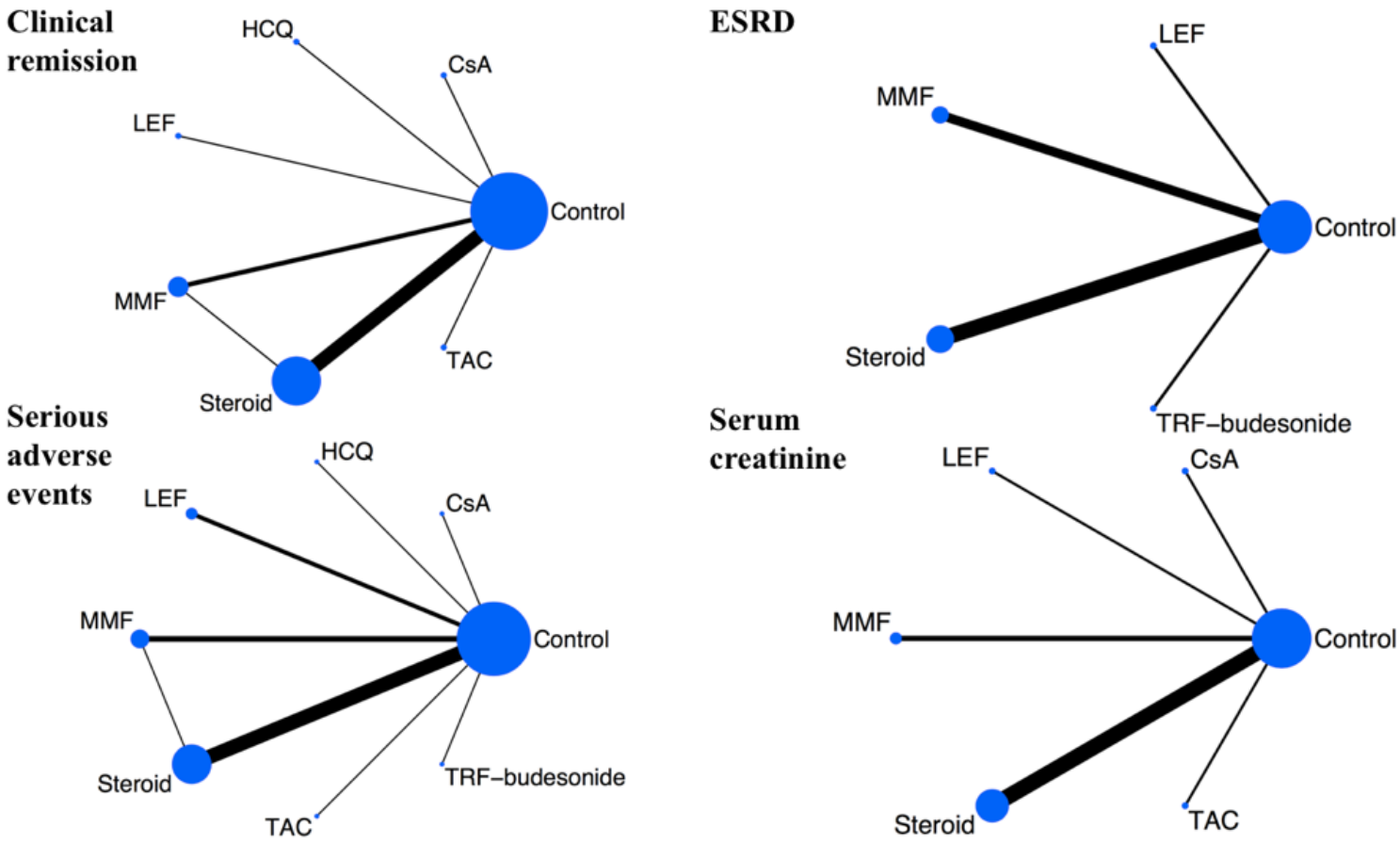

Figure 2

Network graphs for the predefined outcome (CsA: Cyclosporine; ESRD: End-stage renal disease; HCQ: Hydroxychloroquine; LEF: Leflunomide; MMF: Mycophenolate mofetil; TRF: Targeted-release formulation; TAC: Tacrolimus. The comparisons were connected by a straight line, of which the thickness and the size of nodes correspond to the number of trials and the sample size of treatments, respectively)

Figure 3

Risk of bias assessment for included studies

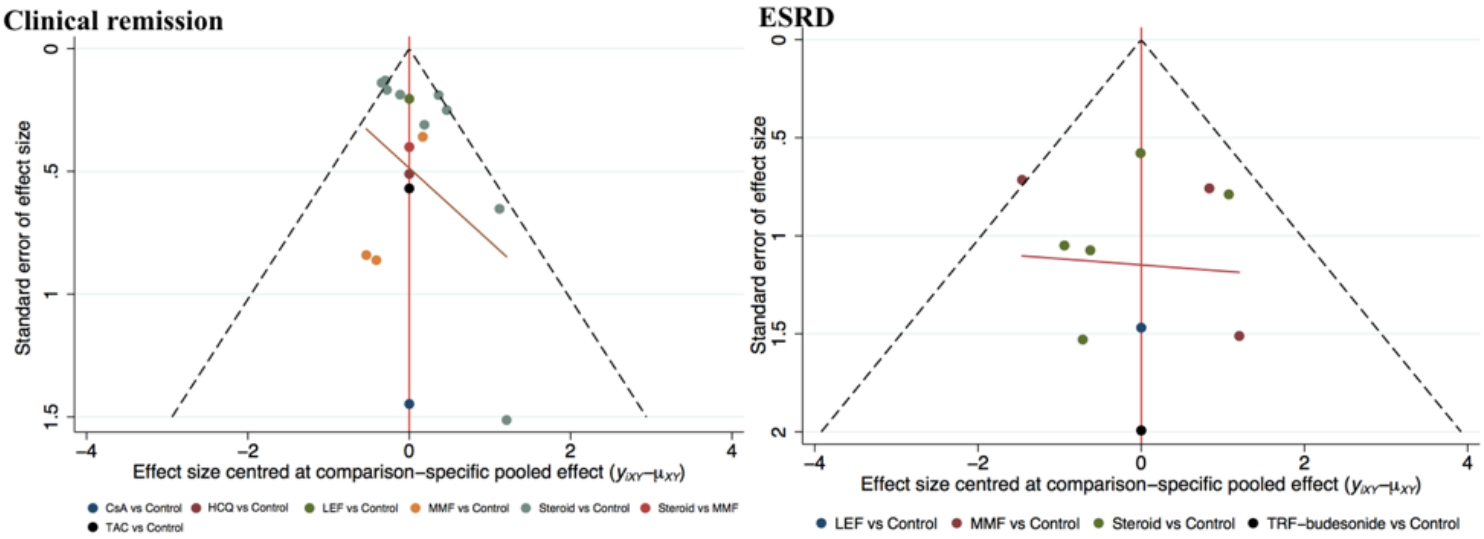

Figure 4

Comparison-adjusted funnel plots for clinical remission and end-stage renal disease (CsA: Cyclosporine; ESRD: End-stage renal disease; HCQ: Hydroxychloroquine; LEF: Leflunomide; MMF: Mycophenolate mofetil; TRF: Targeted-release formulation; TAC: Tacrolimus)

Supplementary Files

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