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Comparative efficacy of 13 immunosuppressive agents for idiopathic membranous nephropathy in adults with nephrotic syndrome: a systematic review and network meta-analysis

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ABSTRACT

Objectives This study aimed to compare the effectiveness of 13 types of immunosuppressive agents used to treat idiopathic membranous nephropathy (IMN) in adults with nephrotic syndrome.

Design Systematic review and network meta-analysis.

Data sources PubMed, EMbase, Cochrane Library, Web of Science, Clinical trials, SinoMed, Chinese Biomedicine, CNKI, WanFang and Chongqing VIP Information databases were comprehensively searched until February 2018.

Eligibility criteria Randomised clinical trials (RCTs) comparing the effects of different immunosuppressive treatments in adult patients with IMN and nephrotic syndrome were included, and all included RCTs had a study-duration of at least 6 months.

Data extraction and synthesis Two reviewers independently screened articles, extracted data and assessed study quality. Standard pairwise meta-analysis was performed using DerSimonian-Laird random-effects model.

Results This study ultimately included 48 RCTs with 2736 patients and 13 immunosuppressive agents. The network meta-analysis results showed that most regimens, except for leflunomide (LEF), mizoribine (MZB) and steroids (STE), showed significantly higher probabilities of total remission (TR) when compared with non-immunosuppressive therapies (the control group),with risk ratios (RRs) of 2.71 (95% CI) 1.81 to 4.06)for tacrolimus+tripterygium wilfordii (TAC+TW), 2.16 (1.27 to 3.69) foradrenocorticotropic hormone, 2.02 (1.64 to 2.49) for TAC, 2.03 (1.13 to3.64) for azathioprine (AZA), 1.91 (1.46 to 2.50) for cyclosporine (CsA), 1.86 (1.44 to2.42) for mycophenolate mofetil (MMF), 1.85 (1.52 to 2.25) for cyclophosphamide (CTX),1.81 (1.10 to 2.98) for rituximab (RIT), 1.80 (1.38 to 2.33) for TW, 1.72 (1.35 to 2.19) for chlorambucil. As for 24 hours UTP, the direct andindirect comparisons showed that AZA (standard mean difference (SMD), −1.02(95% CI −1.90 to −0.15)), CsA (SMD, −0.70 (95% CI −1.33 to −0.08)),CTX (SMD, −1.01 (95% CI −1.44 to -0.58)), MMF (SMD, −0.98 (95% CI −1.64 to −0.32)), MZB (SMD, −0.97 (95% CI −1.90 to−0.04]), TAC (SMD, −1.16 (95% CI −1.72 to −0.60)) and TAC+TW(SMD, −2.03 (95% CI −2.94 to −1.12)) could significantly superior thancontrol, except for chlorambucil, LEF, RIT and STE. Thechanges of serum creatinine (Scr) was not significantly different between eachtreatments of immunosuppressive agents and the control, except for STE whichhas the possibility of increasing Scr (SMD, 1.00 (95% CI 0.36 to 1.64)). Comparisons among all treatments of immunosuppressive agents showed nostatistical significance in the outcome of relapse. A drenocorticotropichormone (85.1%) showed the lowest probability of relapse under the cumulativeranking curve values among all immunosuppressants. Infection,gastrointestinal symptoms, and bone marrow suppression were the common adverseevents associated with most of the immunosuppressive therapies.

Conclusions This study demonstrates that TAC+TW, TAC and CTX are superior to other immunosuppressive agents in terms of TR and 24 hours UTP. Moreover, they are all at risk of infection, gastrointestinal symptoms,

Strengths and limitations of this study

- ► This review integrates direct evidence with indirect evidence from 13 immunosuppressive agents for idiopathic membranous nephropathy in adults with nephrotic syndrome to estimate the interrelations across all treatments, which aims to make trustworthy recommendations regarding new research that might change clinical practice.
- ► We used subgroup analysis, sensitivity analysis and meta regression to evaluate the sources of heterogeneity or stability of the results. We used the Grading of Recommendations Assessment, Development, and Evaluation approach to assess the quality of evidence of estimates derived from pairwise and network meta-analysis.
- ► This systematic review just provides data about the frequency of the most common adverse effects and lacking statistical comparison based on large amounts of data.

and myelosuppression. Furthermore, TAC could increase the risk of glucose intolerance or new-onset diabetes mellitus. Conversely, STE alone, LEF and MZB seem to have little advantage in clinical treatment of IMN.

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INTRODUCTION

Idiopathic membranous nephropathy (IMN) remains one of the most common causes of nephrotic syndrome in adults.[1] Since the clinical features and prognosis of IMN are variable, the disease has a high rate of spontaneous remission. Spontaneous complete remission (CR) of proteinuria is observed after a variable period of time (4–120 months) in approximately 30%–40% of adult patients.[2 3] Despite this, 30%–40% of patients progress toward end-stage renal failure within 5–15 years.[4]

The treatment of IMN mainly includes conservative treatment and immunosuppressive therapy. Supportive therapy with angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, a diet low in salt and protein, and statins are initiated in all patients for 6 months.[5] Immunosuppression can induce disease remission and reduce the risk of progression to end-stage renal disease or death.[6 7] Given the slowly progressive natural course and substantial spontaneous remission rate of this disorder, immunosuppressive agents are recommended for patients who develop complications of nephrotic syndrome or for those at high risk of disease progression.[8] Immunosuppressive therapy was already used more than 30 years ago to treat nephrotic syndrome in membranous nephropathy.[9] Since then, many different immunosuppressive regimens have been proposed. Still, the use of immunosuppressive therapy is heavily debated.[10] In addition, there is a paucity of well-controlled, RCTs, and as a consequence hard evidence to support treatment protocols is lacking.[10] Most previous pairwise meta-analyses[11 12] only provided direct comparisons, lacking proper indirect comparisons to enhance the adequacy of results. Additionally, the numbers of corresponding studies related to mycophenolate mofetil (MMF), adrenocorticotropic hormone (ACTH), azathioprine (AZA), mizoribine (MZB) and *Tripterygiumwilfordii* are still very limited to draw reliable conclusions, and more evidence is needed through indirect comparisons.

Network meta-analyses, a novel evidence integration technique, in contrast to the traditional pairwise meta-analysis, can assess the relative efficacy of multiple treatment comparisons including both direct and indirect comparisons simultaneously. This may enhance precision of the estimated effect size.[13] Therefore, a comprehensive systematic review and network meta-analysis for drawing more reliable conclusions to estimate the efficacy of different immunosuppressive agents that were used to treat IMN in adults with nephrotic syndrome was conducted.

METHODS

The study protocol is available on the International Prospective Register of Systematic Review [14](online supplement 1) and was prepared according to the guidelines of the Cochrane Multiple Interventions Methods Group.[15]

Patient and public involvement

Patients were not involved.

Data sources and searches

We comprehensively searched PubMed, EMbase, Cochrane Library, Web of Science, clinicaltrials.gov, SinoMed, Chinese Biomedicine, China National Knowledge Infrastructure, WanFang and Chongqing VIP Information databases from inception until 1 February 2018 for RCTs investigating any immunosuppressive agents treatment for IMN in adults with nephrotic syndrome. Additional studies were searched in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews. (The details of the search strategy that included electronic databases and key terms are presented in eTable 1 of online supplement 2.)

Study selection

RCTs comparing the effects of different immunosuppressive treatments in adult patients with IMN and nephrotic syndrome were included, and all included RCTs had a study-duration of at least 6 months. All included patients were diagnosed as having IMN by renal puncture. Diagnosis of nephrotic syndrome was defined by the authors in each single study. In the absence of an explicit definition of nephrotic syndrome, the cut-off value of proteinuria above 3.5 g/24 hours was used. The primary outcomes were total remission (TR, defined as either CR or partial remission (PR)) and 24 hours urine total protein (24 hours UTP). CR was defined as urinary protein excretion <0.3 g/day (urine protein: creatinine ratio (uPCR)<300 mg/g or <30 mg/mmol), confirmed by two values at least 1 week apart, accompanied by a normal serum albumin concentration and a normal serum creatinine (Scr). PR was defined as urinary protein excretion <3.5 g/day (uPCR <3500 mg/g or <350 mg/mmol) and a 50% or greater reduction from peak values, confirmed by two values at least 1 week apart, accompanied by an improvement or normalisation of the serum albumin concentration and stable Scr.[8] The secondary outcomes included Scr, relapse and adverse events.

Secondary forms of membranous nephropathy were excluded. Moreover, studies where it was impossible to identify how many adult patients with IMN had nephrotic syndrome were also excluded, unless it was assessed that this information could be inferred by baseline characteristics. Further, the studies that used immunosuppressive agents combined with Chinese herbal compound (except for single Chinese herb or herbal extracts with definite immunosuppressive effect) were also excluded.

Data extraction and quality assessment

Two reviewers (XZ and QZ) independently extracted data from original trial reports using a standardised form. Data extracted included study characteristics (first author, publication year, single or multi-centre, sample size, intervention and control, period of treatment, and duration of follow-up), characteristics of patients (inclusion criteria, background treatments, mean age, proportion of men, baseline of 24 hours UTP and baseline of Scr), reported outcomes (TR, 24 hours UTP, Scr, relapse and adverse events), and information on methodology. If multiple reports from the same population were retrieved, only the most complete and/or most recently reported data were used. Risk of bias was assessed using the Cochrane Collaboration's tool addressing six domains: sequence generation, allocation concealment, blinding of participants/outcome assessors, incomplete outcome, selective outcome reporting and other source of bias. Two investigators independently completed the assessments; discrepancies were discussed with a third party and resolved by consensus. Additionally, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to assess the quality of evidence contributing to each network estimate, which characterises the quality of a body of evidence on the basis of the study limitations, imprecision, inconsistency, indirectness and publication bias for the primary outcomes.[16]

Data analysis

Methods for direct treatment comparisons

Standard pairwise meta-analysis was performed using DerSimonian-Laird random-effects model. Risk ratio (RR) and standard mean difference (SMD) with 95% CI of the outcomes were calculated as effect measure. The I^2-statistic was calculated for heterogeneity, as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity.

Methods for indirect and mixed comparisons

A random-effects network meta-analysis within a frequentist framework[17] was then performed. RR and SMD for outcomes with 95% CI were summarised. The ranking probabilities for all treatments of being at each possible rank for each intervention were estimated. The treatment hierarchy was summarised and reported as surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA is a percentage interpreted as the probability of a treatment that is the most effective without uncertainty on the outcome, which is equal to one when the treatment is certain to be the best and 0 when it is certain to be the worst.[18] To check the assumption of consistency in the entire analytical network, a design-by-treatment approach was used.[19] A loop-specific approach was used to evaluate the presence of inconsistency locally in each closed loop.[19] The node-splitting method and heatmap were used to assess the inconsistency of the model with separating evidence on a particular comparison into direct and indirect evidence. A global heterogeneity was assessed with I^2-statistic, and predictive interval plot[20] that incorporates the extent of heterogeneity was used to evaluate the extent of uncertainty in the estimated effect size locally. Uncertainty affected by heterogeneity was defined as disagreement between the CIs of relative treatment effects and their predictive intervals. The transitivity assumption underlying network meta-analysis was evaluated by comparing the distribution of clinical variables that could act as effect modifiers across treatment comparisons. Contribution plot was used to assess the contribution of each direct comparison to the estimation of each network meta-analytic summary effect, since it was helpful to evaluate the overall quality of evidence from network meta-analysis.[20] Additionally, a comparison-adjusted funnel plot was used to detect the potential publication bias in the results between small and large studies. To assess whether the results were impacted by study characteristics (effect modifiers), subgroup analysis was conducted according to study duration (<12 months, 12–24 months, or ≥24 months), recruitment of participants (Asian or non-Asian) and centre (single-centre or multi-centre). Univariate and multivariate meta-regression was further conducted to control the confounding factors. In addition, sensitivity analysis of network meta-analysis was conducted to validate the robustness of the results by omitting intermediate time point data. All analyses were conducted using R V.3.5.0 (network meta-analysis, assessment of global heterogeneity) and STATA V.13.0 (pairwise meta-analysis, estimation of inconsistency, transitivity and local heterogeneity, and SUCRA graphs, funnel plot).

RESULTS

Study characteristics

A total of 1829 citations were retrieved based on electronic searches, and 12 additional studies were retrieved after checking the references of relevant reviews and guidelines. Ultimately, 48 studies[21–68] including 2736 adults were available for network meta-analysis. These trials evaluated 13 different immunosuppressive treatment regimens, including ACTH, AZA, chlorambucil (CH), cyclophosphamide (CTX), cyclosporine (CsA), leflunomide (LEF), MMF, MZB, rituximab (RIT), steroids (STE), tacrolimus (TAC), tacrolimus+tripterygiumwilfordii (TAC+TW) and TW for patients with IMN. Figure 1 shows the screening process. eTable 2 in online supplement 2 shows the main characteristics of included trials. The mean age of the included 2657 participants was 45.2 years. Moreover, the mean baseline 24 hours UTP was 7.53 (SD, 1.98), and Scr level was 96.83 (SD, 38.82). The median study duration was 18 months (range: 6–360 months).

Quality of included studies

Most studies were judged to be at a low or unclear risk of bias for sequence generation, allocation concealment, incomplete outcome data and selective reporting. Because no information was provided, most studies were judged to

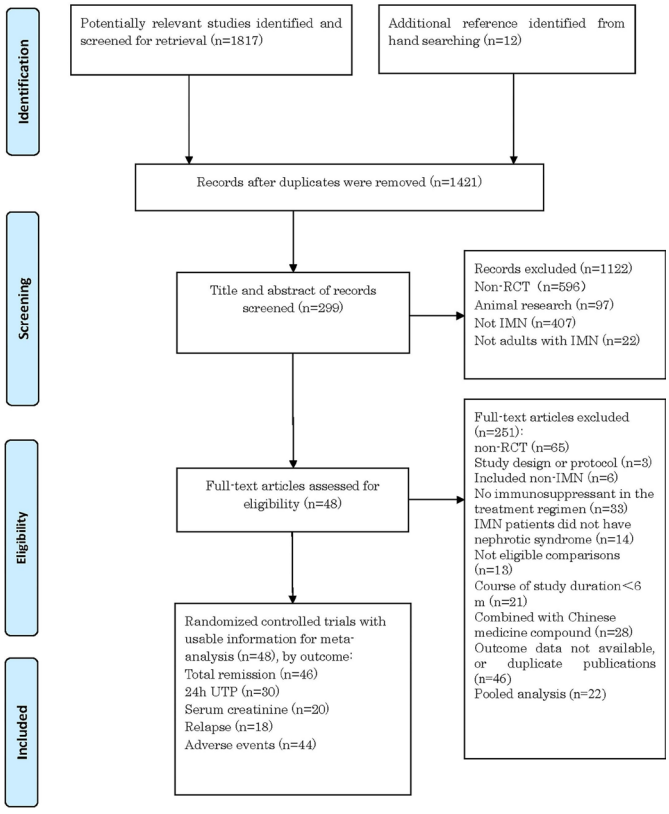

Figure 1 Flow chart of literature search and selection. IMN, idiopathic membranous nephropathy; RCT, randomised clinical trial.

be at high risk of bias for blinding of participants and staff and for blinding of outcome assessment, however, these could not be done. The open random location schedules were used in open-label trials and were judged as high risk in the allocation concealment and blinding. The outcome measures in these open-label trials were objective parameters, so they are not self-reported and blinded

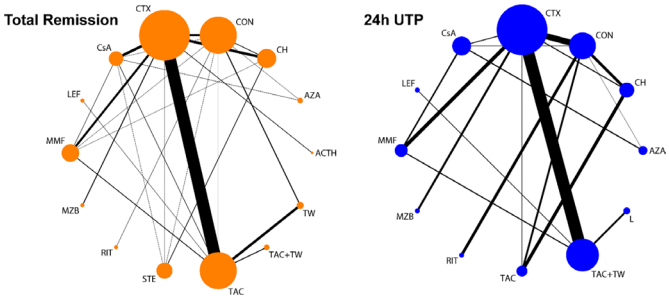

Figure 2 Network meta-analysis of eligible comparisons for total remission and 24 hours UTP. The width of the lines represents the number of each pairwise comparison. The size of each node is proportional to the number of randomly assigned participants (ie, sample size). ACTH, adrenocorticotropic hormone; AZA, azathioprine; CH, chlorambucil; CON, non-immunosuppressive therapies (the control group); CsA, cyclosporine; CTX, cyclophosphamide; LEF, leflunomide; MMF, mycophenolate mofetil; MZB, mizoribine; RIT, rituximab; STE, steroids; TAC+TW, tacrolimus+tripterygium wilfordii.

or not would not influence the results. Therefore, open-label RCTs were included in the present study. Risk of bias assessment of included trials was shown in eTable 3 of online supplement 2.

Heterogeneity analysis and evaluation of inconsistency

In the heterogeneity analysis, the global I^2 value were 46.6% (TR, eFigure 1 in online supplement 3), 71.7% (24 hours UTP, eFigure 2 in online supplement 3), 33.1% (relapse rate, eFigure 3 in online supplement 3) and 55.9% (Scr, eFigure 4 in online supplement 3), respectively. Predictive intervals indicated that no comparisons had estimated heterogeneity in TR, relapse rate and Scr, however, there were several comparisons with heterogeneity for 24 hours UTP (see eFigures 5–8 in online supplement 3). Evaluation of the local inconsistency of all outcomes showed that most loops were consistent according to the CI (eFigrues 9–12 in online supplement 3). Evaluation of the inconsistency by node-splitting model showed no significant difference in 24 hours UTP and relapse rate between direct and indirect model, and only two comparisons and four comparisons have significant difference in TR and Scr, respectively (eTables 1–4 in online supplement 3).

Results of pairwise meta-analysis

The effects of 13 immunosuppressive agents for IMN in adults with nephrotic syndrome from pairwise meta-analysis were shown in eTables 1–4 of online supplement 4.

Results of network meta-analysis

Primary outcomes

Total remission

TR (complete or PR) was reported in 2581 of the 2736 patients from a total of 45 studies.[19–34 36–48 50–65] There were 13 immunosuppressive agents, including ACTH (1 trial, 16 patients), AZA (2, 18), CH (9, 268), CTX (21, 665), CsA (8, 167), LEF (2, 25), MMF (7, 139), MZB (1, 30), RIT (1, 37), STE (6, 179), TAC (15, 412), TAC+TW (2, 35) and TW (2, 93). Network geometry was displayed in figure 2 and eFigure 1 in online supplement 4.

Compared with non-immunosuppressive therapies (the control group), all the drugs, except for LEF, MZB and STE, were associated with significantly higher probabilities of TR (figure 3), with RRs of 2.71 (95% CI 1.81 to 4.06) for TAC+TW; 2.17 (1.26 to 3.72), ACTH; 2.02 (1.63 to 2.49), TAC; 2.08 (1.15 to 3.76), AZA; 1.96 (1.47 to 2.61), CsA; 1.87 (1.44 to 2.43), MMF; 1.86 (1.52 to 2.26), CTX; 1.81 (1.10 to 2.99), RIT; 1.79 (1.37 to 2.34), TW; and 1.73 (1.35 to 2.20), CH (see figures 3 and 4 ; eFigures 2 and 3 in online supplement 4).

Table 1 shows evidence that the SUCRA for the 13 treatments was 93.9%, 73.5%, 72.7%, 68.9%, 65.3%, 58.2%, 56.5%, 56.0%, 52.4%, 46.2%, 21.0%, 20.8% and 9.0% for TAC+TW, ACTH, TAC, AZA, CsA, MMF, RIT, CTX, TW, CH, MZB, LEF and STE, respectively. Further details of the analyses on the TR are presented in eFigure 4 and eTable 5 in online supplement 4.

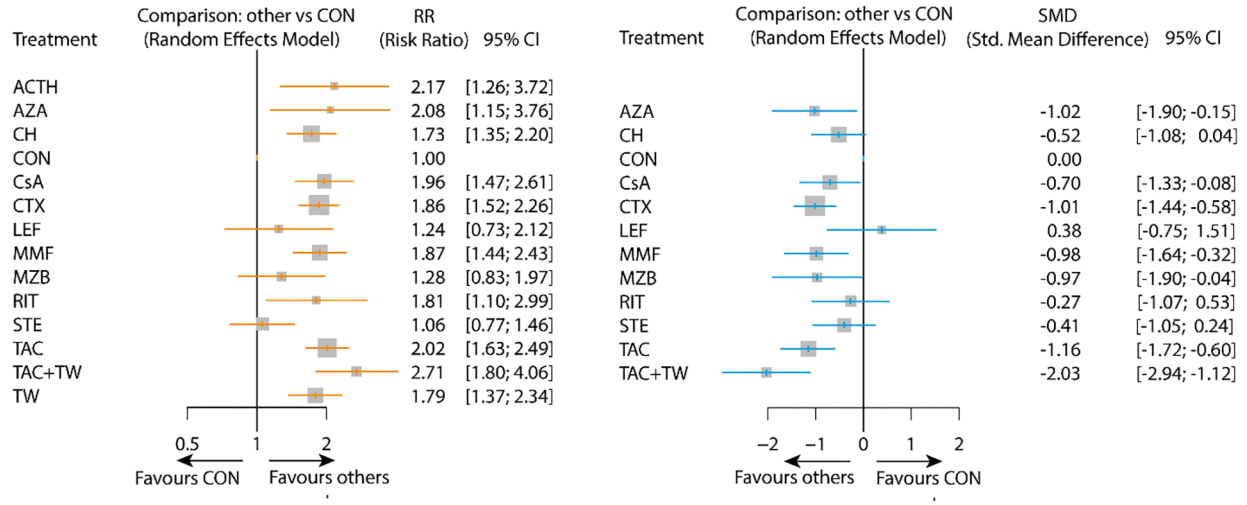

Figure 3 Result of network meta-analysis for total remission and 24 hours UTP. ACTH, adrenocorticotropic hormone; AZA, azathioprine; CH, chlorambucil; CON, non-immunosuppressive therapies (the control group); CsA, cyclosporine; CTX, cyclophosphamide; LEF, leflunomide; MMF, mycophenolate mofetil; MZB, mizoribine; RIT, rituximab; STE, steroids; TAC+TW, tacrolimus+tripterygium wilfordii.

Total Remission[RR] | **Treatments** | **24h UTP [SMD]**

ACTH	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
1.04 [0.49; 2.23]¶	**AZA**	-0.50 [-1.50; 0.49]¶	-1.02 [-1.90; -0.15]†	-0.32 [-1.03; 0.39]¶	-0.01 [-0.88; 0.86]†	**-1.41 [-2.76; -0.05]¶**	-0.04 [-0.96; 0.88]¶	-0.05 [-1.26; 1.15]¶	-0.75 [-1.94; 0.43]¶	-0.62 [-1.67; 0.43]¶	0.13 [-0.81; 1.07]¶	1.01 [-0.18; 2.19]¶	NR
1.26 [0.72; 2.19]¶	1.21 [0.66; 2.22]¶	**CH**	-0.52 [-1.08; 0.04]†	0.18 [-0.59; 0.96]†	0.49 [-0.09; 1.07]¶	-0.90 [-2.10; 0.29]¶	0.46 [-0.32; 1.24]¶	0.45 [-0.56; 1.46]¶	-0.25 [-1.23; 0.73]¶	-0.11 [-0.69; 0.46]†	0.64 [-0.05; 1.32]¶	**1.51 [0.52; 2.50]†**	NR
2.17 [1.26; 3.72]¶	**2.08 [1.15; 3.76]¶**	**1.73 [1.35; 2.20]¶**	**CON**	**0.70 [0.08; 1.33]¶**	**1.01 [0.58; 1.44]¶**	-0.38 [-1.51; 0.75]¶	**0.98 [0.32; 1.64]¶**	**0.97 [0.04; 1.90]¶**	0.27 [-0.53; 1.07]†	0.41 [-0.24; 1.05]†	**1.16 [0.60; 1.72]†**	**2.03 [1.12; 2.94]¶**	NR
1.10 [0.63; 1.93]‡	1.06 [0.63; 1.79]¶	0.88 [0.64; 1.21]†	**0.51 [0.38; 0.68]¶**	**CsA**	0.31 [-0.28; 0.90]¶	-1.08 [-2.28; 0.11]†	0.28 [-0.36; 0.92]¶	0.27 [-0.75; 1.28]¶	-0.43 [-1.45; 0.58]†	-0.30 [-1.14; 0.55]†	0.45 [-0.23; 1.14]¶	**1.33 [0.34; 2.32]†**	NR
1.17 [0.71; 1.93]¶	1.12 [0.63; 1.99]†	0.93 [0.73; 1.18]¶	**0.54 [0.44; 0.66]†**	1.06 [0.83; 1.34]¶	**CTX**	**-1.39 [-2.44; -0.35]¶**	-0.03 [-0.58; 0.52]¶	-0.04 [-0.87; 0.78]¶	-0.74 [-1.65; 0.17]†	-0.61 [-1.27; 0.06]¶	0.14 [-0.22; 0.50]¶	**1.02 [0.21; 1.82]¶**	NR
1.74 [0.85; 3.56]¶	1.67 [0.78; 3.58]¶	1.39 [0.80; 2.42]¶	0.80 [0.47; 1.38]¶	1.58 [0.91; 2.74]¶	1.49 [0.90; 2.48]¶	**LEF**	**1.36 [0.20; 2.53]¶**	**1.35 [0.02; 2.68]¶**	0.65 [-0.73; 2.04]¶	0.79 [-0.45; 2.03]¶	**1.54 [0.56; 2.52]¶**	**2.41 [1.19; 3.63]†**	NR
1.16 [0.67; 1.99]†	1.11 [0.61; 2.01]¶	0.92 [0.69; 1.23]†	**0.53 [0.41; 0.70]¶**	1.05 [0.79; 1.39]¶	0.99 [0.81; 1.21]†	0.66 [0.39; 1.14]¶	**MMF**	-0.01 [-1.00; 0.98]¶	-0.71 [-1.75; 0.33]¶	-0.58 [-1.42; 0.27]¶	0.17 [-0.45; 0.80]¶	**1.05 [0.09; 2.00]¶**	NR
1.69 [0.90; 3.18]¶	1.63 [0.82; 3.24]¶	1.35 [0.86; 2.11]¶	0.78 [0.51; 1.20]¶	1.53 [0.98; 2.40]†	1.45 [0.99; 2.12]¶	0.97 [0.51; 1.83]¶	1.46 [0.95; 2.25]¶	**MZB**	-0.70 [-1.93; 0.53]¶	-0.56 [-1.62; 0.50]¶	0.19 [-0.71; 1.09]¶	1.06 [-0.09; 2.21]¶	NR
1.19 [0.57; 2.50]¶	1.15 [0.53; 2.50]¶	0.95 [0.55; 1.66]¶	**0.55 [0.33; 0.91]‡**	1.08 [0.61; 1.93]¶	1.02 [0.60; 1.76]¶	0.69 [0.33; 1.43]¶	1.03 [0.59; 1.82]¶	0.71 [0.36; 1.37]¶	**RIT**	0.14 [-0.89; 1.17]¶	0.88 [-0.09; 1.86]¶	**1.76 [0.55; 2.97]¶**	NR
2.05 [1.13; 3.72]¶	**1.97 [1.04; 3.72]¶**	**1.63 [1.21; 2.20]‡**	0.95 [0.69; 1.31]†	**1.86 [1.29; 2.67]¶**	**1.76 [1.27; 2.42]†**	1.18 [0.65; 2.14]¶	**1.77 [1.23; 2.55]¶**	1.21 [0.74; 2.00]¶	1.72 [0.95; 3.11]¶	**STE**	0.75 [-0.01; 1.51]¶	**1.62 [0.58; 2.67]¶**	NR
1.07 [0.64; 1.80]¶	1.03 [0.58; 1.84]¶	0.86 [0.66; 1.11]¶	**0.50 [0.40; 0.61]†**	0.97 [0.76; 1.25]¶	0.92 [0.81; 1.04]¶	0.62 [0.38; 1.01]¶	0.93 [0.74; 1.16]†	**0.63 [0.43; 0.95]¶**	0.90 [0.52; 1.55]¶	**0.52 [0.37; 0.73]¶**	**TAC**	**0.87 [0.15; 1.59]†**	NR
0.80 [0.43; 1.49]¶	0.77 [0.39; 1.51]¶	**0.64 [0.41; 0.98]¶**	**0.37 [0.25; 0.56]¶**	0.72 [0.47; 1.11]¶	**0.69 [0.47; 0.99]¶**	**0.46 [0.25; 0.84]¶**	0.69 [0.46; 1.05]¶	**0.47 [0.28; 0.80]¶**	0.67 [0.35; 1.28]¶	**0.39 [0.24; 0.63]¶**	0.75 [0.53; 1.06]†	**TAC+TW**	NR
1.21 [0.68; 2.13]¶	1.16 [0.62; 2.16]¶	0.96 [0.69; 1.34]¶	**0.56 [0.43; 0.73]†**	1.09 [0.78; 1.54]¶	1.04 [0.80; 1.35]¶	0.69 [0.40; 1.21]¶	1.04 [0.76; 1.44]¶	0.71 [0.45; 1.14]¶	1.01 [0.57; 1.78]¶	**0.59 [0.40; 0.87]¶**	1.13 [0.88; 1.45]†	1.51 [0.98; 2.32]¶	**TW**

Figure 4 The league table of all comparisons of total remission and 24 hours UTP. Treatments are reported in alphabetical order. Data are RRs (95% CI) for total remission and SMDs (95% CI) for 24 hours UTP in the column-defining treatment compared with the row-defining treatment. RRs higher than one favour the column-defining treatment and SMDs lower than 0 favour the row-defining treatment. Significant results are in bold and underscored. ACTH, adrenocorticotropic hormone; AZA, azathioprine; MZB, mizoribine; NR, not reported; CH, chlorambucil; CON, non-immunosuppressive therapies (the control group); CsA, cyclosporine; CTX, cyclophosphamide; LEF, leflunomide; MMF, mycophenolate mofetil; MZB, mizoribine; RR, risk ratio; RIT, rituximab; SMD, standard mean difference; STE, steroids; TAC, tacrolimus; TAC+TW, tacrolimus+tripterygium wilfordii. The certainty of the evidence (according to grade) was incorporated in this figure (online supplement 6). ‡Moderate quality of evidence. †Low quality of evidence. ¶Very low quality of evidence.

Table 1 SUCRA value of total remission and 24 hours UTP

	Total remission			24 hours UTP		
Treatments	SUCRA	PrBest	Mean rank	SUCRA	PrBest	Mean rank
ACTH	73.5	17.9	4.5	NR	NR	NR
AZA	68.9	16.3	5.0	66.8	4.1	4.7
CH	46.1	0.2	8.0	37.5	0.0	10.8
CON	5.7	0.0	13.3	10.9	0.0	7.9
CsA	65.3	1.0	5.5	46.8	0.1	6.9
CTX	56.0	0.0	6.7	68.2	0.1	4.5
LEF	20.8	0.3	11.3	7.1	0.0	11.2
MMF	58.2	0.3	6.4	65.6	1.0	4.8
MZB	21.0	0.0	11.3	63.2	3.5	5.1
RIT	56.5	7.0	6.7	26.3	0.3	9.1
STE	9.0	0.0	12.8	31.5	0.0	8.5
TAC	72.7	0.3	4.6	77.4	0.4	3.5
TAC+TW	93.9	56.4	1.8	98.7	90.6	1.1
TW	52.4	0.4	7.2	NR	NR	NR

ACTH, adrenocorticotropic hormone; AZA, azathioprine; CH, chlorambucil; CON, non-immunosuppressive therapies (the control group); CsA, cyclosporine; CTX, cyclophosphamide; LEF, leflunomide; MMF, mycophenolate mofetil; MZB, mizoribine; NR, not reported; RIT, rituximab; STE, steroids; SUCRA, surface under the cumulative ranking curve; TAC, tacrolimus; TAC +TW, tacrolimus combined Tripterygiumwilfordii; TW, Tripterygiumwilfordii.

24 hours UTP

For the 24 hours UTP, 30 RCTs[21 23 24 26–29 31 32 34 37–39 42 43 45 47 48 51 52 56–60 63–67] with 1682 patients were included in the network meta-analysis. There were 11 immunosuppressive agents, including AZA (2 trials, 18 patients), CH (4, 112), CTX (16, 487), CsA (6, 78), LEF (2, 25), MMF (3, 85), MZB (1, 30), RIT (1, 37), STE (4, 122), TAC (10, 257) and TAC+TW (2, 35). Network geometry was displayed in figure 2 and eFigure 5 in online supplement 4.

Network meta-analysis of drugs through direct and indirect comparisons showed that AZA (SMD, −1.02 (95% CI −1.90 to −0.15)), CsA (SMD, −0.70 (95% CI −1.33 to −0.08)), CTX (SMD, −1.01 (95% CI −1.44 to −0.58)), MMF (SMD, −0.98 (95% CI −1.64 to −0.32)), MZB (SMD, −0.97 (95% CI −1.90 to −0.04)), TAC (SMD, −1.16 (95% CI −1.72 to −0.60)) and TAC+TW (SMD, −2.03 (95% CI −2.94 to −1.12)) could significantly reduce in 24 hours UTP compared with control, except for CH (SMD, −0.52 (95% CI −1.08 to 0.04)), LEF (SMD, 0.38 [(95% CI −0.75 to 1.51)), RIT (SMD, −0.27 (95% CI −1.07 to 0.53)) and STE (SMD, −0.41 (95% CI −1.05 to 0.24)) (figures 3 and 4; eFigures 6 and 7 in online supplement 4).

In terms of 24 hours UTP, TAC+TW had the highest SUCRA value (98.7%), followed by TAC (77.4%), CTX (68.2%), AZA (66.8%), MMF (65.6%), MZB (63.2%), CsA (46.8%), CH (37.5%), STE (31.5%) and RIT (26.3%), while LEF (7.1%) had the lowest SUCRA value (table 1; eTables 6 and 8 in online supplement 4).

Secondary outcomes

Relapse rate

For the outcome of total relapse, 18 RCTs with 1117 patients were included in the network meta-analysis. No significant difference was observed between each comparison in terms of 10 immunosuppressive agents in the network meta-analysis when compared with the control (eFigures 9–11 in online supplement 4). eTable 7 and eFigure 12 in online supplement 4 show the rank probabilities of all treatments calculated using the SUCRA.

Serum creatinine

For the outcome of Scr, 20 RCTs with 966 patients were included in the network meta-analysis. Except for STE (SMD, 1.00 (95% CI 0.36 to 1.64)), no significant difference was observed between each comparison in terms of the 10 immunosuppressive agents in the network meta-analysis when compared with the control (eFigures 13–15 in online supplement 4). eTable 8 and eFigure 16 in online supplement 4 show the ranking of treatments using the SUCRA.

Adverse events

The occurrence of adverse reactions according to immunosuppressive agents for IMN is listed in eTable 9 in online supplement 4. Infection was the most common adverse event associated with most of the immunosuppressive therapies. Moreover, gastrointestinal symptoms are also common side effects during immunosuppressive therapy. The three immunosuppressive agents associated with higher frequency of bone marrow suppression were

AZA (38.5%), CH (20.1%) and LEF (8.0%). In contrast, the incidence of the above common side effects was very low when using TAC+TW or RIT for IMN. In addition, it should be noticed that tacrolimus was related to the highest incidence rate of diabetes mellitus (4.7%) or glucose intolerance (11.7%).

Small-study effects analysis

The comparison-adjusted funnel plots against non-immunosuppressive therapies (the control group) suggest that there might be small-study effects for 'TR' '24 hours UTP' 'relapse rate' and 'Scr' (see eFigures 17–20 in online supplement 4).

Subgroup analysis, meta-regression and sensitivity analysis

Subgroup analysis by the different study duration (<12 months, 12–24 months and ≥24 months) in the literatures suggested that the effects of TAC+TW, TAC and CTX were significantly better than those of the controls regardless of the study duration. However, the effects of TW, RIT and MMF were comparable with the control when the study duration was <12 months; meanwhile, the effects of AZA and CsA had no significant difference with the control when the study duration was >24 months. Therefore, the different study durations may partially explain heterogeneity (see eTable 1 in online supplement 5).

In network meta-regression with covariates, study duration, location of participants and centre of studies were adjusted for primary outcome of TR. However, after adjusting location of participants, no significant difference was observed between MZB, which was used in Asian patients with IMN, and the control. Moreover, adjusting for centre of studies diminished the differences between CTX and control for TR in single-centre group, as well as TW (eTables 2 and 3 in online supplement 5).

The data that were not at the end of the follow-up were excluded for sensitivity analyses. The results showed that TR of AZA was insignificant when compared with the control, while the TR of other drugs did not change substantially. As for 24 hours UTP, AZA, CsA, MMF and MZB were inferior to before, that is, these drugs had no significant difference in reducing 24 hours UTP in sensitivity analyses when compared with the control (see eTables 4–7 in online supplement 5).

GRADE judgments (quality of evidence)

We incorporated the GRADE judgments in figure 4. It was low or very low for most of the comparisons. GRADE framework showed that the ranking of treatment was both very low for TR and 24 hours UTP (online supplement 6).

DISCUSSION

The present network meta-analysis provides evidence based on current clinical trials and allows for the comparisons of widely used but controversial immunosuppressive agents. Direct and indirect comparison results showed some evidence. First, compared with non-immunosuppressive therapies, TAC+TW, TAC, ACTH, AZA, CTX, MMF, RIT, CsA, TW and CH showed significantly higher probabilities of TR, while TAC+TW, TAC, CTX, AZA, MMF, MZB and CsA (46.8%) could significantly reduce 24 hours UTP. Second, the highest SUCRA ranking of TAC and TW treatment for several endpoints, including TR, 24 hours UTP, suggests that future trials of these drugs combination are necessary and would strongly benefit clinical practice. Third, when compared with the control group, all immunosuppressive agents had no significant advantages in reducing Scr and preventing relapse based on the current evidence.

According to KDIGO's Clinical Practice Guideline for IMN in 2012,[8] alkylating agents (CTX and CH) were recommended as the initial therapy of IMN. Meanwhile, CNI (CsA or tacrolimus) were recommended as the alternative regimens for the initial therapy of adult IMN with nephrotic syndrome, and the use of other agents, including RIT, MMF and/or ACTH, are worthy of further research.[8] In the present study, TAC+TW seems to be significantly better than CTX in improving remission rate and reducing 24 hours UTP. It is a pity that patients who received treatment with TAC+TW in the included studies were only limited to Chinese, and the rest of the population needs to be studied. Although the beneficial effects of other drugs (except for TAC+TW) compared with CTX did not reach statistical significance, TAC consistently showed higher probabilities of being in the superior ranking positions in the primary outcome and reducing 24 hours UTP. It is noteworthy that the study duration in the related studies on TAC is relatively short (range: 6–24 months). Compared with the other studies and reviews, the same outcome could be found. Meta-analyses[69 70] demonstrating that both CsA and TAC have better short-term efficacy and greater safety profiles than CTX are available. Moreover, TAC is more favourable than CsA for patients with IMN.[69] Another meta-analysis showed that tacrolimus was comparable with CTX for inducing renal remission of patients with primary MN within 1 year.[71] Therefore, the short-term efficacy of TAC in the treatment of IMN is positive, but its long-term effect remains to be further studied. The results of our study also showed that ACTH, as one of drugs mentioned in the KDIGO's Clinical Practice Guideline for IMN in 2012,[8] is associated with high remission rate and low relapse rate in treating IMN. Conversely, MMF was found to be effective only when the study-duration is >12 months on the basis of subgroup analysis. In the present study, RIT was superior to the control group in complete or PR, but it had no advantage over the control group in reducing 24 hours UTP. Similarly, Fervenza *et al*[72] found that the number of B lymphocytes decreased rapidly after RIT administration, but the decline of proteinuria lagged behind. Furthermore, RIT was well tolerated in the treatment of IMN, and the most common side effect is cardiovascular events (10.8%) according to our study.

In addition to the drugs mentioned above, TW, a traditional Chinese medicine with exact inhibitory effect,[73] is

significantly better than the control group in improving remission rate and reducing 24 hours UTP for patients with IMN. Liu *et al*[74] found that the emergence of TW therapy has actually reduced the heavy medical burden, because this medication is cost-effective than other immunosuppressive remedies such as TAC, CSA and LEF, particularly for patients in low-income and middle-income countries. Therefore, TW, although it is only used for the Chinese at present, is a promising alternative therapy for patients with IMN. Further, AZA also showed some remarkable effect in the short term, but the long-term effect is not obvious, and the associated recurrence rate is higher than other immunosuppressive agents in this study. As for STE alone, LEF and MZB, they had no obvious advantages in improving TR or urinary protein when compared with the control. Therefore, the use of these drugs in clinical practice requires careful selection in combination with the patient's condition.

Ren and colleagues[75] reported a network meta-analysis of immunosuppressive treatments for IMN. In contrast with Song's study, this search was more comprehensive and eventually included 48 articles, while 36 articles are included in Song's meta-analysis. For the outcome indicators, the changes of 24 hours UTP independently were not mixed with complete or PR rate, because the standard of partial or CR is not just based on the level of urinary protein. Moreover, we analysed the Scr, which made the assessment of effectiveness more adequate. As for the meta-analysis for primary outcome TR, when compared with non-immunosuppressive therapies, only four immunosuppressive agents (ACTH, CTX, TAC and CsA) showed significantly improved TR (CR or PR) in Song's study. Our review found 10 different immunosuppressive agents that are significantly superior than the control, in which TAC+TW showed the best therapeutic effect among all the immunosuppressive therapies, followed by TAC, ACTH, AZA, CTX, MMF, RIT, CsA and TW. Finally, in statistical methods, subgroup analysis, sensitivity analysis and meta regression were used to evaluate the sources of heterogeneity or stability of the results. In addition, the GRADE was used to evaluate the level of evidence.

Nevertheless, the present study has some limitations. First, our systematic review just provides data about the frequency of the most common adverse effects and lacking statistical comparison based on large amounts of data. Moreover, our study was limited to the evaluation of RCTs and therefore lacks data from observational studies that may provide better evidence for rare but serious adverse effects. Second, the standards of CR and PR were not unified in the literature. Third, the time of treatment included in the literature was not uniform, and most studies lacked long-term follow-up. Fourth, most studies lack the use of blinding methods, which may result in large bias. Fifth, our review did not evaluate information on costs, and the evaluation of drugs is not comprehensive enough. Finally, the number of relevant studies about some intervention measures is too small, and the evidence level is very low.

CONCLUSION

In conclusion, this study demonstrates that TW+TAC, TAC and CTX are superior to other immunosuppressive agents in terms of total remission and 24 hours UTP. Moreover, they are all associated with a risk of infection, gastrointestinal symptoms and myelosuppression. In addition, TAC could increase the risk of glucose intolerance or new-onset diabetes mellitus. Conversely, STE alone, LEF and MZB seem to have little advantage in the clinical treatment of IMN. Although current estimates of the effects of most immunosuppressants for IMN are significant and clinically relevant, they have a very low level of GRADE evidence. Thus, the use of these agents, including TAC+TW, TAC, CTX and so on, in this group of subjects is worthy of further study, especially in terms of safety, and the evidence is currently insufficient to make any specific recommendations.

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