Immunosuppressive Treatment for Idiopathic Membranous Nephropathy: A Network Meta-Analysis and GRADE Assessment

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Research article

Keywords: idiopathic membranous nephropathy，immunosuppressive treatment，network meta-analysis，GRADE.

Posted Date: June 27th, 2019

DOI: https://doi.org/10.21203/rs.2.10734/v1

Abstract

BACKGROUND and AIMS Immunosuppressive therapy for IMN remains a controversial topic. In light of this, we performed a network meta-analysis to compare the efficacy and safety of different pharmacological treatments for idiopathic membranous nephropathy. METHODS: Twenty-eight randomized clinical trial (RCT) cases were included with 1759 instances of idiopathic membranous nephropathy with a minimum of a 6-month follow-up. Treatment with tacrolimus (TAC), cyclophosphamide (CTX), mycophenolate mofetil (MMF), chlorambucil, cyclosporin A (CsA), steroids, rituximab and supportive therapy were compared with each other. Outcomes were measured using the remission rate and incidence of side effects. Summary estimates were expressed as the odds ratio and 95% confidence intervals (OR; CI). The quality of findings was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. RESULTS Low evidence found herein supports the fact that the remission rate of CTX was slightly inferior to that of TAC (OR 0.83, CI: 0.41, 1.7). Stronger evidence suggests that the incidence of leukopenia (OR 0.50, CI: 0.20, 0.80) and hepatotoxicity (OR 0.40, CI: 0.19, 0.81) in patients treated with TAC was much lower than that of CTX. It was also found that the remission rate of treatment with steroids was lower than that of CTX (OR 0.24, CI: 0.08, 0.73). Compared with chlorambucil, modearte evidence supports the claim that the rate of infection (OR 0.29, CI: 0.08, 1.01) and leukopenia (OR 0.13, CI: 0.03, 0.54) in patients undergoing treatment with CTX was much lower. CONCLUSION: Due to the equivalent remission rate with a decreased incidence of side effects, TAC should be regarded as the first line therapy instead of CTX for idiopathic membranous nephropathy over IMN.

Background

Idiopathic membranous nephropathy (IMN) is the primary cause of adult nephrotic syndrome[1]. Although the overall disease progress is slow, the prognosis of IMN is difficult to predict. About 20% of IMN patients can recover spontaneously. However, if not be treated actively, about 40% of these patients will progress to end-stage renal disease within 10-15 years [2-4] . Immunosuppressive therapy is the current mainstay in the treatment of IMN. In 2012, guidelines issued by Kidney Disease Improving Global Outcomes (KDIGO) recommended that alkylating agents in conjunction with steroids should be considered the first choice immunosuppressive therapy for IMN (1B). Currently, cyclophosphamide was chosen as the alkylating agent in place of chlorambucil (2B). Meanwhile, calcineurin inhibitors (CNIs) including tacrolimus and cyclosporine A were suggested to be the alternative regiment (2C) [5]. However, much controversy surrounds the use of immunosuppressive therapy for IMN. Alkylating agents typically provide higher remission rates with lower recurrence. However, they suffer from prominent adverse effects, include pancytopenia, infertility, and carcinogensis[6]. These adverse events greatly hinder their clinical application, for good reason. CNIs suppress immunological functions by downregulating IL2, a key cytokine produced by CD4 Th1 cells to stimulate CD8 T cells. Some randomized controlled trials (RCTs) have shown that CNIs have a higher remission rate than alkylators. Nevertheless, CNIs also has a higher relapse rate and can cause reversible renal impairment.Based on KDIGO guidelines, MMF is not

recommended as an immunosuppressive therapy for IMN. Yet, several RCTs[7-8] indicated that in comparison with CTX or CsA, the clinical remission rate of MMF is comparable. On the other hand, rituximab, a specific monoclonal antibody, has been shown to induce B cell-depletion. In fact, it has been used in the treatment of IMN for more than ten years. Compared with traditional immune agents, rituximab has considerable or even better short-term efficacy and tolerance.

In recent years, several meta-analyses have compared the advantages and disadvantages of various immunosuppressive treatments for IMN. For example, Zhu et al. [9] have compared the efficacy and safety of tacrolimus and cyclophosphamide in the treatment of membranous nephropathy. A total of 339 patients over four RCTs were included. The results showed that tacrolimus had better short-term efficacy with a comparable relapse rate to cyclophosphamide. However, cyclophosphamide caused serious side effects such as leukopenia. Zhang et al. [10] included 353 patients in five studies. The efficacy and safety of rituximab and conventional conservative treatment were compared. It was found that rituximab had significantly greater efficacy and fewer side effects. However, direct meta-analysis studies can only compare the advantages and disadvantages of two treatments with each other. It cannot simultaneously evaluate a variety of regiments to provide optimal information for clinical decisions. Network meta-analysis, on the other hand, can achieve this function by calculating the magnitude of the combined effect between the various measures. Based on Bayesian frequency method, the direct effect (direct comparison between the two treatment schemes) and the indirect effect (comparison between the two treatment schemes with the reference to the other) are calculated and analyzed respectively. The mixed effect is then generated to evaluate the advantages and disadvantages of the two schemes. Therefore, this study has performed such a network meta-analysis to compare the efficacy and safety of various regimens for IMN. Furthermore, this study follows the Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria[11-15] to assess each effect and provide the corresponding level of evidence for the final results.

Methods

This network meta-analysis was carried out in accordance with the previously submitted protocol and is consistent with the statements of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We followed good research practices as outlined in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) report on interpreting indirect treatment comparisons and network meta-analysis for healthcare decision making.

Inclusion Criteria

The included studies must be an RCT, and the observation time should not be less than 6 months. In addition, the following points must be met: 1) The patients must be adults (older than 18 years) who were diagnosed with IMN by renal biopsy; 2) The interventions in treatment group must be CTX, Chlorambucil,

MMF, TAC, CsA, rituximab or steroids, of which the first five immune regiments can be combined with steroids or used alone. The measures in control groups included placebo/no treatment, conservative treatments (ACEI/ARB or other supportive treatment), steroids, CTX, chlorambucil or CsA. The latter three immunotherapies can be combined with steroids or used alone. 4) Outcomes must include remission rate (including complete remission and partial remission) or incidence of side effects, or both.

Exclusion Criteria

Literature was excluded according to the following criteria: 1) Studies which were non-randomized trials or observational studies; 2) Studies with patients of secondary membranous nephropathy (e.g. hepatitis B-related nephropathy); 3) Studies which included patients younger than 18 years; 4) Studies with an observation time less than 6 months; 5) Studies which two or more immunosuppressive drugs were used in one intervention or; 6) used drugs which are not widely used such as ACTH and leflunomide; 7) Chinese medicine was excluded; 8) Azathioprine and mizoribine were also excluded due to their documented poor efficacy, and serious side profile.

Retrieval Strategy

Two researchers (NB and XY) performed literature retrieval independently and only articles written in English were included. The retrieval databases include Pubmed, Embase, Cochrane Database and Medline. The timeline for retrieval was from the establishment of each database to March 2019. In the case of a duplicate, each case will be resolved through negotiation. The details of the retrieval strategy are shown in *supplement 2.*

Baseline characteristics and quality assessment

Detailed information such as the study design, sample sizes, specific dosage of therapeutic drugs and specific characteristics of patients included in the study will be extracted separately by two researchers (M-JG and XY). Outcomes were extracted at the end of each study. When multiple time points were reported, the last time-point was used. We used the Cochrane Risk of Bias assessment tool to assess the quality of individual literature. According to the Cochrane Risk of Bias assessment, remission rate and the incidence of side effects were objective indicators and thus, could not be affected by performance bias and detection bias. Therefore, while most of the included studies were not double-blinded, the aforementioned sources of bias can be assumed to be low. Any doubts were resolved by direct discussion with the group through consultation.

Statistic Methods for Outcomes

This study primarily analyzed the remission rate and the incidence of adverse effects such as leukopenia and infection. We used the intention-to-treat (ITT) approach to calculate the remission rate. Specifically, all patients in treatment groups were analyzed using statistical analysis. All patients lost to follow-up were considered as failures of treatment. While the ITT method is well suited for the remission rate, the per-protocol (PP) method was better suited to measure the incidence of adverse events. Specifically, only patients demonstrating a high level of compliance that completed treatment were included.

Data Extraction and Synthesis

In this study, the rate of remission and the incidence of adverse events can be expressed by dichotomous variables. A direct comparison was made using the random effect model to determine the odds ratio (OR) with Revman 5.3 (Cochrane Collaboration, Copenhagen, Denmark). The confidence interval (CI) is was set at 95%. Heterogeneity was determined by analyzing the value of I^2. If $I^2 > 50\%$, the heterogeneity was said to be high, otherwise it was low. Publication bias will be tested through the Egger's regression test[11]. If the P-value > 0.1, then no publication bias was said to have occurred between these papers; otherwise publication bias was suggested. Stata 15 (Stata Corp. 2017. Stata Statistical Software) was used to carry out network meta-analysis, including network diagram, contribution plots, and inconsistency tests. In addition, we used R software x64 3.5.0 (Department of Statistics, University of Auckland, New Zealand) to indirectly evaluate the size between these interventions with OR within the random effect model and the confidence interval was set at 95%. To make an indirect comparison between the two interventions, it is necessary to find a reference which performs a direct comparison with both and merge the effects. If there were both direct and indirect comparisons between two interventions, the node splitting method was used to calculate the value for direct and indirect comparisons respectively. Then the Markov chain Monte Carlo model was used to diagnose convergence and draw trajectory density maps with 20,000 simulated draws after a burn in of 5,000 iterations. Finally, the GEMTC package was used to rank each intervention in terms of alleviation rate and side effects respectively. The higher the percentage, the greater the possibility of ranking ahead. If the percentage was 100%, the drug ranks first.

Evidence Quality Assessment

We evaluated the quality of the included direct comparisons based on the RCT evidence quality assessment method published by the GRADE working group[12-16]. At the beginning of the assessment, all included RCTs were set at a high level of quality. Then the assessment was performed according to five aspects including study limitations, publication bias, imprecision, inconsistency, and indirectness. For each criterion a study failed to meet, the level of guidance was lowered by one. For serious cases, two

points were removed for the infraction. Results were summarized after the assessment of five items was completed.

The quality assessment for indirect comparisons was carried out according to the method described by Puhan et al[17]. First of all, the best comparable path needs to be selected. The lower the number of interventions in the indirect comparison path, the more credible the results will be. After the best indirect comparison path was determined, the quality of evidence for a single direct comparison in the path was assessed according to the method mentioned above. The lowest level of evidence was chosen to reflect the final quality of evidence for this group of indirect comparisons. If there are both direct and indirect effects in a group of comparisons, both comparisons were assessed individually, and the higher level of evidence was selected to reflect the final result. The final step was to evaluate the inconsistencies in results, which included differences in baseline characteristics, common references, and measurements for outcomes among different groups. If the differences were significant, the final quality level will be further reduced by one. This work was performed on Stata.

Results

A total of 662 articles were indexed using the retrieval strategy mentioned above. After eliminating duplication and other unrelated articles, 39 articles were suitable for analysis. After carefully reviewing each article according to the inclusion and exclusion criteria mentioned above, a total of 28 articles[7-8,18-43] were included. Among the 11 articles excluded, 4 regarded traditional Chinese medicine; 4 were single-arm studies; 1 paper contained two immunosuppressive drugs in the same treatment regimen; one had a different baseline of renal function between the two groups, and the outcome indicators of one article did not meet the inclusion criteria. Details were shown in *Figure 1.*

Characteristics and Quality of Included Studies

Table 1&2 summarized the basic characteristics of studies which included 28 RCTs with a total sample size of 1759 and a follow-up period of 6-120 months. Among them, 21 were single-center studies and the remaining 7 were multi-center studies. The average sample size was 62.8 (17-158). The complete remission rate was defined as 24-hour proteinuria less than 0.3 g plus stable renal function. The partial remission rate was defined as 24-hour proteinuria less than 3.5 g or less than 50% of baseline along with stable renal function. The average serum creatinine of the three trials mentioned above was 200 μmol/L, while the others were about 100 μmol/L or less than 100 μmol/L. All studies reported their remission rate except the one conducted by Howman Et al. All studies reported the incidence of various side effects in detail except for Murphy Et al. Of the 28 studies included, 26 were two-arm studies and the remaining 2 were three-arm studies.

Literature quality assessment was performed based on the Cochrane Risk of Bias assessment tool. The overall quality was a low-medium bias risk. Because both remission rate and side effects are objective

indicators, single-blinded or non-blinded studies seemed to have little impact on these outcomes. 9 trials did not report random allocation, and 14 studies did not describe whether allocation concealment was used, both demonstrated an increased risk of bias. Details of the literature quality assessment are listed in *Figure 2&3* and *Supplement 3.*

1. **Remission rate**

Remission rate was conducted by network meta-analysis (*Figure 4)*. TAC and CTX ranked first and second respectively for best remission rate (*Table 3 and Figure 5).* The remission rate of CTX was slightly inferior to that of TAC, but there was no statistical difference (OR 0.83, CI: 0.41, 1.7) and the evidence level was low. Compared with CTX, the confidence interval (CI) of rituximab and CSA for remission rates were broad and had no clinical significance. The results were (OR 0.78, CI: 0.11, 6.0) and (OR 0.50, CI: 0.12, 2.2) respectively with a low level of evidence. In comparison with CTX, the remission rate of MMF was much worse (OR 0.39, CI: 0.11, 1.5). Although there was no significant difference, the remission rate of Chlorambucil was inferior to that of CTX (OR 0.56, CI: 0.22, 1.4) with moderate evidence. The remission rate of treatment with steroids was lower than that of CTX (OR 0.24, CI: 0.08, 0.73) with moderate evidence as well. The difference was statistically significant. Details of remission rate were shown in *Table 4.*

2. **Side-Effect Profiles**

The incidence of side effects was determined by direct comparison with Revman. Compared with CTX, the infection rate of TAC was lower (OR 0.57, CI: 0.18, 1.84). The incidence of leukopenia for TAC was also lower (OR 0.50, CI: 0.20, 0.80) with a high level of evidence. The incidence of hepatotoxicity with TAC was much lower (OR 0.40, CI: 0.19, 0.81), with moderate evidence. The incidence of Gastrointestinal symptoms in TAC groups was lower (OR 0.74, CI: 0.30, 1.81). Remarkedly the difference between the two groups regarding the incidence of leukopenia and hepatotoxicity was statistically significant. The incidence of tremor with TAC was much higher (OR 11.25, CI: 2.05, 61.68) in comparison with CTX, and the level of evidence was moderate. The difference was statistically significant.

Compared with chlorambucil, moderate evidence supports the claim that the incidence of infection in CTX groups was much lower (OR 0.29, CI: 0.08, 1.01), and moderate evidence supports the claim that the incidence of leukopenia was lower too (OR 0.13, CI: 0.03, 0.54). The difference between the two groups was statistically significant. *Table 5.*

3. **Publication Bias**

A general funnel plot generated by Revman was included (*Figure 6*). The results indicated that there was no publication bias in the included studies. An Egger's test was also used to detect the publication bias of each direct comparison which had more than two studies. If P > 0.1, there was reported to be no publication bias; otherwise, publication bias was implied (Details were shown in GRADE assessment *Supplement 6*).

4. **Inconsistency Tests**

Stata was used to perform the inconsistency test. If P > 0.1, there was no inconsistency among these studies, otherwise the inconsistency was present. The results indicated that there was no inconsistency in all comparisons between these groups, as shown in *Supplement 7*.

Discussion

Guidelines issued by KDIGO in 2012 recommend cyclophosphamide (CTX) plus steroids as the preferred immunosuppressive therapy for idiopathic membranous nephropathy (IMN). Tacrolimus (TAC) should be chosen as an alternative if patients have contraindications, fail in treatment or refuse to use CTX. TAC, a calcineurin inhibitor (CNI), was first used to prevent allograft rejection. Its mechanism of reducing urinary protein functions mainly by inhibiting the potential cationic transient potential of the TRPC6 protein receptor, expression of calcineurin, and protecting the podocyte cytoskeleton [44-45]. In recent years, many studies have evaluated the efficacy and safety of TAC and CTX in the treatment of IMN. According to our network meta-analysis, while there is no statistical significance, the short-term efficacy of TAC (within 2 years) was slightly better than CTX with low evidence. TAC has a high remission rate in the short term, which is due to its reduction of IL-2 production, inhibition of NK cell activity[46-48] and partial inhibition of IL-6 effect on serum albumin secretion[49]. The high recurrence rate of TAC is an important factor which affects its ultimate efficacy. Over time, the recurrence rate demonstrated an upward trend for TAC, however. The follow-up time of all eight RCTs in this study is relatively short (6-24 months). Therefore, there is no relevant data for more than five years. It is hopeful that future, high-quality RCTs can provide these data.

In the investigation toward adverse effects to treatment, CTX demonstrated an increased propensity toward infection, leukopenia, gastrointestinal symptoms and hepatotoxicity than TAC. In the particular case of the incidence of leucopenia and hepatotoxicity, the difference was statistically significant, and the evidence level was high, and moderate respectively. CTX also increases the risk of infertility and malignant tumors, greatly limiting its clinical application. A six-year retrospective study found that patients using CTX were three times as likely to develop malignant tumors as untreated controls[7]. The side effects of TAC are relatively more benign. Most commonly, the occurrence of tremor which is easily managed is common, but far from the effects of CTX. TAC, however, is known to cause nephrotoxicity, which was evaluated in all eight RCTs included in this study (details were shown in *Table 6*). With the

exception of Ramachandran who reported 8 patients with nephrotoxicity and Li who reported one patient, none of the other 6 studies reported nephrotoxicity in the TAC groups. This may be due to the fact that almost all patients were classified as having stage I-III IMN with normal renal function. In other words, TAC should be used cautiously in IV IMN patients with renal insufficiency. In conclusion, although long-term efficacy is difficult to conclude, based on current data and evidence levels, TAC is a favorable first-line immunosuppressive regimen for the treatment of IMN, especially in patients with normal renal function and stage I-III disease.

Rituximab has been a focus in the treatment of IMN in recent years as it avoids the prominent side effects of steroids and immunosuppressive drugs. It functions by inducing immune-mediated B-cell lysis through the CD20 antigen on the B-cell surface. Thus, the effective result is the clearance of B-cells *in-vivo* and an overall reduction in the production of antibodies manifesting with a lower rate of proteinuria. In recent years, there have been many observational trials to study the efficacy and safety of rituximab. One such meta-analysis[50] showed that rituximab has better efficacy and fewer side effects than placebo. Nevertheless, it should be pointed out that the quality of these studies was poor and the credibility of these results are low. There is only one RCT with small sample included in our study, which leads to a wide confidence interval of our statistical results and a low level of evidence with no clinical significance. It is therefore, necessary to be cautious to conclude that rituximab is superior to other regimens for treating IMN. Two large RCTs named MENTOR trial (ClinicalTrials. gov identifier NCT 01180036) and STARMEN (ClinicalTrials. gov identifier NCT 01955187) are ongoing. The results of the two studies may provide more evidence for the efficacy and safety of rituximab. CsA, which belongs to CNIs, was also recommended by KDIGO guidelines as an alternative regiment for CTX. Unlike TAC, there are few high-quality RCTs about CsA in the treatment of IMN. Therefore, results have wide confidence intervals and a low level of evidence. There was no significant difference in the remission rate or the incidence of side effects. As a representative drug of CNIs, CsA still maintains prospect for the treatment of IMN. It is hopeful that future RCTs can be performed to study the efficacy and safety of CsA in the treatment of IMN.

The KDIGO guidelines in 2012 also suggested that mycophenolate mofetil (MMF), chlorambucil and single-use steroids should not be used as treatment regimens for IMN.It is consistent with the results of our network meta-analysis. MMF was originally used to prevent allogeneic rejection. It selectively inhibits the proliferation of T and B cells by reducing the synthesis of guanine glycic acid, thereby reducing the production of antibodies. Our results indicate that MMF has a poorer therapeutic effect in comparison with TAC or CTX. Some experts have proposed that the poor therapeutic efficacy of MMF in IMN is due to the low dosage used clinically, and an increased dosage may improve treatment outcomes[51]. However, there is no high-quality RCT to date to verify this. Therefore, our conclusions are in accordance with the KDIGO guidelines; that MMF should not be recommended for immunosuppressive therapy in patients with IMN due to its questionable efficacy.

Chlorambucil has repeatedly demonstrated poor efficacy and high rates of toxicity. Compared with CTX which is also an alkylating agent, Chlorambucil has lower remission rate and a higher incidence of

leukopenia and infection with a moderate level of evidence.Meanwhile, single-use steroids demonstrated a lower remission rate with a statistically significant difference in comparison with TAC or CTX. The evidence level of this claim was moderate. Hence, our conclusion again aligns with that of the KDIGO; chlorambucil and single-use steroids should be avoided for the treatment of IMN.

The advantages of this study are as follows. First and foremost, this study evaluated the credibility of results strictly following the guidelines formulated by a GRADE working group. The level of evidence is the core content of evidence-based medicine. Poor credibility results have little reference value and lead to misguided clinical decisions. Secondly, this study utilized a method recommended by the Cochrane Risk of Bias assessment tool to evaluate the quality of the included papers. In comparison with other methods such as Jada, the Cochrane method evaluates the quality of literature in more aspects and allows for more specific outcomes. Thirdly, network meta-analysis can compare the difference between multiple therapeutic measures by direct comparison and indirect transmission. The inclusion of direct and indirect comparisons allows for a robust evaluation of therapeutic efficacy.

There are, however, several limitations in this study. The protective efficacy of renal function is an important index for the treatment of IMN, especially for patients with impaired renal function. However, most of the included patients in this study have a normal renal function. Therefore, it is difficult for this study to draw conclusive evidence regarding it. Secondly, while the drugs used within different trials may be the same, several parameters may vary such as the dosage, mode of administration and use immunosuppressive therapy with or without steroids. All of the aforementioned parameters can influence the ultimate efficacy of the treatment. It can also lead to different baselines for the included studies. Lastly, the number and sample sizes of these studies are relatively small.It can reduce the statistical power.

Conclusions

Our results indicate that although remission rate requires long term observation, TAC should be used as the first line therapy for immunosuppressive treatment of IMN over CTX, especially for patients with normal renal function and a pathological stage of I-III. Rituximab and CSA have good research prospects, but larger sample data are still needed to evaluate their efficacy and safety. Meanwhile, MMF, chlorambucil and single-use steroids should be abandoned in the clinic.

Abbreviations

IMN:idiopathic membranous nephropathy;

RCT:randomized clinicaltrial;

TAC:tacrolimus; CTX:cyclophosphamide;

MMF:mycophenolate mofetil; CsA:cyclosporin A;

OR:odds ratio;CI:confidence intervals;

GRADE:Grading of Recommendations, Assessment, Development and Evaluation;

KDIGO:Kidney Disease Improving Global Outcomes;

CNIs:calcineurin inhibitors;ITT:intention-to-treat;PP:per-protocol.

PRISMA:Preferred Reporting Items for Systematic Reviews and Meta-Analyses;
ISPOR:Pharmacoeconomics and Outcomes Research;

ACEI/ARB:angiotensin converting enzyme inhibitors/ angiotensin receptor blocker;
ACTH:adrenocorticotropic hormone;

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study did not require ethics approval

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study

COMPETING INTERESTS

All authors declare no conflicts of interest.

FUNDING

Not applicable.

AUTHORS' CONTRIBUTIONS

WK conceived and designed the project. WK performed the review. M-JG and XY analyzed the data and

ACKNOWLEDGEMENTS

Not applicable.

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Tables

Due to technical limitations, the tables have been placed in the Supplementary Files section.

Figures

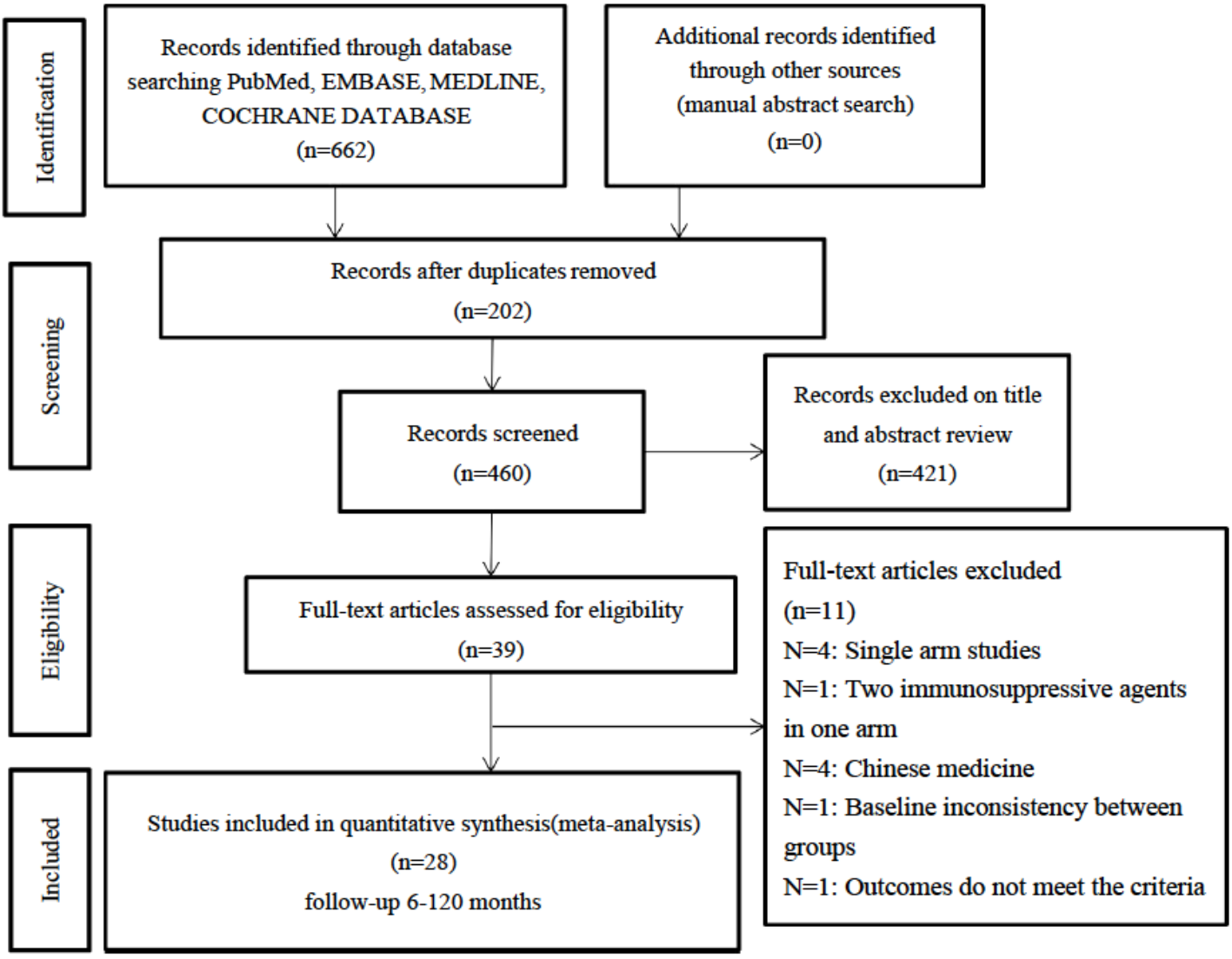

Figure 1

Flow chart depicting the process of identification of studies.

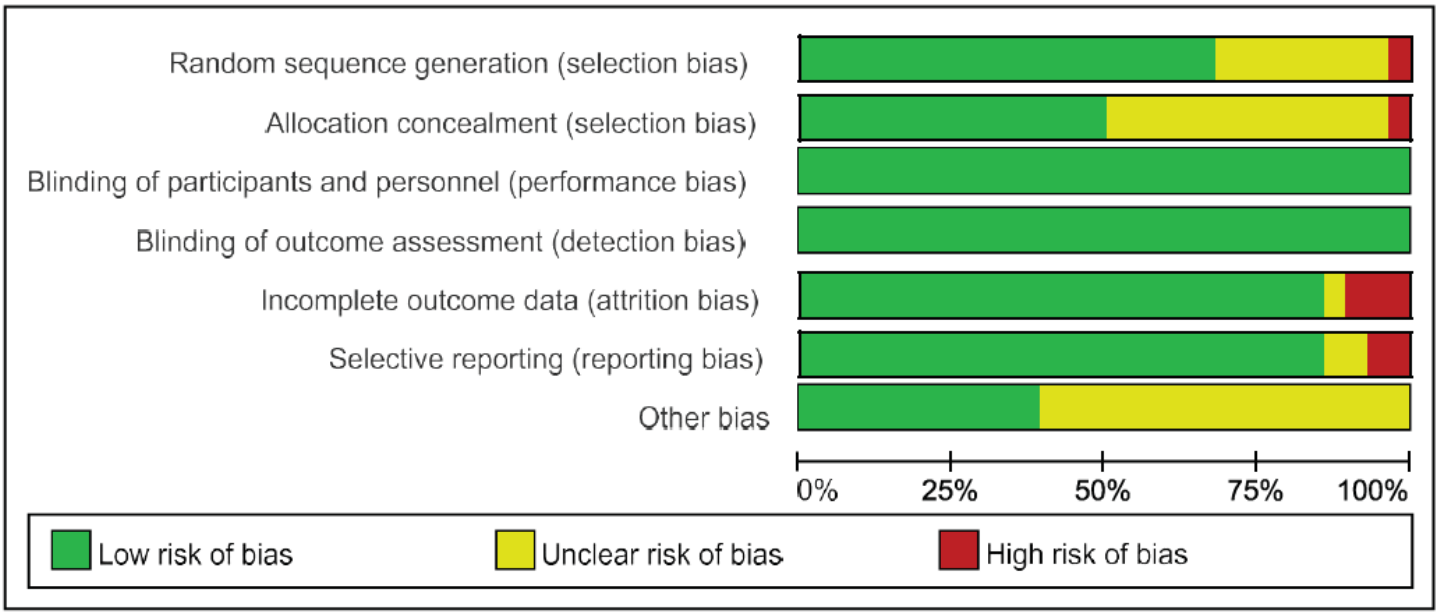

Figure 2

Risk of bias assessment: overall risk of bias for all included trials.

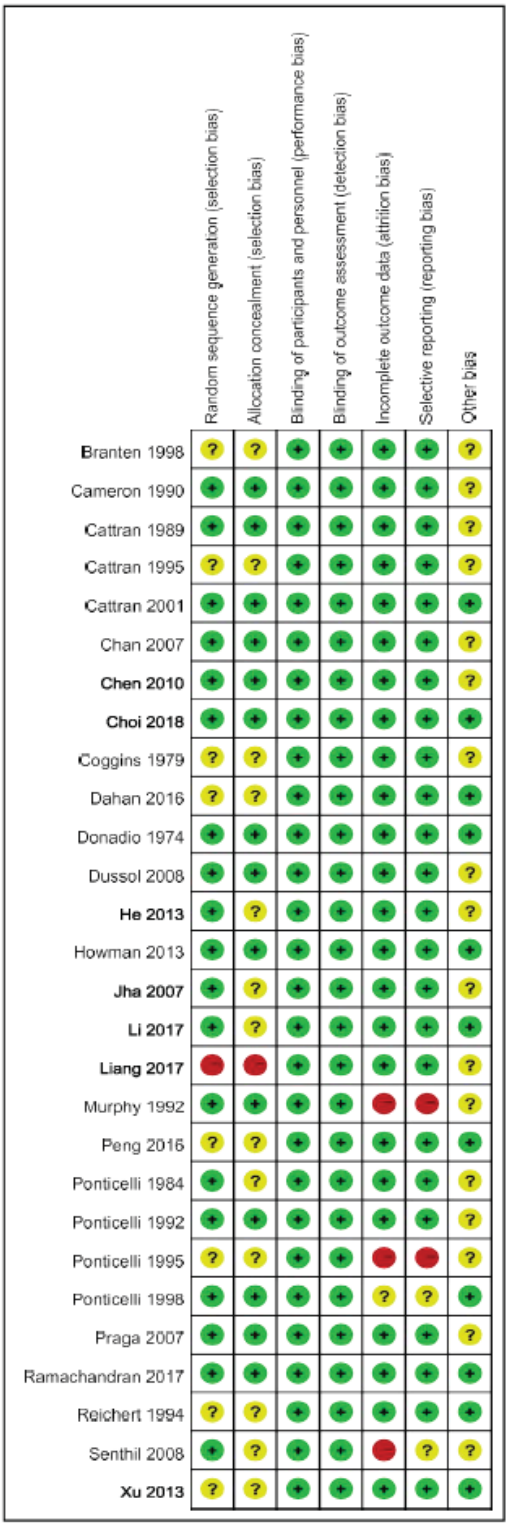

Figure 3

Risk of bias summary: overall risk of bias for all included trials.

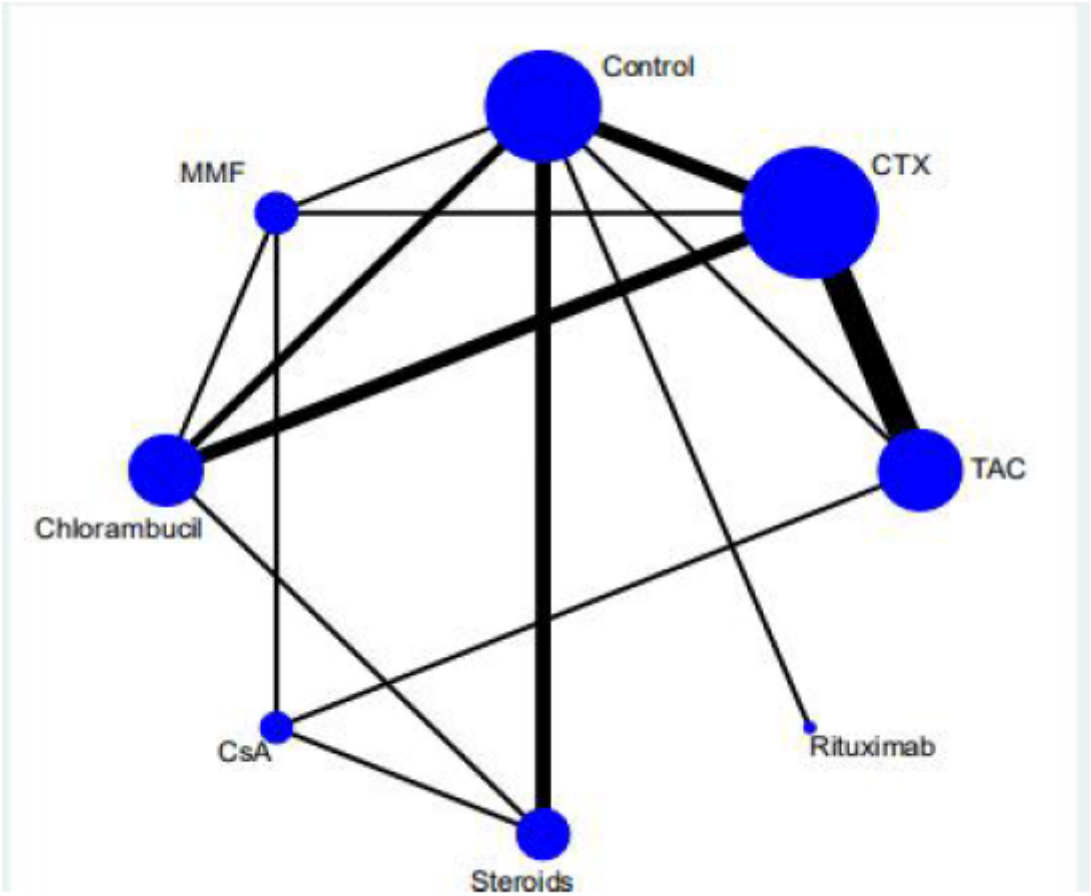

Figure 4

Network geometry. Network of all the included regiments for evaluating remission rate. The size of the nodes was proportional to the number of patients randomized to each modality and thickness of the lines to the number of direct comparisons. For example, the circle area for CTX was the largest, and the edge between CTX and TAC was the widest one, indicating that the number of studies on CTX was the highest, and the direct comparisons between CTX and TAC were the most common in the existed literatures.

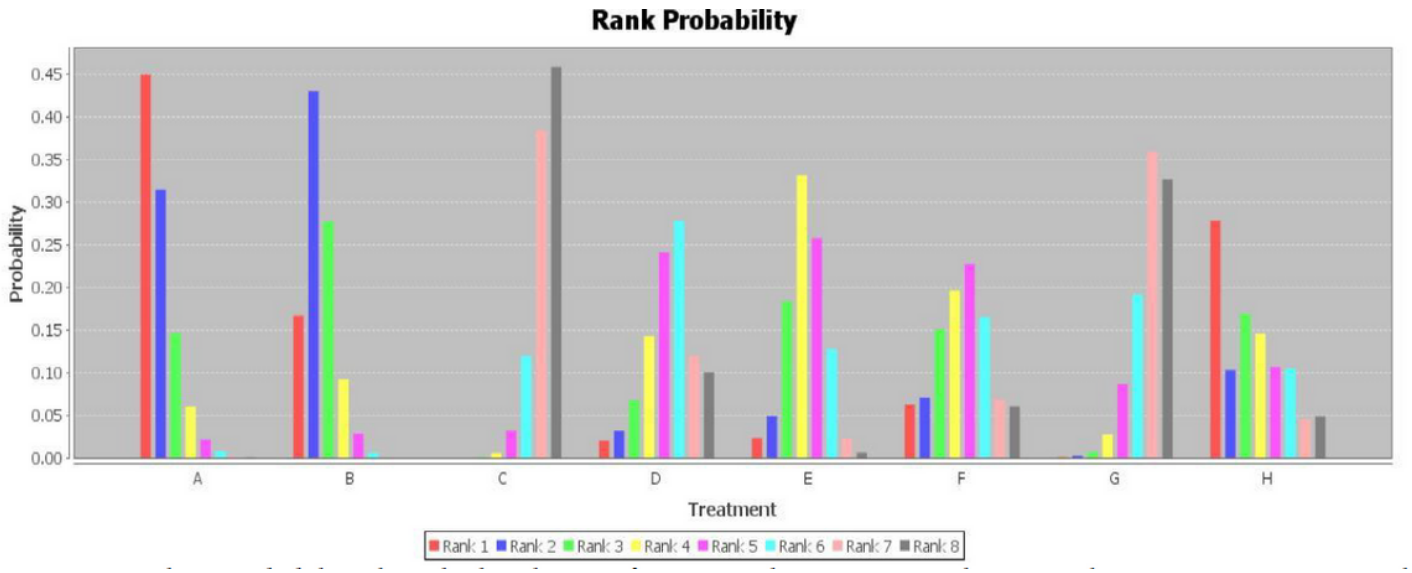

Figure 5

Ranking probability.The cylindrical area of various colours corresponding to each intervention represents the probability of ranking, and each colour represents the ranking order is shown above. For example, the red cylindrical area in intervention A is 0.45, means that the probability of A ranking first is 45%.Final ranking order is TAC > CTX > rituximab > CsA > chlorambucil > MMF > steroids > placebo/supportive therapy. *Note A:TAC;B:CTX;C:placebo or supportive therapy;D:MMF;E:chlorambucil;F:CsA ;G:steroids;H:rituximab.

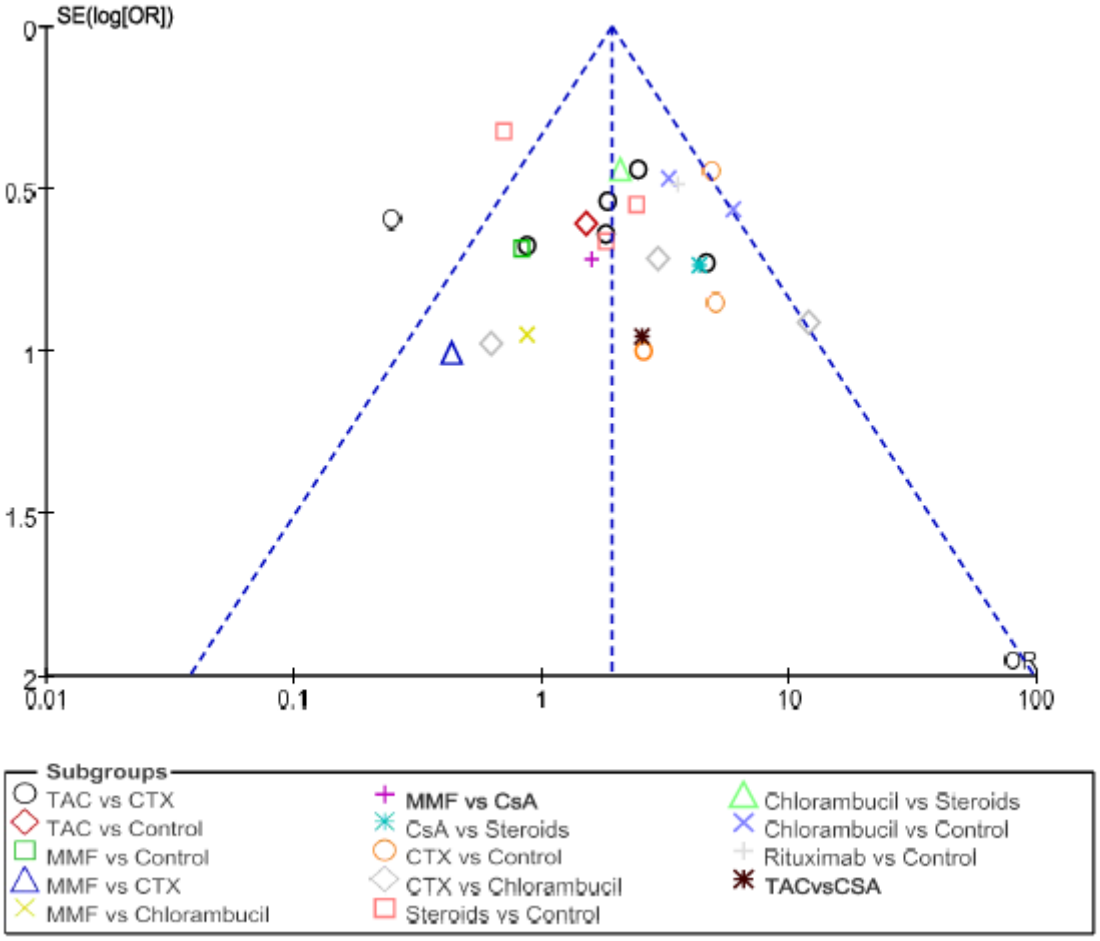

Figure 6

Funnel plot for remission rate, with a complex evidence network including 14 sets of head-to-head randomized trials as shown above.Single markers represented the individual primary studies, while the dashed vertical line showed the summary effect estimate, and the dashed oblique lines showed the 95% confidence intervals at varying degree of precision.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table6.DetailsofnephrotoxicityinTACgroups.pdf
- Supplement7.Inconsistencytest.pdf
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- Supplement4.ConvergenceDiagnosticGraphforRemssionrate.pdf
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