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Review

Risk of infection with different immunosuppressive drugs combined with glucocorticoids for the treatment of idiopathic membranous nephropathy: A pairwise and network meta-analysis

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ABSTRACT

Introduction: Idiopathic membranous nephropathy (IMN) is a common cause of nephrotic syndrome in adults and one of the leading causes of end-stage renal disease (ESRD). During recent years, the incidence of IMN has been increasing. The main treatment option for IMN is the use of immunosuppressive (IS) drugs combined with glucocorticoids (GC). However, the infection risk with different IS drug treatments has not been systematically compared. Therefore, a network meta-analysis was performed to compare the risk of infection of different IS drug treatments for IMN.

Methods: Randomized controlled trials (RCTs) that assessed the risk of infection in patients with IMN treated with different IS drugs combined with GC were included in the network meta-analysis. Risk ratios for dichotomous data with 95% confidence intervals (CI) were calculated and the data were pooled with a random-effects model. The surface under the cumulative ranking area (SUCRA) was calculated to rank the risk of infection with different interventions.

Results: A total of 38 RCTs with 2066 participants were included for comparison of nine interventions. Tacrolimus combined with GC (TAC + GC) was associated with a significantly lower risk of infection than that with intravenous cyclophosphamide (IVCTX) + GC with a risk ratio (95% CI) of 0.52 (0.34–0.79). IVCTX + GC was associated with a significantly higher risk of infection than that with TAC + GC, cyclosporin (CSA) + GC, and oral cyclophosphamide (POCTX) + GC. A sensitivity analysis, excluding studies with a very long follow-up period, revealed minimal differences in the estimates. The SUCRA showed that CSA + GC had the lowest risk of infection (SUCRA 86.0%), and the second best treatment was POCTX + GC (SUCRA 78.6%). Conversely, IVCTX + GC (SUCRA 16.2%) had a higher risk of infection than that with the other IS drugs.

Conclusions: CSA + GC and POCTX + GC were associated with a lower risk of infection than that with other IS drugs combined with GC for IMN. Combined with comparative efficacy data, these results can help patients make informed decisions about treatment options for IMN.

PROSPERO registration: CRD42018104849

1. Introduction

Membranous nephropathy (MN) is one of the most common types of idiopathic nephrotic syndrome in adults, second only to IgA nephropathy [1]. In MN, approximately 80% of cases are idiopathic MN (IMN) and 20% are secondary MN [2]. In the United States and European countries, the annual incidence of MN is estimated to be approximately 12 per million [3]. Some studies have shown that the incidence of MN is increasing [1]. For example, in China, it has increased by 13% per annum in the past 10 years, and has already exceeded the trend of IgA nephropathy [4]. IMN is common among whites followed by Asians, blacks, and Hispanics [2]. Typically, patients with MN are aged between 50 and 60 years, with a 2:1 male predominance [2].

IMN is an immune-mediated disease, as evidenced by recent studies of phospholipase A2 receptor and thrombospondin type 1 domain-containing 7A [5]. The disease is characterized by an apparent thickening of glomerular capillary walls, which is derived from the subepithelial deposition or in situ formation of immune complexes [6]. The

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most common presentations of IMN are severe proteinuria and hypoproteinemia. Without immunosuppression therapy, one-third of patients with IMN progress to the end-stage renal disease (ESRD) within 5–15 years, especially patients with persistent high-grade proteinuria [6]. Therefore, immunosuppressive (IS) treatment has been widely used for patients with IMN [5]. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines [7] recommend that the initial therapy should consist of a six-month course of alternating monthly cycles of cyclophosphamide (CTX) combined with glucocorticoids (GC). Calcineurin inhibitors (CNIs), including tacrolimus (TAC) and cyclosporine (CSA), combined with GC are recommended for contraindications or alkylation intolerance.

A key concern for patients treated with IS drugs and GC is the risk of opportunistic and non-opportunistic infections, as both medications can lead to reduced immune function [8]. A meta-analysis published in 2017 [9], which included twenty-one randomized controlled trials (RCTs) with 1187 patients, showed that TAC was not associated with any significantly different risk of infection compared with that of CTX (OR = 0.80; 95% CI: 0.27–2.38). However, significant heterogeneity was found between studies (P = 0.004, I^2 = 67%) and the authors did not perform further analysis. A meta-analysis that included six studies with infection data for 389 patients revealed the same result (TAC vs. CTX RR = 0.81, 95% CI: 0.39–1.68, P = 0.006, I^2 = 69.6%) [6]. In another network meta-analysis (NMA) [5], the authors conducted only a descriptive analysis of the risk of infection, without analyzing variation between treatments. As none of the recently published meta-analyses made an in-depth comparison of the risk of infection caused by different IS regimens and different RCTs have different reports on the risk of infection caused by different IS agents, the risk of infection between IS treatments is unclear and controversial.

In this study, we performed an NMA of all IMN trials conducted to date to compare the risk of infection induced by different IS medications combined with GC treatment for IMN, aiming to provide credible evidence for clinical decision making for people at risk of infection.

2. Methods

2.1. Search strategy

We conducted an NMA based on the Cochrane handbook [10], and reported it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The study protocol was registered in PROSPERO, CRD42018104849. PubMed, EMBASE, Cochrane Library, and three Chinese databases (WanFang Data, Chongqing VIP, and China National Knowledge Infrastructure) were searched from inception through May 2018 to identify RCTs that compared different IS drugs and GC in patients with IMN. The search terms included “glomerulonephritis, membranous”, “glucocorticoids”, “corticosteroids”, “cyclophosphamide”, “mycophenolate mofetil”, “cyclosporin”, “tacrolimus”, “leflunomide”, “chlorambucil”, “azathioprine”, and their associated words. We also checked each reference listed in the included studies, and all related reviews and guidelines to find any previously ignored papers.

2.2. Inclusion criteria and study selection

RCTs (in Chinese or English) with the following criteria were included: (1) the study population was aged 14 years or older with biopsy-proven IMN, (2) different IS drugs combined with GC were compared with each other or with non-IS treatments (placebo, renin angiotensin system blockers, or other supportive therapies), and (3) the study reported infection (all infection: bacterial, viral, fungal, or other types of infections). We excluded single drug trials (only one immunosuppressant or only GC) to ensure good transmission of the network as it is difficult to differentiate the treatment effects as a result of the combined effect or the sum of monotherapy effects. In addition, glucocorticoid therapy alone for IMN has been shown to be ineffective in reducing proteinuria and the efficacy of monotherapy with IS agents needs to be confirmed; the combination of GC and IS agents is widely used [12]. Studies (1) that focused on secondary membranous nephropathy, (2) that assessed the same IS agents with different doses in different arms but with no other comparator, and (3) from one arm with two IS agents were excluded. Study eligibility was independently determined by two investigators (DFL and YY) and disagreements were resolved by discussion.

2.3. Data extraction and quality assessment

Data extraction was performed by two independent reviewers (DFL and YY) according to a predesigned review form. Disagreements were resolved by discussion among all authors. Variables related to the studies were extracted, including the study characteristics (the authors and publication year), population characteristics (number of patients, age, and gender), intervention regimens (administration route and dose), number of infected persons, and types of infection and follow-up time.

Two authors (DFL and YY) assessed the risk of bias according to the Cochrane risk of bias tool for the following six aspects: random sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessors, incomplete outcome data, and selective reporting. A third reviewer (XY) resolved any disagreements.

2.4. Statistical analysis

We conducted conventional pairwise meta-analyses (based on pairwise head-to-head direct comparison) for treatments that were directly compared in RCTs using RevMan software (version 5.3). Dichotomous outcomes were expressed as a risk ratio (RR) with 95% confidence intervals (CI). Heterogeneity was assessed by Q test (P < 0.1 indicating statistical significance) and I^2 test (I^2 statistics of 25%, 50%, and 75% were interpreted as indicating low, medium, and high levels of heterogeneity, respectively). A random-effects model (REM) (Mantel–Haentzel) was used for data analysis (P < 0.05 indicating statistical significance). Considering that different administration routes of CTX may result in different conclusions [9], an additional subgroup analysis based on oral and intravenous CTX (POCTX and IVCTX) was performed.

We used STATA (version 14.0, Stata MP, StataCorp, College Station, TX) to perform the NMA with a random–effects mixed-treatment comparisons model for multi-armed trials (it includes two or more experimental intervention groups with a common control group, or two control intervention groups such as a placebo group and a standard treatment group) within the frequency probability method on the effects of outcomes. To summarize the risk of infection for all treatments, we calculated the surface under the cumulative ranking area (SUCRA); thus, larger SUCRA scores indicated lower probabilities of infection. We also used loop-specific inconsistency and node-splitting approaches to assess the inconsistencies that were the actual differences between direct and indirect comparisons [13]. We used consistency models to perform the NMA when there was no statistically significant difference between direct and indirect comparisons. We performed a sensitivity analysis based on differences in data on the type of infection (all infection excluding herpes zoster virus infection vs. all infection), and excluding any studies with very long follow-up period, to determine the extent to which these factors unduly influenced the results. Publication bias was identified by comparison-adjusted funnel plots.

3. Results

3.1. Study cohort characteristics

A total of 38 studies with 39 publications comprising 2066

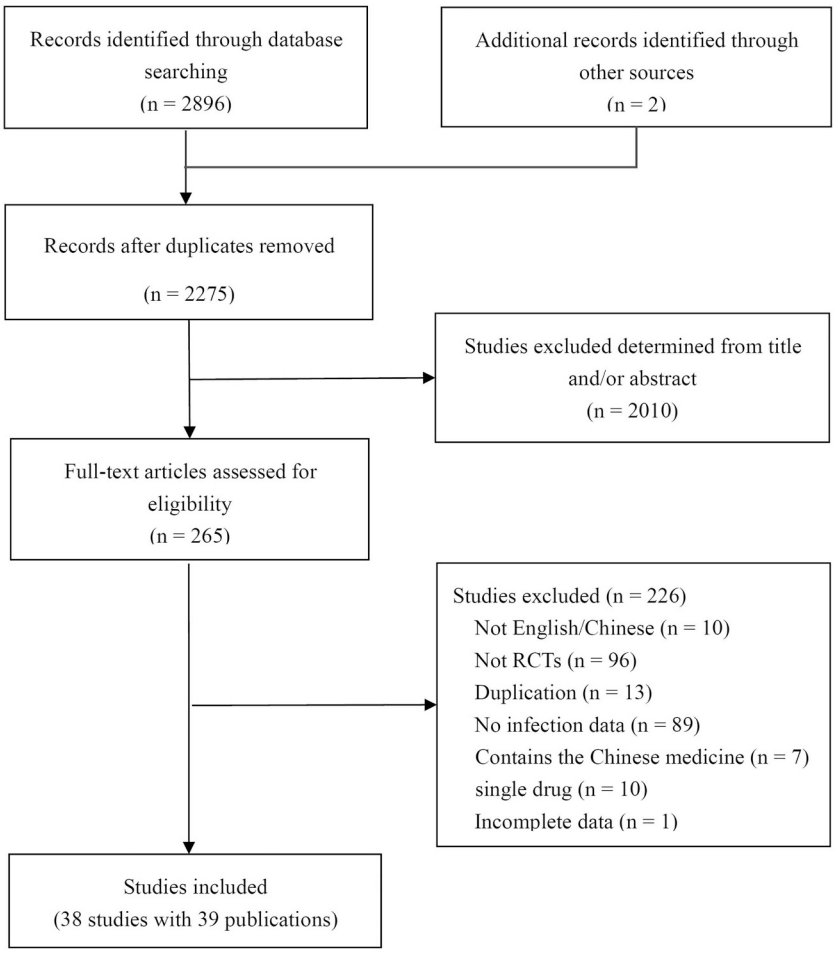

Fig. 1. PRISMA study flow diagram.

participants met inclusion criteria and provided data on infections. The detailed steps of the study selection process are shown in Fig. 1. Twenty-eight studies were conducted in China [12,14–40], two each in India (one study published two articles) [41–43], the Netherlands [44,45], Italy [46,47], and one each in Korea [48], Greece [49], Serbia [50], and the UK [51]. Table S1 summarizes the essential baseline characteristics of these studies. Approximately 62% of the patients in the included studies were male. Of these studies, 36 were two-arm (one IS drug combined with GC was compared with another IS drug combined with GC or with non-IS treatment) and 2 were three-arm (one IS drug combined with GC versus another IS drug combined with GC versus non-IS treatment or the third IS drug combined with GC), and they were published in full text. The number of patients included in each study ranged from 17 to 108, and the follow-up for patients ranged from 6 to 120 months. There were no infections reported with mizoribine. The following immunosuppressants for IMN were used in these studies: control (placebo, renin angiotensin system blockers, or other supportive therapies), CTX combined with GC (CTX + GC), TAC + GC, CSA + GC, MMF + GC, leflunomide (LFT) + GC, chlorambucil (CHB) + GC, and azathioprine (AZA) + GC.

The quality of included studies was not generally high (Fig. 2). Most of the included studies provided only limited details on the method of randomization and the concealment of allocation. All studies were open label and thus blinding was not performed.

3.2. Pairwise meta-analysis

The pairwise meta-analysis showed no statistically significant difference between the IS medications (CTX + GC or CHB + GC) and controls (three trials, n = 181, RR = 0.82, 95% CI: 0.37–1.84; or two trials, n = 151, RR = 1.89, 95% CI: 0.41–8.60, respectively). There were no infections associated with the CSA + GC treatment and control, so the RR of the comparison was not estimated. There was also no statistically significant difference in the incidence of infection between the different interventions (Table 1). However, medium heterogeneity was found for TAC + GC versus CTX + GC (P = 0.04, I^2 = 47%). The administration route of CTX was a possible source of heterogeneity. Therefore, a subgroup analysis allowing for such variation was performed, which indicated that TAC + GC was associated with a significantly lower risk of infection than that with IVCTX + GC (ten trials, n = 557, RR = 0.52, 95% CI: 0.34–0.79, Fig. 3). There was no statistically significant difference in the infection rates between TAC + GC and POCTX + GC (two trials, n = 143, RR = 2.32, 95% CI: 0.41–13.24).

3.3. Network meta-analysis

In the traditional pair-wise meta-analyses, almost no direct comparisons was statistically significant. There was no trials comparing the outcomes of POCTX + GC and IVCTX + GC, and direct comparisons of other immunosuppressants were limited. In order to further compare the different therapeutic regimens, we performed an NMA. The network plot for infections between different treatment regimens is shown in Fig. 4. Data regarding IVCTX + GC and POCTX + GC were not combined as a CTX + GC node because the administration route of CTX was a potential source of heterogeneity. As expected, most studies compared TAC + GC and CTX + GC (12 studies), whereas only one small trial reported AZA + GC. The network included several direct comparisons

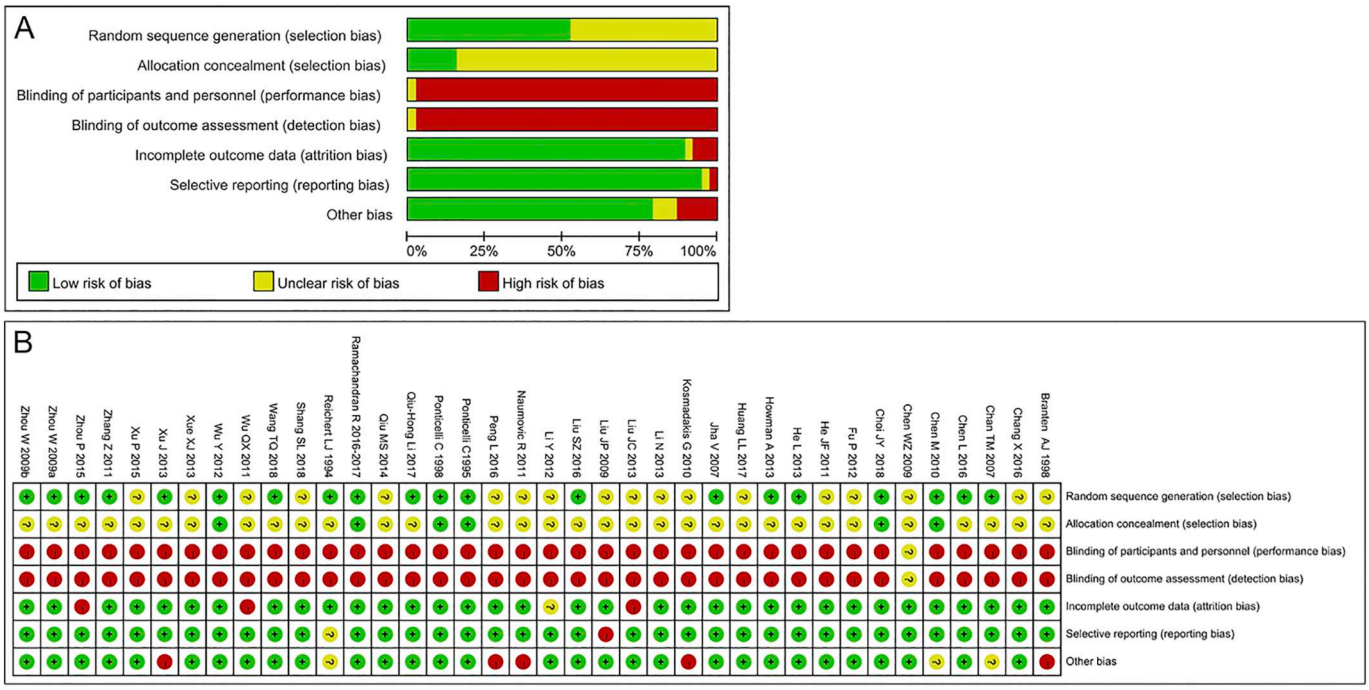

Fig. 2. Risk of bias in the study. A, the judgments about each risk of bias item presented as percentages across all eligible studies; B, reviewers' judgments about each risk of bias item for eligible studies.

of various medications and regimens. These studies included 2066 patients with 237 infections. A total of 19 out of the 38 studies had at least one arm with zero events (Table S2).

The staircase diagrams showed similar results to those of pair-wise meta-analysis (IVCTX + GC vs. TAC + GC: RR = 1.98, 95% CI: 1.25–3.13), and IVCTX + GC was associated with a significantly higher risk of infection than that with POCTX + GC and CSA + GC (POCTX + GC vs. IVCTX + GC: RR = 0.39, 95% CI: 0.20–0.76; IVCTX + GC vs. CSA + GC: RR = 3.35, 95% CI: 1.31–8.55). Besides, CSA + GC was associated with lower odds of infections than that of the control, AZA + GC, LFT + GC, CHB + GC, and MMF + GC. However, these differences were not statistically significant (Fig. 5). The SUCRAs of infection risk with treatment are shown in Fig. 6. CSA + GC and POCTX + GC were most likely to be ranked the best/safest or second best (SUCRA of 86.0% and 78.6%, respectively); controls and TAC + GC had the same SUCRA rank with a similar possibility of infection (SUCRA of 62.3% and 60.3%, respectively); IVCTX + GC was ranked as the worst/least safe treatment (SUCRA 16.2%).

In order to check the consistency of the NMA results, we conducted an inconsistency analysis and compared these with our consistent NMA results. Using the node-splitting method, no statistically significant difference between the direct and indirect comparisons was observed ($P > 0.05$), and the risk bias was low in all of the above NMAs (Tau < 1) (Table S3). The loop-specific inconsistency test did not reveal evidence of inconsistency in any of the closed loops (95% CI contained 0) (Fig. S1). No consistency issues were detected in this model.

3.4. Sensitivity analysis and publication bias

Two sensitivity analyses were planned. One possibility was to change the data on the type of infection (i.e., exclude herpes zoster virus). However, in five studies, the types of infections were unclear [18,20,21,24,30], and there were mixed infections in two studies (e.g., pneumonia and varicella-zoster) [44,45], so the sensitivity analyses were not performed. We excluded two studies with very long follow-up periods (10 years) [43,47], and no change in estimates or significance was revealed (Table S4), except that in control versus POCTX + GC, 1.23 (0.55, 2.74) versus 0.82 (0.18, 3.65), the order of control and POCTX + GC rankings changed; its SUCRA (74.5%) was similar to that of POCTX + GC (72.8%) and superior to that of TAC + GC (56.8%)

Table 1
Direct comparison of IS treatments versus control/other IS treatments.

Comparison	Studies	Participants	Statistical method	Effect estimate	P value	Heterogeneity
TAC + GC vs. CTX + GC	12	700	Risk Ratio (M-H, Random, 95% CI)	0.80[0.47, 1.37]	0.41	P = 0.04, I^2 = 47%
TAC + GC vs. CSA + GC	1	31	Risk Ratio (M-H, Random, 95% CI)	0.94[0.06, 13.68]	0.96	Not applicable
TAC + GC vs. MMF + GC	1	60	Risk Ratio (M-H, Random, 95% CI)	0.75[0.30, 1.90]	0.54	Not applicable
TAC + GC vs. LFT + GC	4	250	Risk Ratio (M-H, Random, 95% CI)	0.29[0.06, 1.38]	0.12	P = 0.99, I^2 = 0%
CSA + GC vs. CTX + GC	4	177	Risk Ratio (M-H, Random, 95% CI)	0.24[0.05, 1.10]	0.07	P = 0.99, I^2 = 0%
CSA + GC vs. MMF + GC	1	39	Risk Ratio (M-H, Random, 95% CI)	0.52[0.19, 1.40]	0.20	Not applicable
CSA + GC vs. Control	1	20	Risk Ratio (M-H, Random, 95% CI)	Not estimable	Not applicable	Not applicable
CTX + GC vs. MMF + GC	5	255	Risk Ratio (M-H, Random, 95% CI)	1.47[0.73, 2.95]	0.28	P = 0.42, I^2 = 0%
CTX + GC vs. LFT + GC	3	130	Risk Ratio (M-H, Random, 95% CI)	1.80[0.44, 7.44]	0.41	P = 0.62, I^2 = 0%
MMF + GC vs. CHB + GC	1	20	Risk Ratio (M-H, Random, 95% CI)	1.23[0.26, 5.82]	0.80	Not applicable
CHB + GC vs. CTX + GC	3	147	Risk Ratio (M-H, Random, 95% CI)	3.52[0.62, 19.90]	0.15	P = 0.13, I^2 = 51%
CHB + GC vs. Control	2	151	Risk Ratio (M-H, Random, 95% CI)	1.89[0.41, 8.60]	0.41	P = 0.78, I^2 = 0%
CTX + GC vs. Control	3	181	Risk Ratio (M-H, Random, 95% CI)	0.82[0.37, 1.84]	0.63	P = 0.4, I^2 = 0%
CSA + GC vs. AZA + GC	1	23	Risk Ratio (M-H, Random, 95% CI)	0.25[0.01, 4.78]	0.36	Not applicable

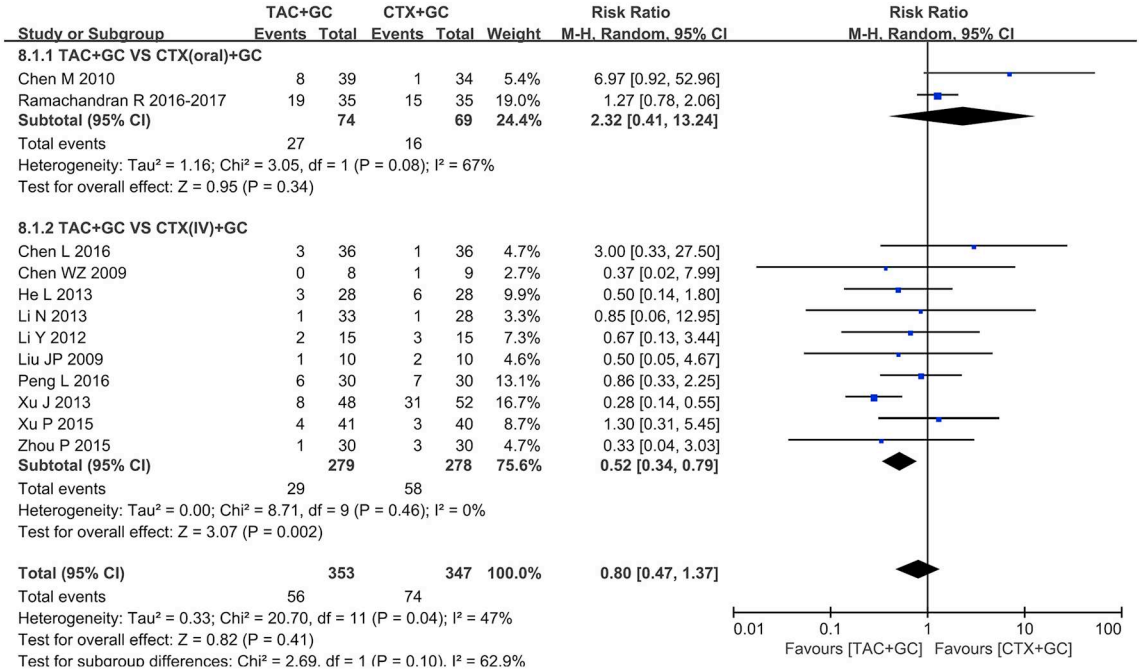

Fig. 3. Risk ratio (RR) of incidence of infection for randomized controlled trials comparing administration routes (PO vs. IV) of CTX + GC with TAC + GC.

(Fig. S2). Publication bias was tested by comparison-adjusted funnel plot (Fig. 7). The results showed that the included comparison groups were symmetrically distributed as a whole, and there was no publication bias or small sample effect in the comparison results of the data.

4. Discussion

In this study, the risk of infection in patients with IMN who were treated with IS drugs combined with GC were compared. For most of the comparisons, direct comparison trials were used, but there were no statistically significant differences between treatments. The present NMA indicated that IVCTX + GC was associated with a higher risk of infection than that with several other IS drugs combined with GC (TAC + GC, POCTX + GC, and CSA + GC). CSA + GC had the lowest risk of infection, followed by POCTX + GC.

TAC and CTX are the most common IS drugs used for the treatment of IMN. Two recent direct meta-analyses for IMN showed that there were no significant differences in the risk of infection between TAC + GC and CTX + GC [6,9]. However, the subgroup analysis including the CTX route of administration, combined with our NMA results, revealed that the infection rate with TAC + GC was lower than that with IVCTX + GC; and also showed that the infection rate with POCTX + GC was lower than that with IVCTX + GC (Fig. 5). This is similar to a previous meta-analysis, in which IVCTX was associated with a higher overall incidence of adverse drug reactions (ADRs) than that with POCTX [9]. The administration of CTX is still controversial. Our research shows that POCTX seems preferable to IVCTX for IMN patients. However, Dede et al. [52], recommended the use of intravenous CTX. Different guidelines provide different suggestions on the use of CTX for IMN: POCTX only is suggested by the “2012 KDIGO guidelines”

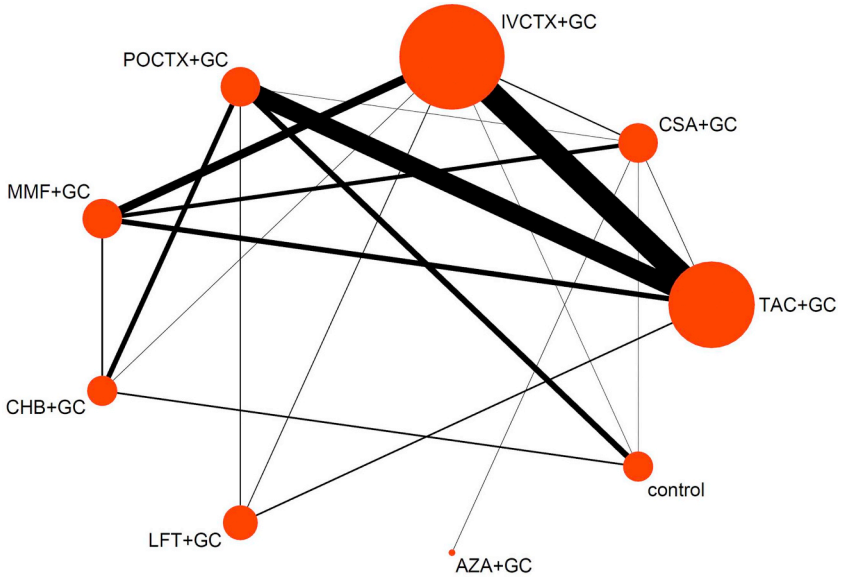

Fig. 4. Network plot of treatment measures among trials. The width of lines corresponds to the number of trials that assessed the comparison, and the size of nodes is proportional to the total sample size of each treatment; the larger the size of the circle, the higher the number of patients who received the treatment.

Control								
0.41 (0.02,10.19)	AZA+GC							
0.68 (0.17, 2.68)	1.68 (0.06,45.12)	LFT+GC						
0.59 (0.22, 1.57)	1.45 (0.06,35.78)	0.86 (0.23,3.24)	CHB+GC					
0.75 (0.26,2.20)	1.86 (0.08,40.87)	1.10 (0.32,3.86)	1.28 (0.48,3.42)	MMF+GC				
1.23 (0.55, 2.74)	3.02 (0.13,70.37)	1.80 (0.58,5.58)	2.08 (0.96,4.51)	1.63 (0.72,3.68)	POCTX+GC			
0.48 (0.18,1.27)	1.17 (0.05,26.27)	0.70 (0.23,2.15)	0.81 (0.32,2.02)	0.63 (0.34,1.19)	**0.39 (0.20,0.76)**	IVCTX+GC		
1.59 (0.45,5.66)	3.93 (0.20,76.09)	2.33 (0.56,9.70)	2.70 (0.80,9.13)	2.11 (0.88,5.07)	1.30 (0.45,3.75)	**3.35 (1.31,8.55)**	CSA+GC	
0.94 (0.37,2.42)	2.32 (0.10,52.61)	1.38 (0.47,4.07)	1.60 (0.67,3.78)	1.25 (0.62,2.52)	0.77 (0.44,1.35)	**1.98 (1.25,3.13)**	0.59 (0.22,1.57)	TAC+GC

Fig. 5. Summary of results of the network meta-analysis (NMA) on the risk of infection. For each comparison, the random effects model risk ratios (RRs) and 95% confidence intervals are provided. The results of the plots are read from top to bottom and left to right. An RR > 1 indicates that the treatment in the top left is worse/less safe than the comparator treatment. Significant results are shown in bold.

[7], while both IV and PO CTX are suggested by the "2014 China Guidelines" [53]. The improved "Ponticelli schedule" (IVCTX + GC) [33] is widely used in China; however, the results of this study showed that IVCTX + GC had a higher risk of infection than that with other IS regimens, which may be related to the fact that nearly 72% of the subjects included were Chinese patients. Further studies are needed to directly compare IVCTX and POCTX in patients with IMN to confirm which is better for Chinese patients.

CSA + GC showed the lowest infection rates among all the immunosuppressants. To the best of our knowledge, this is a novel finding. Although the available evidence supported that CTX + GC is the first-line treatment for IMN (and CSA + GC is the alternative treatment), CSA only inhibits T cell-mediated cellular immunity without significantly affecting the body's general defense capabilities [54]. This may be associated with a lower risk from CSA + GC than from CTX + GC. In addition to POCTX + GC, CNIs + GC infection is relatively low compared with that of other IS agents. Mueller et al. [55], reported that steroid and CNIs may have a beneficial effect on infectious complications in transplant patients. The superior safety of CNIs may result from their ability to promote glomerular podocyte repair by reducing angiopoietin-like 4 in podocytes [56], which may also be the mechanism by which CNIs induce remission more quickly than other agents [15,56]. Faster remission might result in even better renal function preservation and could be associated with lower rates of infection.

Two studies demonstrated that CNIs + GC had better short-term (6–12 months) efficacy and greater safety profiles than those of CTX + GC [6,9], but the long-term effects need to be investigated. Besides, several studies have reported that infection usually occurs in 3–5 months [14,46,57,58]. Third, in the United States, many clinicians prefer to initiate therapy with CNIs to avoid the more severe adverse events associated with alkylating agents [2]. Therefore, we suggest that this should be individualized so that patients with existing risk factors for infection (e.g., aging, diabetes, and other co-morbidities) can use CNIs + GC for the first six months. The suggestion proposed above can not only improve the efficacy but also reduce the incidence of infection in susceptible groups.

There was no significant difference between the control and other IS medications in terms of infection risk, and the control group did not present the lowest risk of infection. This is an area of interest as most studies have reported an increased likelihood of infection in patients treated with GC and IS agents [47,58–60]. Jha et al. [43] proposed that

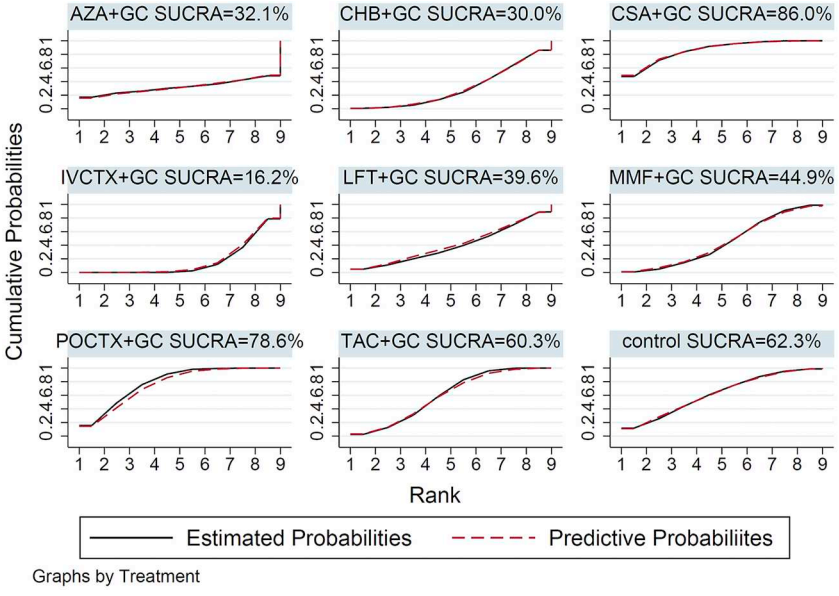

Fig. 6. Rankings of SUCRA for risk of infection to all IS treatments.

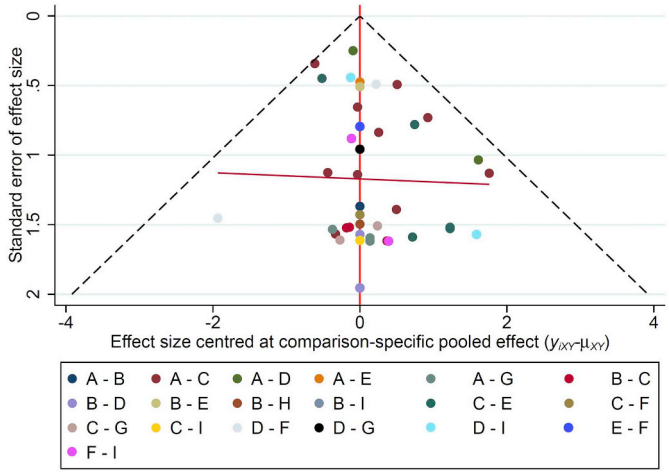

Fig. 7. Publication bias of comparison-adjusted funnel plot. Each point in the graph represents a direct comparison of each of the two treatment regimens, with different colors representing different comparison groups. A, tacrolimus plus glucocorticoid; B, cyclosporine plus glucocorticoid; C, intravenous cyclophosphamide plus glucocorticoid; D, oral cyclophosphamide plus glucocorticoid; E, mycophenolate mofetil plus glucocorticoid; F, chlorambucil plus glucocorticoid; G, leflunomide plus glucocorticoid; H, azathioprine plus glucocorticoid; I, Control.

the infection rate of the control group was higher than that of the POCTX + GC group. This is consistent with our findings. This may be because in a long follow-up study, a lowered immune status as a result of a continued nephrotic state in the control group counterbalanced the increased risk due to IS drug use [43]. The results of the additional sensitivity analysis showed that the infection rate of the control group was lower than that of the POCTX + GC group. This indicates that the duration of the follow-up had an effect on the infection rate in the control group. The control group had a higher incidence of infection than that of the CSA + GC group, which may be partly related to the renal function state of the patients. However, individual data were unavailable and our analysis only included two 10-year studies, resulting in a lack of power to draw firm conclusions.

In general, the usage of anti-infection drugs will not archive the purpose of prevention, instead, it will induce secondary infections in patients with IMN. Therefore, the patients need not have to use anti-infective agents to prevent infection when they are treated with GC combined with IS agents. If a patient uses an anti-infective drug after infection, we must pay close attention to the degree of renal function and the possible interferences with immunosuppressors. The interference between macrolides or azole antifungal agents and calcineurin inhibitors is well known [61,62]. Because TAC and CSA are cytochrome 450 (CYP) 3A4 substrates and inhibitors, and they are also substrates of P-glycoprotein (P-gp) [63], their coadministration with an inhibitor of CYP3A4 and P-gp (like macrolides or azole antifungal agents) may increase blood concentrations of CNIs [62], and thereby increasing the risk of adverse treatment outcomes. Majority of drug–drug interactions could be prevented if the prescribers are aware of them while prescribing; however, data on the possible interaction between IS agents and anti-infective agents are limited.

For the first time, in this study, we extensively analyzed the risk of infection with different treatments for IMN via an NMA. The advantage of this approach is the comparison of various treatment options used for the same disease. A larger meta-analysis is more powerful for evaluating the moderate treatment effects; thus, our conclusions should be more reliable and clinically useful [64]. However, this study had some limitations. First, the quality of the included studies could compromise the validity of the results; however, blinding was difficult due to the need for drug monitoring and dose adjustment. Second, the dosage and use of IS drugs were not uniform, and there were also differences in the courses of treatment. Third, we did not consider the stage of renal function in patients at the beginning of the studies. Fourth, some of the included studies were poorly documented, incomplete, or had inconsistent criteria for infection data and types, which posed difficulties in our analyses and might affect the reliability. Finally, most of the studies had relatively short follow-up times (six months) except for two very long follow-up studies. These limitations posed difficulties in our analyses and affected the reliability of the results. More infection data from long, large, and multicenter RCTs are required to obtain more robust results.

5. Conclusions

In conclusion, the NMA showed that POCTX + GC had a lower risk of infection than that of IVCTX + GC, and CSA + GC had the lowest risk of infection compared with that of other IS drugs. The risk of infection in the control group was related to the follow-up time. This study provides data that can be used by clinicians who need to closely monitor the immune function of patients with IMN during the follow-up period to prevent infection; and more importantly, discuss the various treatment regimens for patients with IMN (especially those with existing risk factors for infection) and inform them of the risk of infection to promote individualized medication and improve patient compliance.

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Conflict of interests

The authors declare that they have no competing interests.

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Authors' contributions

Study design/protocol development: DL, YY, FK, SQ, BH, XY. Data collection or management: DL, YY. Data analysis and interpretation: DL, YY, FK, SQ, BH, XY. Manuscript writing/editing: DL, YY, FK, SQ, BH, XY. Final version approval of publication: DL, YY, FK, SQ, BH, XY.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.03.002.

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