RENAL FAILURE
2024, VOL. 46, NO. 2, 2395451
https://doi.org/10.1080/0886022X.2024.2395451

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GLOMERULONEPHRITIS AND IMMUNOLOGIC DISORDERS

Efficacy and safety of biologics, multitarget therapy, and standard therapy for lupus nephritis: a systematic review and network meta-analysis

Gui-Qing Tian and Zhen-Qiong Li

Department of Nephrology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

ABSTRACT

Objective: This study aimed to compare the efficacy and safety of biologics, multitarget therapy, and standard therapy for the induction of lupus nephritis.

Methods: A systematic search of electronic databases (EMBASE, Web of Science, PubMed, Cochrane Library, and ClinicalTrials.gov) was conducted from inception to 30 August 2023. Our study included randomized controlled trials enrolling adult lupus nephritis patients treated with biologics or multitarget therapy, in comparison with standard therapy. The primary outcomes were the rates of complete renal remission (CRR) and serious adverse events (SAE). Stata 15.0 was used to conduct the network meta-analysis.

Results: Ten randomized controlled trials with a total of 1989 patients met the inclusion criteria. The network meta-analysis indicated that compared with standard therapy, multitarget therapy, obinutuzumab, belimumab, and voclosporin therapy demonstrated superior efficacy in achieving complete renal remission. Among these options, multitarget therapy had the greatest effect (OR = 2.78, 95% CI = 1.81–4.26). Regarding safety, it was observed that there were no significant statistical differences among the various treatment options. Cluster analysis revealed that both obinutuzumab and belimumab exhibited good efficacy and safety.

Conclusions: belimumab and obinutuzumab stood out as promising treatments due to their good performance in terms of efficacy and safety. Multitarget therapy may be the most effective approach for treating lupus nephritis. However, since the study population consists exclusively of Asian patients, further research is needed to verify the efficacy of multitarget therapy in lupus nephritis patients of non-Asian descent.

ARTICLE HISTORY
Received 20 June 2024
Revised 15 August 2024
Accepted 18 August 2024

KEYWORDS
Biologics; multitarget therapy; lupus nephritis; network meta-analysis

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic diffuse connective tissue disease of unclear etiology that can affect multiple systems throughout the body. Patients with SLE produce numerous autoantibodies, leading to immune system attacks on their own tissues, resulting in damage to multiple organs and tissues throughout the body [1–3]. Renal lesions are found *via* renal biopsy in up to 90% of SLE patients, and approximately 50% of them exhibit clinical manifestations of renal damage [4–6]. Lupus nephritis (LN) is a crucial factor contributing to renal failure and mortality in SLE patients, with approximately 5–30% of patients developing end-stage renal disease within a decade after LN diagnosis [7–9].

The current standard induction therapies for LN are primarily mycophenolate mofetil (MMF) or cyclophosphamide (CYC) in combination with glucocorticoids (GCs) [10, 11]. However, these regimens have limited efficacy in achieving complete renal remission of LN and increasing the incidence of adverse events [12]. Hence, there is an urgent need for more effective and safer therapies for patients with LN. In recent years, as the pathogenesis of LN has been intensively studied, an increasing number of targeted biologics [13–15], including rituximab, belimumab, obinutuzumab, anifrolumab, voclosporin, and baricitinib, have been developed. However, due to the absence of direct head-to-head comparisons, clinicians face challenges in assessing the relative safety and efficacy of these treatment options, making it difficult for them to make well-informed decisions. Consequently, biologics are frequently employed as alternative therapies following the failure of conventional treatments.

Although previous studies have used network meta-analyses to compare the safety and efficacy of different immunosuppressive agents [16, 17], the results of these previous meta-analyses have either included low-quality literature or excluded new biologics and treatment regimens.

CONTACT Zhen-Qiong Li drlizhenqiong@163.com Department of Nephrology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Supplemental data for this article can be accessed online at https://doi.org/10.1080/0886022X.2024.2395451.

Hence, there is a compelling necessity to update and expand these studies through network meta-analyses that combine direct and indirect evidence to provide clinicians with current references for treating lupus nephritis. The main aim of this research was to conduct a network meta-analysis comparing the safety and efficacy of biologics, multitargeted therapy, and conventional therapy for lupus nephritis.

2. Methods

2.1. Search strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extended Statement for Network Meta-Analyses [18, 19], this network meta-analysis conducted an extensive systematic search of electronic databases, including EMBASE, Web of Science, PubMed, and the Cochrane Library, from their respective inception dates until 30 August 2023. The search encompassed conference records and reference lists. Additionally, clinicaltrials.gov was searched for supplementary data from recently completed trials or potentially eligible randomized controlled trials. There were no restrictions on publication language or status. Our study was recorded in the PROSPERO registry (CRD42023445632). The search terms used were "lupus nephritis", "LN", "biologics", "rituximab", "belimumab", "obinutuzumab", "anifrolumab", "voclosporin", "baricitinib", "multitarget therapy", "mycophenolate mofetil", "cyclophosphamide", and "tacrolimus". Detailed information on the PubMed search strategy can be found in Supplement 1.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients with lupus nephritis who were adults (≥18 years old); (2) patients who received either biologics plus standard therapy or multitarget therapy, while the control group received placebo plus standard therapy or standard therapy alone; (3) Outcome measures: efficacy metrics in this study included the complete renal remission rate (CRR) and the total renal remission rate (TRR), where the TRR was defined as the aggregate of the CRR and the partial renal remission rate (PRR). The typical definition of CRR is a reduction in proteinuria to 0.5 grams per day, accompanied by an improvement in renal function. PRR, varying by study, generally indicates a proteinuria decrease not meeting CRR criteria yet showing some improvement, such as reduced urinary protein and/or stable kidney function.

Safety metrics included the incidence of serious adverse events (SAE), serious infections, and all-cause mortality. Serious adverse events refer to events during clinical trials necessitating hospitalization, prolonging hospital stays, causing disability, impairing workability, posing life-threatening risks, or resulting in death. Serious infection incidence involves the frequency of severe infection events such as sepsis, pneumonia, cellulitis, etc., requiring medical intervention and significantly impacting patient health during clinical trials. (4) Study type: Only RCTs were included.

The exclusion criteria included retrospective studies, animal studies, systematic reviews, case reports, studies with incomplete or duplicated data, and studies without relevant outcome indicators. Furthermore, we excluded several RCTs that were terminated prematurely due to failure to meet the primary endpoint or because they exhibited unacceptable drug toxicity.

2.3. Data extraction and quality assessment

The literature was screened by two researchers according to the exclusion and inclusion criteria. The researchers excluded literature by reading abstracts and full texts and finally cross-checked both the statistical results and the extracted data. The following data were independently collected by both investigators: the first author's surname, year of publication, study design, age, sample size, male/female ratio, type of renal biopsy, duration of follow-up, therapeutic agents (interventional and comparative agents), and outcome indicators. Disagreements were resolved through discussion or inquiry involving a third reviewer.

The quality of the included studies was assessed using the Cochrane Library's recommended risk of bias evaluation tool based on the quality assessment standards [20]. This tool mainly included random sequence generation, allocation concealment, blinding, completeness of outcome data, and selective reporting of results and other biases. Two investigators strictly assessed the included literature according to the criteria and assigned each entry as "low risk," "high risk," or "unknown risk".

2.4. Statistical analysis

The network meta-analysis (NMA) using the random effects model of Stata software (version 15.0) was based on the frequentist theoretical framework [21], which summarized the results of each study [22]. Evidence from randomized controlled trials, encompassing both direct and indirect comparisons, was synthesized. Direct evidence involved head-to-head assessments of two interventions, while indirect evidence arose from comparisons of each intervention to a standard comparator [23]. Considering the heterogeneity that might be influenced by clinical or trial design, the analysis utilized a random effects model.

The dichotomous variables are expressed as odds ratios (ORs) and are presented along with their corresponding 95% confidence intervals (CIs). To assess and rank the effectiveness of various interventions, this study applied the surface under the cumulative ranking curve (SUCRA) method. A higher SUCRA value indicates a more advantageous position in the efficacy ranking. The K-means clustering method is used to group interventions according to their similarity in safety and effectiveness [24]. With different colors representing different groups of interventions, the mean SUCRA values

of the effectiveness indicators and safety indicators were plotted on a coordinate system.

Inconsistency, which measures the degree of inconsistency between direct and indirect evidence, is an essential component of network meta-analyses [25]. Conduct node-splitting analysis and loop inconsistency detection to assess the degree of inconsistency. Utilize tau^2 values and the Chi-squared test to evaluate heterogeneity among studies in the network meta-analysis. Conduct sensitivity analysis to assess the robustness of the results. Employ funnel plots and the Egger test to evaluate publication bias and small-study effects.

3. Results

3.1. Description of included studies

Initially, 4718 studies were considered for this review. After removing 2647 duplicates and reviewing the titles, keywords, and abstracts, 52 articles were selected for full-text evaluation. Out of these, 42 articles did not meet the criteria and were excluded, resulting in a final selection of 10 randomized controlled trials (RCTs) [26–35]. These RCTs included eight two-armed trials and two three-armed trials, one of which was a conference abstract. The study population comprised 1989 patients, with nine studies being multicenter trials and one being a single-center trial. The majority of the patients were female, and the follow-up duration ranged from 24 to 104 weeks. An overview of the literature search and screening process is presented in Figure 1, while the baseline characteristics of the studies are presented in Table 1. All RCTs employed randomization techniques and adequately described the randomization process. Most of the included RCTs provided details regarding the concealment of the allocation sequence, and reporting bias was effectively addressed. The risk of bias assessment for the included studies was summarized in Figure 2.

3.2. Efficacy

3.2.1. Complete renal remission rate (CRR)

Of the included studies, nine involving 1914 patients described the outcomes of CRR and included a total of ten interventions. The network evidence map is presented in Figure 3A. Node-splitting analysis and loop inconsistency detection were utilized to evaluate network inconsistency between direct and indirect comparison results. The results indicated no inconsistency ($p > 0.05$). For detailed results, refer to supplementary Tables 1 and 2. Thus, we conducted a network meta-analysis based on the consistency model. The results of the NMA indicated that, compared to standard

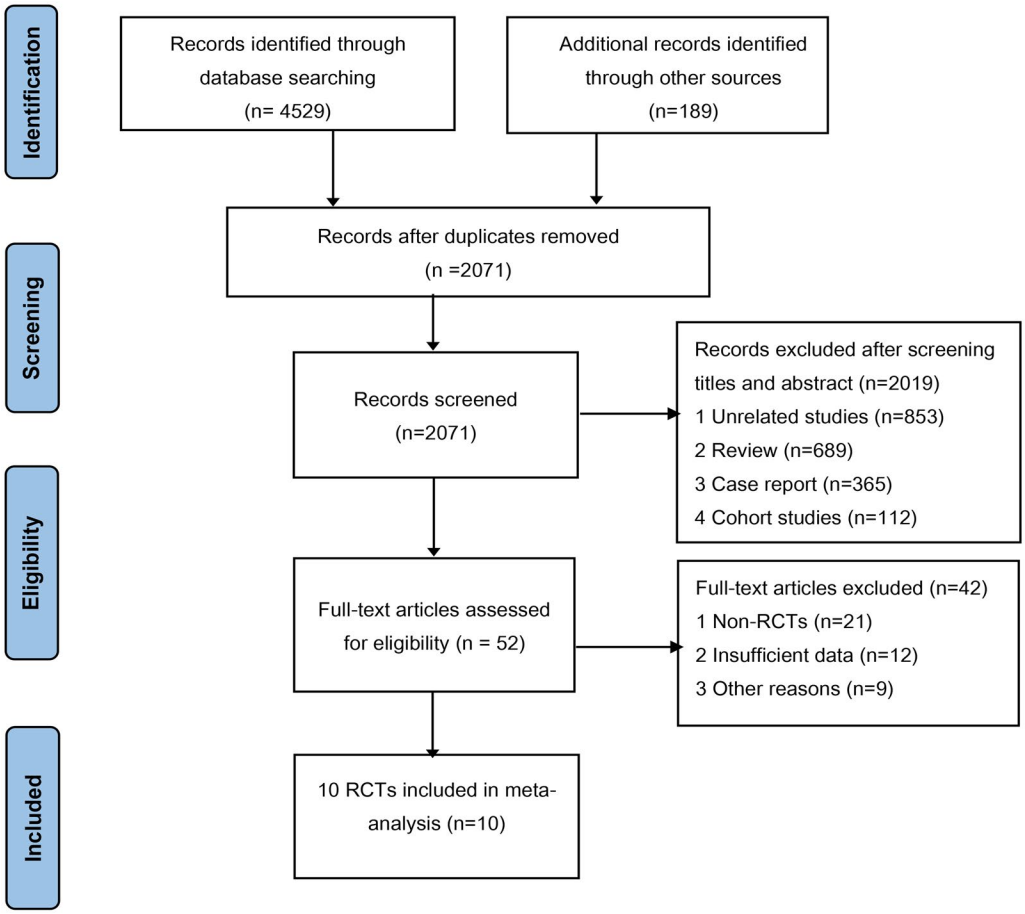

Figure 1. Flowchart of study search and selection.

Table 1. Baseline characteristics of included studies.

Study	Trial registration	Study design	biopsy class	Total number	Interventions	Age (years)	Patients (n)	Female (n)	Follow-up period	Outcomes
Rovin 2012	NCT00282347	multicenter RCT	III、IV、V	144	Rituximab + SOC	31.8 ± 9.6	72	63	78 weeks	CRR, TRR, SAE, Infection, ACM
					SOC	29.4 ± 9.3	72	67		
Furie 2020	NCT01639339	multicenter RCT	III、IV、V	446	belimumab + SOC	33.7 ± 10.7	223	197	104 weeks	CRR, TRR, SAE, Infection, ACM
					SOC	33.1 ± 10.6	223	196		
Yemil 2021	NCT02260934	multicenter RCT	III、IV、V	43	Rituximab + belimumab + SOC	34.5 ± 9.14	21	19	96 weeks	CRR, TRR
					Rituximab + SOC	32.3 ± 11.43	22	18		
Jayne 2021	NCT02547922	multicenter RCT	III、IV、V	147	Anifrolumab (BR, 300 mg)+SOC	34.0 (19, 67)	45	37	52 weeks	CRR, SAE, Infection, ACM
					Anifrolumab(IR, 900 mg ×3, 300 mg) +SOC	35.0 (18, 65)	51	45		
					SOC	32.0 (18, 58)	49	38		
Furie 2022	NCT02550652	multicenter RCT	III、IV、V	125	obinutuzumab + SOC	33.1 ± 9.8	63	55	104 weeks	CRR, TRR, SAE, Infection, ACM
					SOC	31.9 ± 10.1	62	51		
Liu 2015	NCT00876616	multicenter RCT	III、IV、V	362	multitarget therapy	30.3 (23.3, 38.6)	181	168	24 weeks	CRR, TRR, SAE, ACM
					SOC	33.6 (24.2, 41.5)	181	161		
Bao 2008	NCT00298506	Single-center RCT	IV、V	40	multitarget therapy	27.2 ± 7.1	20	16	36 weeks	CRR, TRR , ACM
					SOC	30.6 ± 4.6	20	18		
Rovin 2019	NCT02141672	multicenter RCT	III、IV、V	265	Voclosporin(23.7 mg) + SOC	31.4 (11.8)	89	76	48 weeks	CRR, SAE, Infection
					Voclosporin(39.5 mg) + SOC	30.6 (9.6)	88	81		
					SOC	33.1 (10.0)	88	73		
Rovin 2021	NCT03021499	multicenter RCT	III、IV、V	357	Voclosporin(23.7 mg) + SOC	31	179	161	52 weeks	CRR, TRR, SAE, Infection, ACM
					SOC	32	178	152		
Hassanien 2023	NCT05432531	multicenter RCT	III、IV	60	Baricitinib 4 mg	32.4	30	30	24 weeks	TRR, SAE, ACM
					SOC	32.4	30	30		

RCT: randomized controlled trial; SOC: standard of care; CRR: complete renal response; TRR: total renal response; SAE: serious adverse event; Infection: serious infection adverse event; ACM: all-cause mortality.

therapy, multitarget therapy, voclosporin (23.7 mg), obinutuzumab, voclosporin (39.5 mg), and belimumab had statistically significant odds ratios (ORs) and 95% confidence intervals (CIs) of 2.78 (1.81, 4.26), 2.61 (1.79, 3.79), 2.41 (1.11, 5.25), 1.90 (1.07, 3.37), and 1.75 (1.13, 2.70), respectively. These findings suggest a greater complete renal remission rate in these patients than in those receiving standard therapy (Figure 4A). The SUCRA-based ranking revealed that multitargeted therapy achieved the highest ranking, followed by voclosporin (23.7 mg), obinutuzumab, voclosporin (39.5 mg), anifrolumab (900 mg), belimumab, rituximab + belimumab, standard therapy, rituximab, and anifrolumab (300 mg) (Figure 5A and Table 2). A forest plot depicting the two-by-two comparison for CRR is presented in Figure 6.

In this analysis, the funnel plot exhibited asymmetry, suggesting the potential presence of publication bias or small-study effects in the meta-analysis. After excluding the small-study research [27], the funnel plot was redrawn, and no significant asymmetry was observed in the adjusted plot (Figure 7).

3.2.2. Total renal remission rate (TRR)

The literature included eight studies with a total of 1577 patients who described the outcomes of TRRs and included eight interventions. Figure 3B shows the network evidence map. As there were no closed loops generated between the interventions, no inconsistency tests were needed. The NMA was conducted using a consistency model. NMA revealed that compared with standard therapy, multitargeted therapy, baricitinib, obinutuzumab, voclosporin, and belimumab had greater total renal remission rates, with odds ratios (ORs) of 3.20 (95% CI: 1.98, 5.19), 3.29 (95% CI: 1.08, 9.95), 2.87 (95% CI: 1.37, 6.00), 2.16 (95% CI: 1.40, 3.34), and 1.56 (95% CI: 1.07, 2.27), respectively (Figure 4B). The SUCRA rankings for the eight interventions for TRRs were as follows: multitarget therapy > baricitinib > obinutuzumab > rituximab + belimumab > voclosporin 23.7 mg > rituximab > belimumab > standard therapy. (Figure 5B, Table 2).

3.3. Safety

3.3.1. Incidence of serious adverse events (SAE)

Eight studies involving 1904 patients reported outcomes of serious adverse events (SAEs) and included a total of ten interventions. The network evidence map is presented in Figure 3C. The inconsistencies between the direct and indirect comparisons were assessed using node split analyses, and no inconsistencies were found ($p > 0.05$) (see Supplementary Table 3).

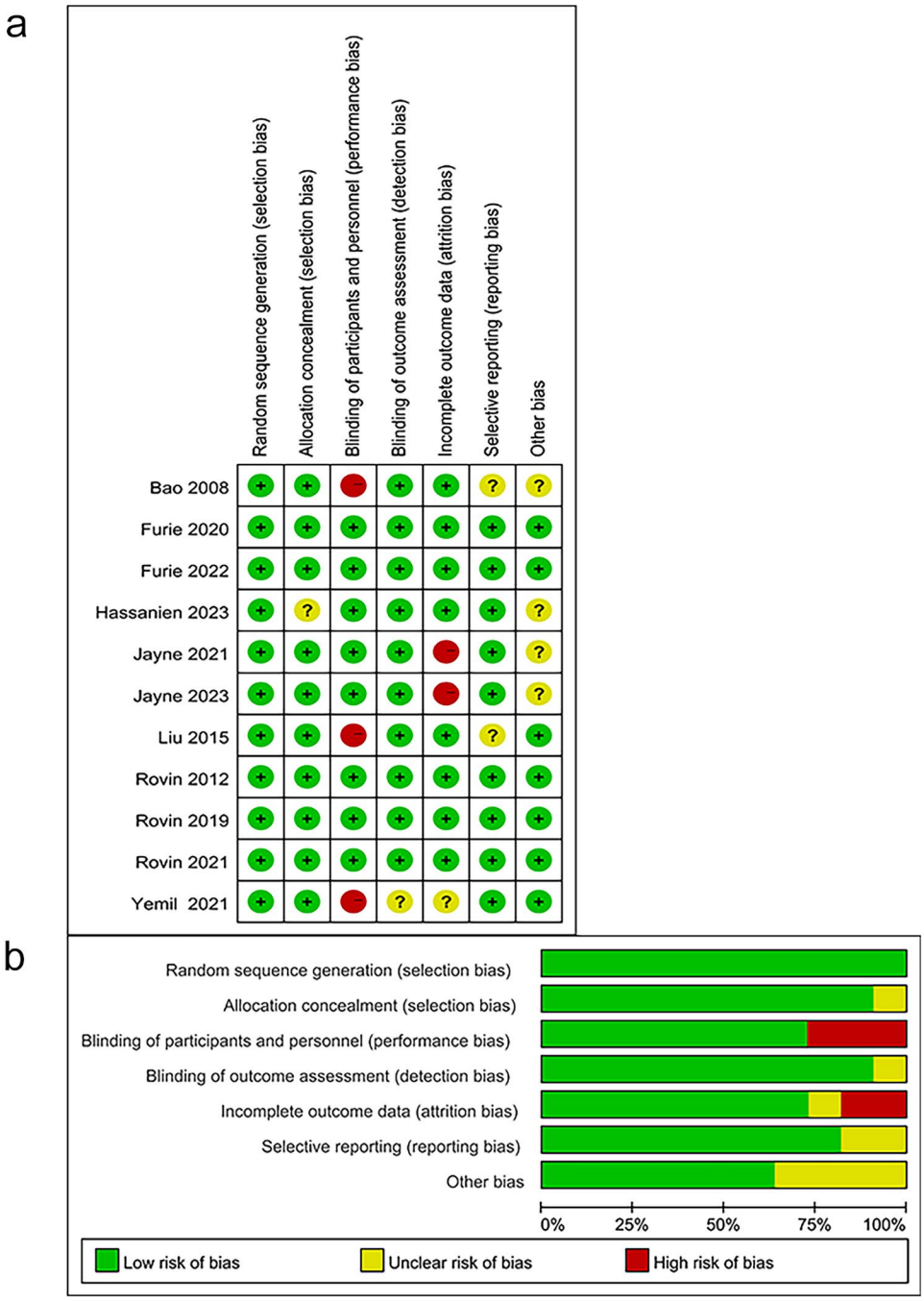

Figure 2. Risk of bias graph and summary of the included studies (a) reviewers' judgments about each risk of bias item for eligible studies and (b) the judgments about each risk of bias item presented as percentages across all eligible studies.

Hence, we conducted a network meta-analysis using a consistency model. According to the NMA results, none of the ten treatment regimens had statistically significant differences (Figure 4C). Based on the SUCRA-based ranked probabilities, rituximab was considered to be the safest treatment due to it having the lowest rate of serious events. The rank results, in order, were rituximab > belimumab > obinutuzumab > standard therapy > anifrolumab 900 mg > voclosporin 23.7 mg > voclosporin 39.5 mg > anifrolumab 300 mg > baricitinib > multitargeted therapy (Figure 5C, Table 2). Compared to standard treatment, the odds ratios (OR) and 95% confidence intervals (CI) for the top three treatments are 0.74 (0.25–2.21), 0.82 (0.32–2.11), and 0.83 (0.26–2.66).

3.3.2. Incidence of serious infections (infection)

Six studies involving 1469 patients reported serious infections, comprising a total of eight interventions. Pairwise comparisons revealed no statistically significant difference in the incidence of serious infections among the eight interventions (Figure 4D). Based on the SUCRA rankings, the following interventions had the highest likelihood of being the most effective at preventing serious infections: anifrolumab 900 mg > anifrolumab

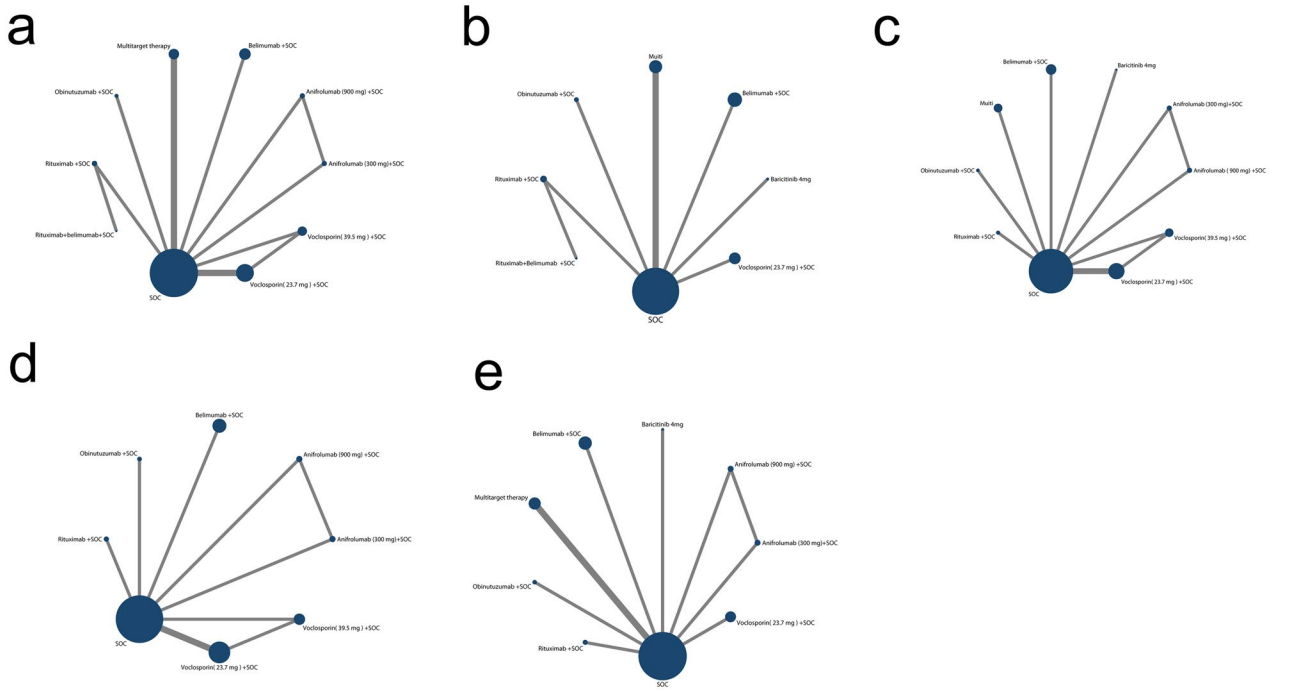

Figure 3. Network analysis of eligible comparison for (a) complete renal remission rate, (b) total renal remission rate, (c) incidence of serious adverse events, (d) incidence of serious infections, and (e) all-cause mortality. The size of each node represents the number of participants, while the thickness of the line represents the number of studies directly comparing the two interventions. *SOC*: standard of care.

300 mg > obinutuzumab > belimumab > rituximab > standard therapy > voclosporin 23.7 mg > voclosporin 39.5 mg (Figure 5D, Table 2). Compared to standard treatment, the odds ratios (OR) and 95% confidence intervals (CI) for the top three treatments are 0.24 (0.03–2.22), 0.24 (0.03–2.28), and 0.40 (0.13–1.23).

3.3.3. All-cause mortality (ACM)

All-cause mortality data from eight studies encompassing 1666 patients were included for nine interventions. The NMA results indicated no statistically significant difference in all-cause mortality among the nine interventions (Figure 4E). The SUCRA rankings of the nine interventions for all-cause mortality were as follows: voclosporin 23.7 mg > obinutuzumab > baricitinib > multitargeted therapy > anifrolumab 300 mg > anifrolumab 900 mg > standard therapy > belimumab > rituximab (Figure 5E, Table 2). Compared to standard treatment, the odds ratios (OR) and 95% confidence intervals (CI) for the top three treatments are 0.19 (0.02–1.68), 0.23 (0.03–2.15), and 1.00 (0.02–52.04).

3.4. Cluster analysis

The 9 interventions were grouped into four categories after applying SUCRA for cluster analysis. One group was composed of anifrolumab 300 mg, the other group consisted of multitargeted therapy, the third group included rituximab and standard therapy, and the fourth group included belimumab, obinutuzumab, anifrolumab 900 mg, voclosporin 23.7 mg, and voclosporin 39.5 mg. The graph indicates that obinutuzumab and belimumab exhibit higher rates of complete renal remission and a lower incidence of severe adverse events, suggesting their superior safety and effectiveness. Figure 8 displays the results of the cluster analysis.

3.5. Subgroup analysis

Taking into account the varying lengths of follow-up, a subgroup analysis was conducted on the biological agents (belimumab, obinutuzumab, and voclosporin) within the network meta-analysis, indicating their superior therapeutic effects over traditional standard therapy. These findings show that the complete renal response rate for these biological agents is higher than that of standard therapy, regardless of the follow-up duration. Furthermore, regarding safety, no significant statistical difference was found between the two types of treatment, consistent with the network meta-analysis results. The detailed results of the subgroup analysis are presented in Figures 9 and 10.

3.6. Heterogeneity and sensitivity analysis

We calculated the tau^2 value for each comparison to evaluate heterogeneity across studies. Tau^2 quantifies heterogeneity in random-effects models, with higher values indicating greater heterogeneity. Detailed results are presented in Supplementary Table 3. To further assess heterogeneity, we conducted a Chi-squared test and created a pairwise comparison forest plot, as illustrated in Supplementary Figure 1. The Chi-squared test, with a *p*-value of 0.8286, showed that heterogeneity among the pairwise comparisons was not statistically significant. Despite observing some heterogeneity, our network meta-analysis results remain robust. Sensitivity analysis

a

Multi									
1.07 (0.60,1.88)	VOC23.7mg								
1.15 (0.47,2.80)	1.08 (0.46,2.57)	OBI							
1.46 (0.72,3.00)	1.37 (0.79,2.39)	1.27 (0.48,3.34)	VOC39.5mg						
1.51 (0.57,3.96)	1.41 (0.55,3.63)	1.31 (0.41,4.18)	1.03 (0.36,2.91)	ANI900					
1.59 (0.86,2.93)	1.49 (0.84,2.65)	1.38 (0.56,3.37)	1.09 (0.53,2.24)	1.06 (0.40,2.79)	BEL				
2.59 (0.57,11.75)	2.43 (0.54,10.86)	2.24 (0.43,11.64)	1.77 (0.37,8.41)	1.72 (0.32,9.31)	1.63 (0.36,7.40)	RTX+BEL			
2.78 (1.81,4.26)	2.61 (1.79,3.79)	2.41 (1.11,5.25)	1.90 (1.07,3.37)	1.85 (0.78,4.39)	1.75 (1.13,2.70)	1.07 (0.25,4.59)	SOC		
3.41 (1.47,7.92)	3.20 (1.41,7.24)	2.96 (1.02,8.57)	2.33 (0.92,5.88)	2.26 (0.73,7.01)	2.14 (0.92,5.00)	1.32 (0.38,4.64)	1.23 (0.59,2.54)	RTX	
6.46 (2.12,19.62)	6.05 (2.03,18.05)	5.60 (1.54,20.29)	4.41 (1.36,14.29)	4.29 (1.57,11.69)	4.06 (1.33,12.38)	2.50 (0.42,14.76)	2.32 (0.83,6.48)	1.89 (0.54,6.65)	ANI300

b

Multi							
0.98 (0.29,3.27)	BAR						
1.12 (0.46,2.70)	1.15 (0.30,4.34)	OBI					
1.29 (0.30,5.54)	1.32 (0.23,7.73)	1.15 (0.24,5.49)	RTX+BEL				
1.48 (0.77,2.83)	1.52 (0.46,4.99)	1.32 (0.56,3.12)	1.15 (0.27,4.85)	VOC23.7mg			
2.05 (0.91,4.64)	2.10 (0.58,7.63)	1.83 (0.68,4.93)	1.59 (0.48,5.31)	1.38 (0.63,3.04)	RTX		
2.06 (1.11,3.80)	2.11 (0.65,6.80)	1.84 (0.80,4.22)	1.59 (0.38,6.63)	1.39 (0.78,2.47)	1.00 (0.47,2.14)	BEL	
3.20 (1.98,5.19)	3.29 (1.08,9.95)	2.87 (1.37,6.00)	2.48 (0.63,9.81)	2.16 (1.40,3.34)	1.56 (0.81,3.02)	1.56 (1.07,2.27)	SOC

c

RTX									
0.91 (0.21,3.84)	BEL								
0.89 (0.18,4.38)	0.98 (0.22,4.40)	OBI							
0.74 (0.25,2.21)	0.82 (0.32,2.11)	0.83 (0.26,2.66)	SOC						
0.68 (0.12,3.82)	0.75 (0.14,3.87)	0.76 (0.13,4.49)	0.91 (0.24,3.51)	ANI900					
0.55 (0.15,2.08)	0.61 (0.18,2.05)	0.62 (0.16,2.48)	0.74 (0.35,1.59)	0.82 (0.17,3.84)	VOC23.7mg				
0.53 (0.12,2.41)	0.59 (0.14,2.40)	0.60 (0.13,2.85)	0.72 (0.25,2.04)	0.79 (0.14,4.34)	0.96 (0.35,2.65)	VOC39.5mg			
0.51 (0.09,2.85)	0.56 (0.11,2.88)	0.57 (0.10,3.35)	0.68 (0.18,2.61)	0.75 (0.20,2.80)	0.92 (0.20,4.27)	0.95 (0.17,5.20)	ANI300		
0.36 (0.02,6.00)	0.40 (0.02,6.29)	0.40 (0.02,6.93)	0.48 (0.04,6.50)	0.53 (0.03,9.92)	0.65 (0.04,9.72)	0.67 (0.04,11.08)	0.71 (0.04,13.17)	BAR	
0.27 (0.05,1.55)	0.30 (0.06,1.57)	0.31 (0.05,1.82)	0.37 (0.09,1.42)	0.40 (0.06,2.73)	0.49 (0.10,2.33)	0.51 (0.09,2.83)	0.54 (0.08,3.61)	0.76 (0.04,14.26)	Multi

d

ANI900								
0.98 (0.06,16.13)	ANI300							
0.60 (0.05,7.26)	0.61 (0.05,7.43)	OBI						
0.30 (0.03,2.92)	0.30 (0.03,2.99)	0.50 (0.15,1.70)	BEL					
0.24 (0.02,2.58)	0.24 (0.02,2.64)	0.40 (0.10,1.61)	0.80 (0.31,2.10)	RTX				
0.24 (0.03,2.22)	0.24 (0.03,2.28)	0.40 (0.13,1.23)	0.80 (0.49,1.31)	1.00 (0.44,2.28)	SOC			
0.22 (0.02,2.22)	0.23 (0.02,2.28)	0.37 (0.11,1.31)	0.75 (0.36,1.58)	0.93 (0.34,2.53)	0.93 (0.53,1.63)	VOC23.7mg		
0.17 (0.02,1.83)	0.17 (0.02,1.88)	0.28 (0.07,1.15)	0.57 (0.21,1.51)	0.70 (0.22,2.30)	0.70 (0.30,1.65)	0.75 (0.33,1.70)	VOC39.5mg	

e

VOC23.7mg								
0.83 (0.04,18.37)	OBI							
0.19 (0.00,17.54)	0.23 (0.00,21.76)	BAR						
0.19 (0.01,6.61)	0.23 (0.01,8.27)	1.00 (0.01,126.19)	Multi					
0.19 (0.00,16.62)	0.22 (0.00,20.62)	0.96 (0.00,253.87)	0.96 (0.01,119.66)	ANI300				
0.19 (0.00,17.00)	0.23 (0.00,21.09)	0.98 (0.00,259.66)	0.98 (0.01,122.38)	1.02 (0.02,52.71)	ANI900			
0.19 (0.02,1.68)	0.23 (0.03,2.15)	1.00 (0.02,52.04)	1.00 (0.06,16.29)	1.05 (0.02,53.88)	1.02 (0.02,52.66)	SOC		
0.16 (0.01,1.90)	0.19 (0.02,2.42)	0.83 (0.01,51.61)	0.83 (0.04,17.31)	0.87 (0.01,53.46)	0.85 (0.01,52.25)	0.83 (0.25,2.76)	BEL	
0.04 (0.00,1.59)	0.05 (0.00,1.98)	0.19 (0.00,28.70)	0.19 (0.00,12.18)	0.20 (0.00,29.79)	0.20 (0.00,29.11)	0.19 (0.01,4.12)	0.23 (0.01,6.24)	RTX

Figure 4. League tables show the results of comparing the efficacy and safety of all drugs, including odds ratios (or) and 95% credible intervals in the network meta-analyses. (a–b) Efficacy: (a) complete renal remission rate, (b) total renal remission rate. (c–e) Safety: (c) incidence of serious adverse events, (d) incidence of serious infections, (e) all-cause mortality. *Multi*: multi-targeted therapy; *BEL*: belimumab; *OBI*: obinutuzumab; *RTX*: rituximab; *RTX + BEL:* rituximab + belimumab; *BAR*: baricitinib; *VOC23.7 mg*: voclosporin23.7 mg; *VOC39.5 mg*: voclosporin39.5 mg; *ANI300*: anifrolumab 300 mg; *ANI900*: anifrolumab 900 mg; *SOC*: standard of care.

confirmed this robustness, as the exclusion of any single study did not significantly alter the effect size estimates or confidence intervals (see Supplementary Figure 2).

4. Discussion

This network meta-analysis compared the relative efficacy and safety of biologics, multitargeted therapy, and standard therapy as induction treatments for LN. We conducted the analysis using a frequentist framework based on a random-effects model, which mitigates the bias associated with subjective prior choices and thus provides more objective results. Network meta-analysis (NMA) combines both direct and indirect evidence, offering a more comprehensive exploration of the relative effects of different treatment options compared to traditional meta-analysis. However, the reliance of NMA on indirect evidence may introduce bias, necessitating cautious interpretation of the results. Future head-to-head clinical trials will be crucial in validating these findings.

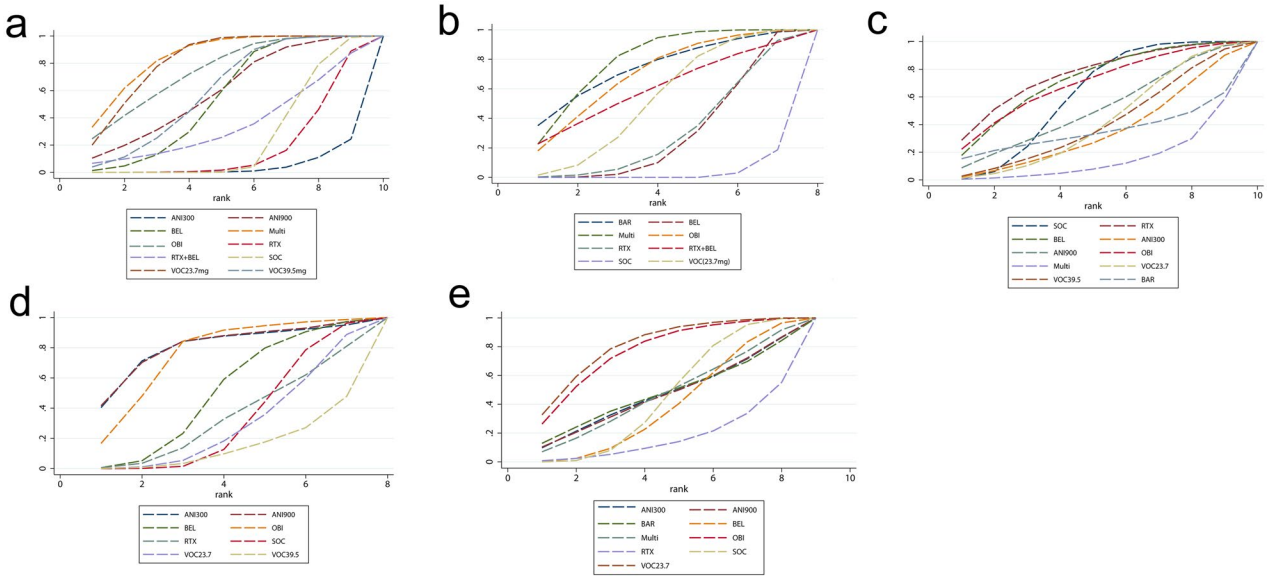

Figure 5. Cumulative ranking probability plots for (a) complete renal remission rate, (b) total renal remission rate, (c) incidence of serious adverse events, (d) incidence of serious infections, and (e) all-cause mortality. *Multi*: multi-targeted therapy; *BEL*: belimumab; *OBI*: obinutuzumab; *RTX*: rituximab; *RTX + BEL:* rituximab + belimumab; *BAR*: baricitinib; *VOC23.7 mg*: voclosporin23.7 mg; *VOC39.5 mg*: voclosporin39.5 mg; *ANI300*: anifrolumab 300 mg; *ANI900*: anifrolumab 900 mg; *SOC*: standard of care.

Table 2. Surface under the cumulative ranking curve (SUCRA) probabilities of eleven interventions.

Treatments	Complete remission	Total remission	Serious adverse events	Serious infections	All-cause mortality
Multi	85.3%	79.3%	17.6%	/	47.3%
VOC23.7	82.3%	53%	42.2%	29.8%	81%
OBI	74.7%	70.1%	68.1%	75.8%	77.3%
VOC39.5	60.6%	/	41.2%	15.1%	/
ANI900	59.6%	/	54.1%	80.4%	46.6%
BEL	55%	29.5%	69.3%	50.8%	39.7%
RTX + BEL	35.3%	60.1%	/	/	/
SOC	24.9%	3.1%	60.3%	33.3%	46%
RTX	17.7%	30.7%	73.2%	34.5%	17.8%
ANI300	4.5%	/	39.6%	80.1%	46.7%
BAR	/	74.2%	54.1%	/	47.6%

SOC: standard of care; Multi: multitargeted therapy; BEL: belimumab; OBI: obinutuzumab; RTX: rituximab; RTX + BEL: rituximab + belimumab; BAR: baricitinib; VOC23.7: voclosporin23.7 mg; VOC39.5: voclosporin39.5 mg; ANI300: anifrolumab 300 mg; ANI900: anifrolumab 900 mg.

In this study, we included two multi-arm randomized controlled trials involving three different interventions and decomposed the comparisons of each intervention group with the common control group into independent pairwise comparisons to ensure data consistency. The study findings revealed that multitargeted therapy, belimumab, obinutuzumab, and voclosporin are more effective than standard therapy in terms of CRR and TRR. Multitargeted therapy provided the most favorable treatment outcome. These findings align with those of a previous meta-analysis [16], which demonstrated that TAC combined with MMF and GC treatment had the highest total renal remission rate. Notably, since the studies included in multitarget therapy were all conducted among Chinese patients, it is imperative to conduct further studies to determine whether the positive outcomes of multitarget therapy can be replicated in LN patients from non-Asian populations. Furthermore, baricitinib demonstrated promising outcomes in patients with total renal remission (OR = 3.29, 95% CI = 1.08–9.95); nevertheless, additional clinical trials are necessary to establish the therapeutic efficacy of baricitinib in lupus nephritis patients, as data on the complete renal remission rate are lacking.

Regarding safety, we focused on the incidence of serious adverse events, serious infections, and all-cause mortality. Our study revealed no statistically significant differences between treatment regimens, which may be attributed to the limited number of included trials. Based on the ranking probabilities provided by the SUCRA, rituximab is considered the safest treatment for serious adverse events, as it has the lowest likelihood of such events occurring. For the incidence of serious infections, anifrolumab had the lowest likelihood. In terms of all-cause mortality, patients treated with voclosporin had the lowest risk of death. Although SUCRA values provide a quantitative approach to ranking, we acknowledge that all ranking methods carry some degree of uncertainty. This uncertainty may arise from factors including data quality, study design, heterogeneity among studies, and potential publication bias.

Moreover, we searched for extended studies related to the included RCTs to assess the long-term safety issues of

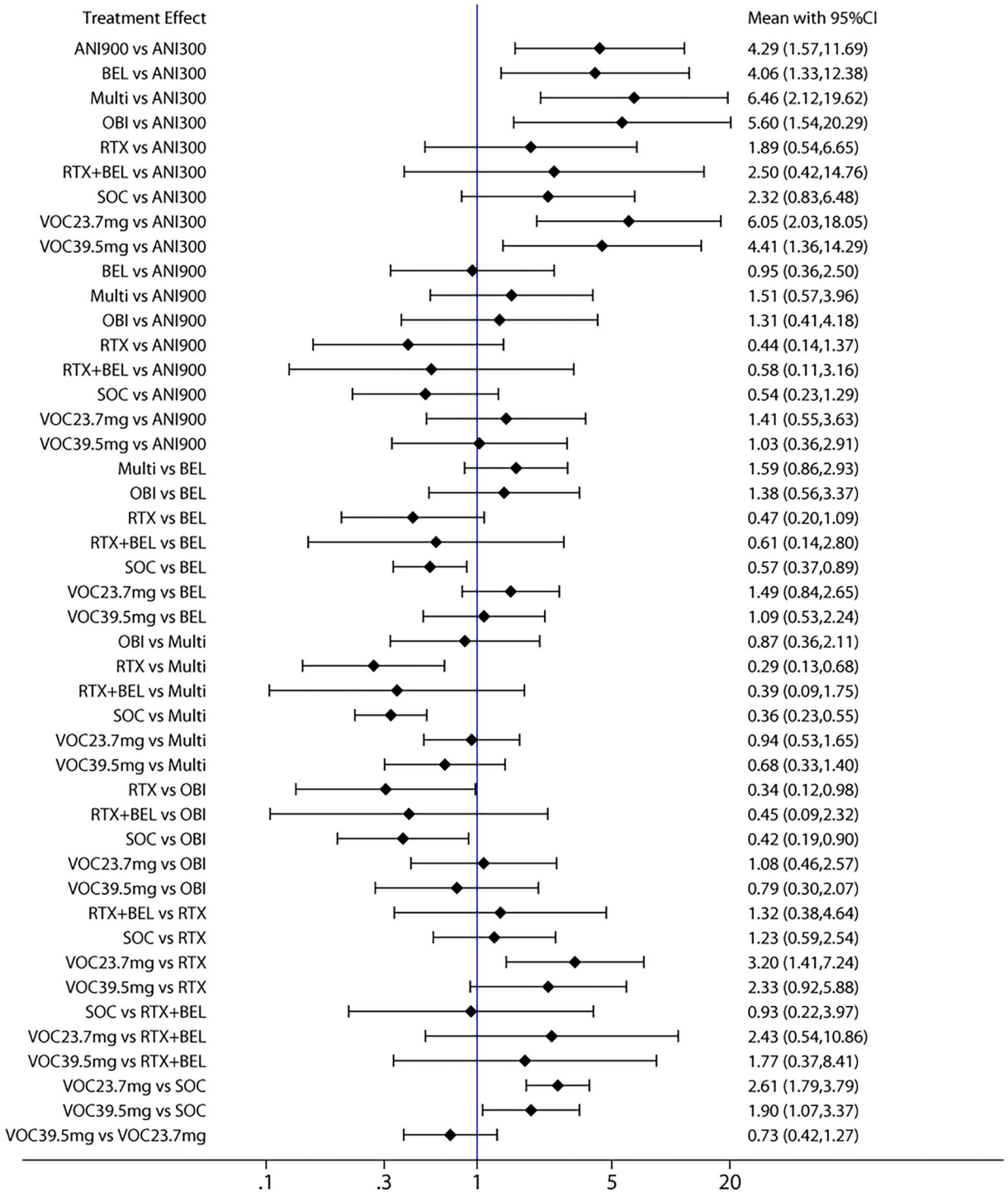

Figure 6. Forest Plot of comparison: relative efficacy of different drug treatments for complete remission in lupus nephritis. *Multi*: multi-targeted therapy; *BEL*: belimumab; *OBI*: obinutuzumab; *RTX*: rituximab; *RTX + BEL:* rituximab + belimumab; *BAR*: baricitinib; *VOC23.7 mg*: voclosporin23.7 mg; *VOC39.5 mg*: voclosporin39.5 mg; *ANI300*: anifrolumab 300 mg; *ANI900*: anifrolumab 900 mg; *SOC*: standard of care.

corresponding treatment measures. A long-term extension study [36] on multitarget therapy suggests that multitarget treatment demonstrates a lower renal relapse rate and fewer adverse events in the maintenance treatment of lupus nephritis, making it an effective and safe therapeutic option. Regarding the long-term safety of biological agents, extension studies related to RCTs for belimumab and anifrolumab both indicate that no new safety issues were found [37, 38]. However, the long-term safety of other biological agents (such as rituximab, obinutuzumab, and voclosporin) cannot be assessed due to the lack of relevant clinical studies.

Additionally, an assessment of the efficacy and safety of the different interventions was carried out using cluster analysis. The analysis showed that multitargeted therapy

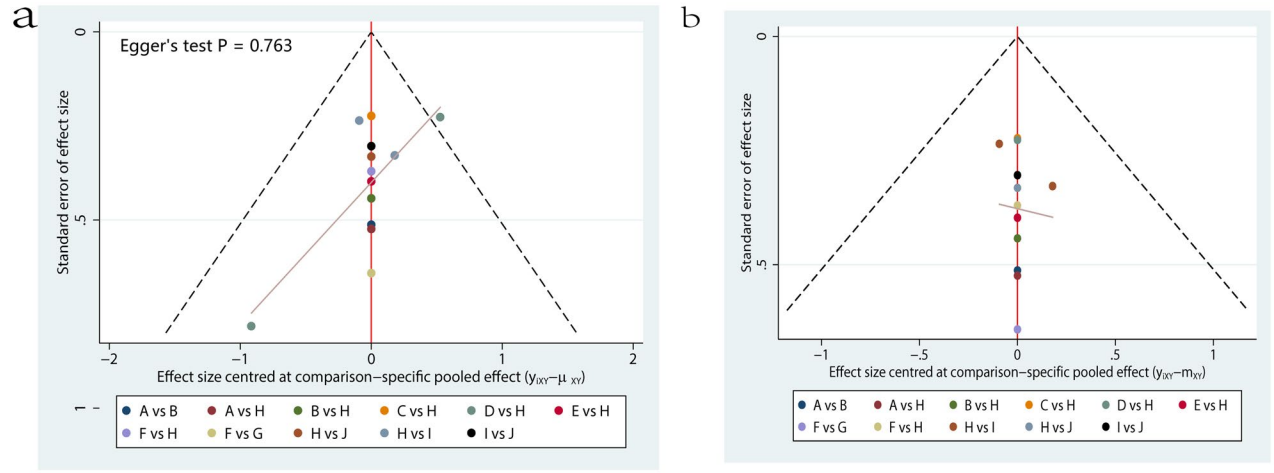

Figure 7. Funnel plot for the complete renal remission rate. A: anifrolumab 300 mg; B: anifrolumab 900 mg; C: belimumab; D: multi-targeted therapy; E: obinutuzumab; F: rituximab; G: rituximab + belimumab; H: standard of care; I: voclosporin23.7 mg; J: voclosporin39.5 mg.

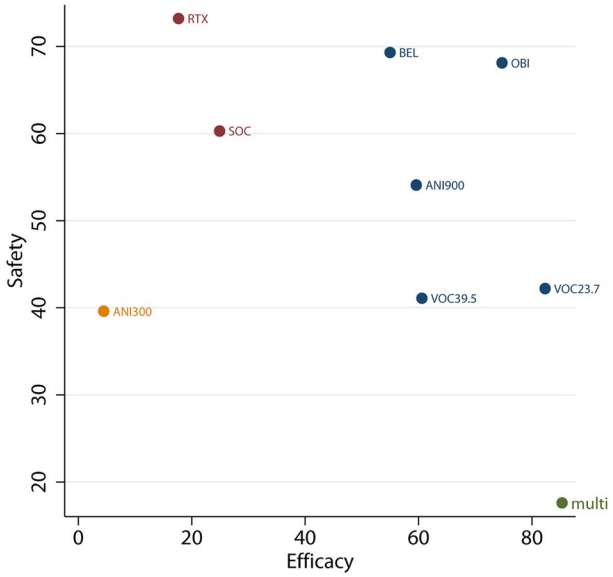

Figure 8. Cluster analysis ranking chart of the efficacy and safety of the nine interventions. The four colors represent the four clusters. x- and y-axes represent the efficacy and safety, respectively, the higher the value, the higher the efficacy or safety. *Multi*: multi-targeted therapy; *BEL*: belimumab; *OBI*: obinutuzumab; *RTX*: rituximab; *VOC23.7*: voclosporin23.7 mg; *VOC39.5*: voclosporin39.5 mg; *ANI300*: anifrolumab 300 mg; *ANI900*: anifrolumab 900 mg; *SOC*: standard of care.

demonstrated superior efficacy but had the highest incidence of serious adverse events compared to other therapies. In contrast, obinutuzumab and belimumab exhibited favorable efficacy and safety profiles. Belimumab is a monoclonal antibody that inhibits B lymphocyte-stimulating factors and effectively prevents B cells from producing autoantibodies, thereby suppressing autoimmune reactions [39]. As the first biological agent approved for active lupus nephritis, the efficacy of belimumab in treating LN has been confirmed in several trials [28, 40, 41]. A study demonstrated that compared with conventional therapy, belimumab can mitigate the progressive decline in the estimated glomerular filtration rate (eGFR) and reduce the incidence of kidney-related complications or mortality in LN patients. Compared with type I anti-CD20 antibodies, obinutuzumab,[42], a fully humanized type II monoclonal antibody targeting CD20, increases the affinity of FcγRIII for CD20, resulting in a more extensive depletion of B lymphocytes [43, 44]. The results of the NOBILITY study demonstrated that obinutuzumab aids in improving the clinical response in patients with LN without increasing the occurrence of serious adverse events [29]. Post hoc analysis of this study indicated that, compared to standard therapy, obinutuzumab can better preserve kidney function and prevent relapse of lupus nephritis [45]. The outcomes of the following phase III clinical trials (NCT04221477) are anticipated to offer more robust evidence supporting the use of obinutuzumab in the treatment of LN.

The 2024 KDIGO [46] Lupus Nephritis Guidelines and the EULAR [47] 2023 SLE Guidelines both highlight the importance of biologics that target B lymphocytes for treating lupus nephritis. For treating active lupus nephritis, the guidelines recommend the use of belimumab, which targets B-cell activating factor (BAFF), and voclosporin, a new-generation calmodulin phosphatase inhibitor. Moreover, for active type III/IV ± V lupus nephritis, especially in patients without severe impairment of renal function (eGFR >45 mL/min/1.73 m^2), multitargeted therapy (GCs + MMF + TAC) is recommended as the first-line induction therapy.

However, due to the various limitations of our study, our findings should be interpreted cautiously. Firstly, although the quality of the included studies is relatively high, the number of studies in our NMA is limited, with some interventions being represented by only one study. Additionally, many comparisons are indirect, which may affect the accuracy of the results. Secondly, due to limitations in data availability and the small number of included studies, we were unable to conduct detailed subgroup and meta-regression analyses to further investigate treatment responses across different patient groups. Thirdly, the results of this network meta-analysis may be influenced by heterogeneity in patient characteristics and follow-up times across the included

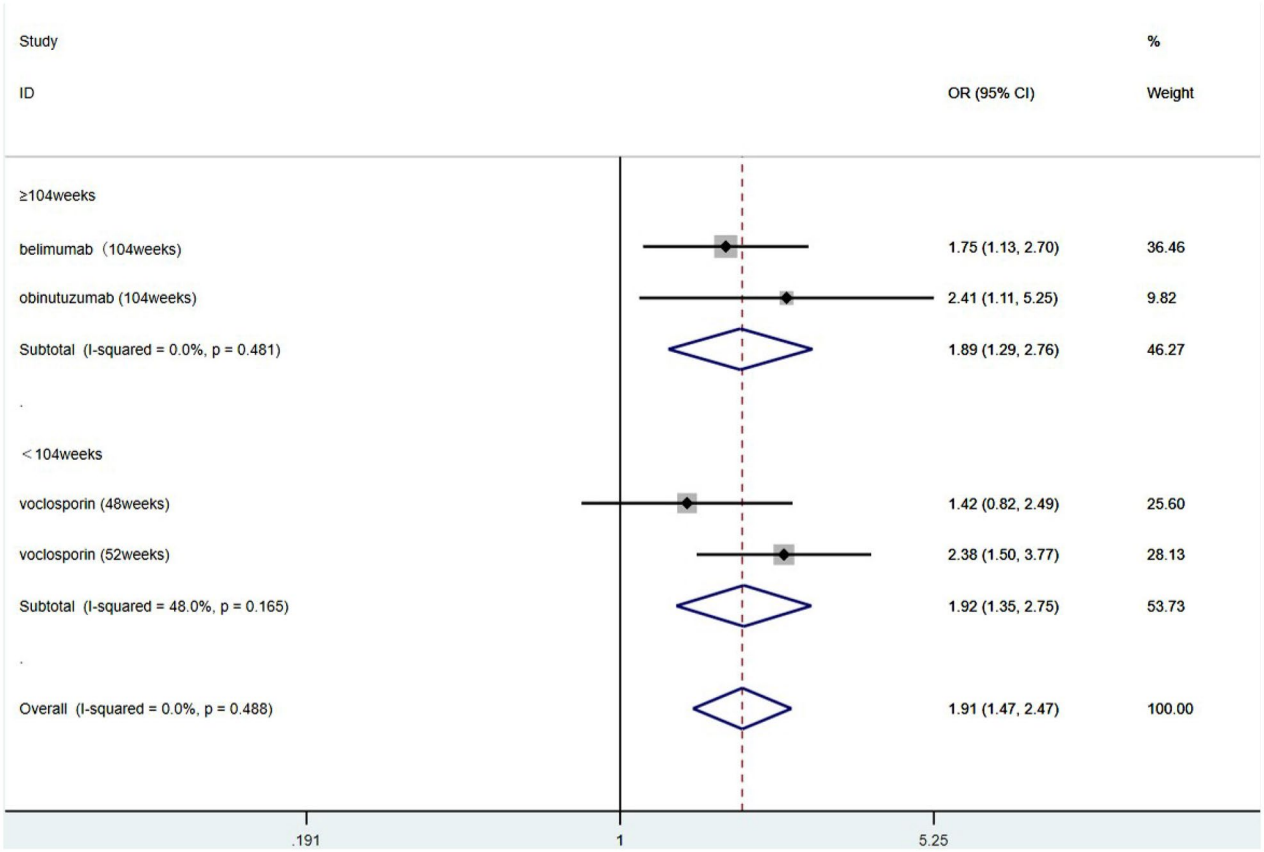

Figure 9. Comparing the complete renal remission rates of biologic therapy for lupus nephritis: a subgroup analysis at different follow-up periods.

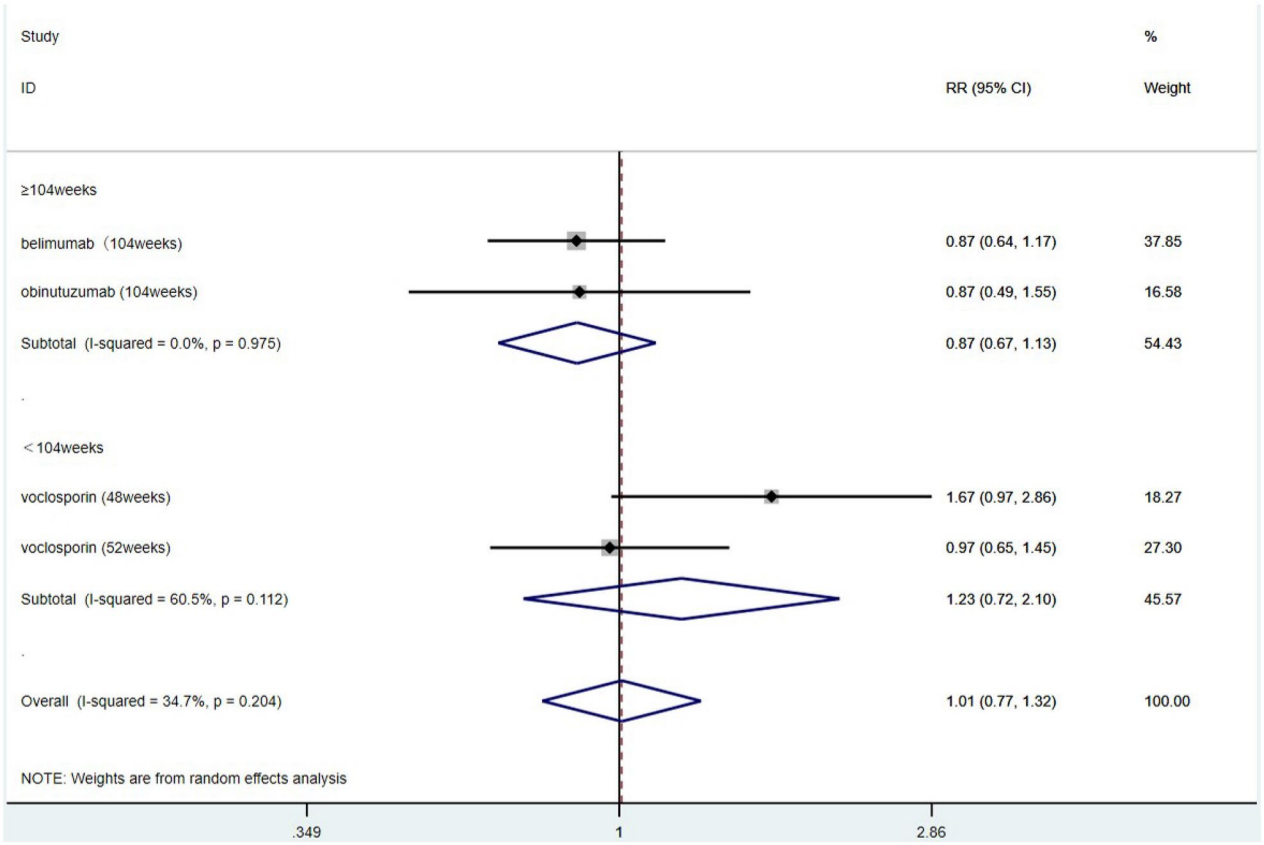

Figure 10. Comparing the incidence of serious adverse events of biologic therapy for lupus nephritis: a subgroup analysis at different follow-up periods.

studies, which could potentially affect the summary results. Moreover, for certain outcome measures, fewer than 9 studies were included, and no funnel plot was generated, which may have led to publication bias or potential events related to the small sample effects. Finally, some of the included studies did not cover all outcome measures, potentially leading to incomplete analysis results.

Nevertheless, our network meta-analysis has several advantages. First, all the included studies were randomized controlled trials, and the majority of the trials were multicenter large-scale clinical studies; these studies have high transparency and provide more genuine and robust research results. In addition, network meta-analysis combines all available information to compare multiple treatment options simultaneously when direct head-to-head comparisons are not feasible [48]. Unlike in individual studies, in this study, the statistical power was improved by summarizing the results of different analyses, thereby providing some reference for clinicians treating LN.

5. Conclusion

In conclusion, both obinutuzumab and belimumab exhibit good efficacy and safety profiles. Multitarget therapy provides the most effective treatment outcomes in terms of complete remission rates but has a high incidence of severe adverse events in terms of safety. Given that the multitarget therapy studies primarily involved Asian populations, our findings should be interpreted with caution. Future research should aim to provide more direct evidence to evaluate and compare the effectiveness and safety profiles of diverse biologics, multitarget therapy, and conventional therapy in the treatment of LN.

Authors' contributions

Gui-Qing Tian participated in the study's conception and design, data acquisition, data analysis and interpretation, and manuscript drafting. Zhen-Qiong Li contributed to the conception, data acquisition, and data analysis and critically revising the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

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