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SYSTEMATIC REVIEW

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Efficacy and safety of belimumab therapy in lupus nephritis: a systematic review and meta-analysis

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ABSTRACT

Background: Belimumab is the first biological agent approved for the treatment of systemic lupus erythematosus (SLE), but the efficacy of belimumab for lupus nephritis (LN) is not clear. We conducted this meta-analysis and systematic review to compare the efficacy and safety of belimumab with those of conventional therapy for LN.

Methods: PubMed, EMBASE, Cochrane Library, Clinical Trials.gov were searched in 31 December 2022 to identify relevant adult human studies reporting effectiveness outcomes of belimumab in patients with LN. Review manager (RevMan 5.4) was used for data analysis with fixed effects model based on heterogeneities.

Results: Six randomized controlled trials (RCTs) were included in the quantitative analysis. A total of 2960 participants were identified. Belimumab plus standard therapy significantly improved total renal response rates (RR, 1.31; 95% CI, 1.11–1.53; $p=0.001$) and complete renal RRs (1.47; 95% CI, 1.07–2.02; $p=0.02$) compared with the control plus standard therapy group. It significantly reduced the risk of renal flare (RR, 0.51; 95% CI, 0.37–0.69; $p<0.001$) and renal function worsening or progression to end-stage renal disease (ESRD) (RR, 0.56; 95% CI, 0.40–0.79; $p=0.001$). When assessed with the incidence of adverse events, no significant differences between the two groups were observed for the occurrence of treatment-related adverse events (RR, 1.04; 95% CI, 0.99–1.09; $p=0.12$).

Conclusions: This meta-analysis showed that belimumab plus standard therapy was more effective and had a favorable safety in patients with LN.

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KEYWORDS
Belimumab; lupus nephritis; systemic lupus erythematosus; meta-analysis

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem immune-mediated disorder of unknown cause that can affect almost every organ of the body. Lupus nephritis (LN) is a common cause of SLE-related incidence rate and mortality. Renal involvement occurs in 30 − 50% of SLE patients, and up to 30% of patients progress to end-stage renal disease (ESRD) and require kidney replacement therapy (KRT) within 10–15 years of diagnosis [1–4]. LN treatment involves glucocorticoid (GC) therapy with various immunosuppressive drugs, however, it is limited by its poor efficacy and multiple toxicity, and new treatments need to be explored. Because of the pathogenic role of autoreactive B cells in LN, it is an attractive therapeutic target. Belimumab, a recombinant monoclonal antibody, binds with soluble B cell activating factor (BAFF) to prevent BAFF from binding with its receptor to exert its biological activity, thus effectively inhibiting the abnormal proliferation of B cells [5].

Belimumab is the first biological drug approved for the treatment of active SLE despite standard of care (SoC) since 2011 [6,7]. However, there is still a paucity of research evidence in patients with active LN and belimumab has not been approved globally for the treatment of LN. Marlene Plüß et al. conducted a retrospective observational cohort study of LN patients and found that belimumab led to a decrease of proteinuria in patients with proteinuria of more

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than 1000 mg/g creatinine [8]. A systematic review based on observation studies involving LN patients treated with belimumab found an annual renal recurrence rate of only 1.7% and 70% of patients with baseline proteinuria quantification higher than 1 g achieved LN remission (remission criteria vary from study to study) [9]. Furthermore, a prospective observational study recently reported that belimumab treatment was associated with an increased frequency and/or shorter time to *de novo* LN (HR: 10.7; 95% CI, 1.7–67.9; $p = 0.012$) [10]. Brådland S et al. reported two cases of LN that developed in SLE patients without preexisting renal disease shortly after commencing treatment with belimumab [11].

However, the level of evidence from observational studies is limited and does not demonstrate definitive efficacy. BLISS-52/76 [12,13], which were randomized controlled trials (RCTs), excluded patients with severe LN. Post-hoc analysis of patients with renal involvement based on BLISS-52 and BLISS-76 data showed inconsistent results. The patients treated with belimumab showed a trend of improvement in renal recurrence, renal remission, renal disease improvement proteinuria, and other indicators after the 52nd week, but the difference was only statistically significant in the reduction of proteinuria [14]. BLISS-LN is the largest randomized controlled double-blind LN study conducted to date, which demonstrated superiority of addition of belimumab to SoC for active LN over SoC alone [15]. However, in patients with active LN who participated in this study, renal function was only mildly decreased.

Previous study suggested an overall promising effect of belimumab on renal outcomes [9], but the association between belimumab and the development of *de novo* LN and therapeutic efficacy has not yet been conclusively established [16–19]. The strength of evidence for these data is limited due to the inherent limitations of this study (e.g., *post hoc* analysis, small sample size, and systematic review). In this article, we conducted a meta-analysis to identify published RCTs on the efficacy and safety of belimumab in LN, so as to provide some clinical implications for the selection of treatment regimens for LN.

Methods

Search strategy and selection studies

We did our best to include all studies of RCT published until date, regarding the association between belimumab and LN. Eligible studies were found by searching the PubMed, EMBASE, Cochrane Library, Clinical Trials.gov database for relevant reports published between 01/01/2012 and 31/12/2022 (Additional search from 12/07/2022 to 31/12/2022); following terms including belimumab AND (LN OR SLE) were used for searching. The full search strategy is shown in Supplementary Tables 1–4. Furthermore, we searched the citation lists of the reviewed studies by hand to find more eligible studies. For studies with overlapping data published by the same author, we selected only the most recent or complete study, unless the publication was derived from another patient cohort. We conducted a comprehensive review of Supplementary materials to identify the data we needed.

Inclusion criteria

This study was performed by Cochrane Collaboration guidelines [20]. The literature we included must meet: (1) RCTs; (2) patients with SLE and renal damage or LN; (3) standard treatment of belimumab and the control group (cyclophosphamide, mycophenolate mofetil (MMF), azathioprine, or methotrexate); (3) the observables were evaluable efficacy and safety, where efficacy referred to renal parameters (complete response, total response including complete response and partial response), and safety referred to the incidence of adverse reactions, including infections and infestations that occurred during treatment.

Exclusion criteria

The following were exclusion criteria: (1) reviews, observational study, comments or case reports; (2) persons younger than 18 years or pregnant women; (3) clinical studies with poor reporting of patient characteristics or no available data reported. There was also no limitation on the form of publication. The retrieved studies were independently reviewed by two reviewers (HZ and JC), (Kappa = 0.688, Se = 0.091, $p < 0.001$). Discrepancies were discussed with other members (YZ) and resolved by consensus.

Statistical analysis

Review Manager software version 5.4 (Cochrane Collaboration, London, UK) was used for the meta-analysis. Dichotomous data were analyzed by using the risk ratio (RR) computed using the Mantel Haenszel method (fixed models). I-square (I^2) test was performed to assess the impact of study heterogeneity on the results of the meta-analysis. According to the Cochrane review guidelines, if severe heterogeneity was present at $I^2 > 50\%$, $p > 0.1$, the random effect models were chosen, otherwise the fixed effect models were used. Moreover, sensitivity analysis was conducted by deleting each study individually to evaluate the quality and consistency of the results. The data in this article are analyzed using a fixed effects model. Visual inspection of the funnel plot to assess publication bias. Statistical significance was set at a p value of 0.05.

Results

Study selection and characteristics

Our search extracted 3263 studies and abstracts (684 from PubMed, 2289 from Embase, 260 from Cochrane library, and 30 from Clinical Trials), of which 879 were duplicated to the studies and excluded. The 2153 studies were excluded

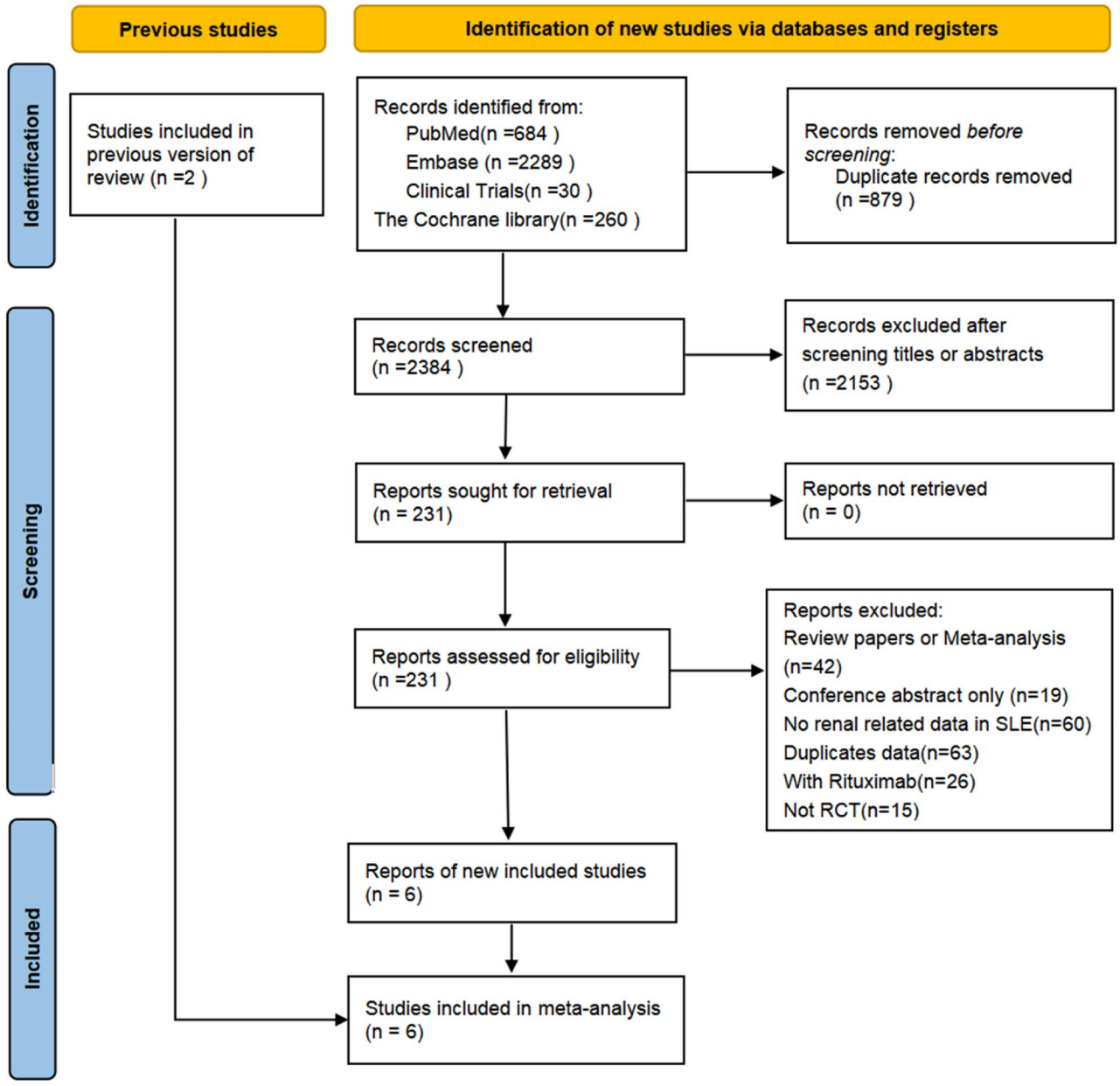

Figure 1. PRISMA flow diagram of the study-selection process.

because they were not relevant to the study. We read the full text of 231 articles, most of the excluded articles were review articles or did not report renal outcomes. Therefore, six articles were eligible for this meta-analysis [14,15,21–24] (Figure 1). The follow-up periods ranged from 52 to 104 weeks, and 93.7% of the 2960 participants were female. The average age of the participants was 36.4 ± 11.1 years. The race of participants included American, Asian, Black, European, and other populations. A total of 43 patients of recurrent or refractory LN were included. The characteristics of the studies are listed in Table 1.

The quality of the included RCTs was assessed by the Cochrane bias risk assessment tool: (1) random sequences were properly generated; (2) the distribution of hidden was properly used; (3) subjects and intervention providers were properly blinded; (4) evaluators of the results were properly blinded; (5) the completeness of outcome data was properly maintained; (6) selective reporting was properly conducted; (7) other biases were properly disposed. Thus, these items should be investigated and classified as low or high or unclear risk of bias. Notably, it was an open-label clinical trial in Yemil Atisha-Fregoso et al. We assessed that this study has a high risk of bias (Figure 2).

Renal response in the belimumab therapy and control groups

Among these articles, five articles provided the renal response rates (RRs) in the belimumab group and control group. The definition of renal response of the studies is listed in Table

Table 1. Characteristics of studies included in the meta-analysis.

Author (years)	Patients (R)	Protocol	Inclusion criteria	Exclusion criteria	Age (years)		Women (%)		Definition of renal response	Outcomes	Follow-up
					Belimumab	Control	Belimumab	Control			
MA Dooley et al. (2013) (BLISS-52 and BLISS-76) [14]	1125 (American/ White/Asian/ Hispanic or Latino)	Belimumab 1 mg/kg or 10 mg/kg, or placebo by intravenous infusion in 1 h on days 0, 14, and 28, and then every 28 d until 48 weeks.	Aged ≥ 18 years; SELENA-SLEDAI score ≥ 6; ANA (titer ≥ 1:80) or anti-dsDNA antibody (≥30 IU/mL); treatment regimen with fixed doses of prednisone (0–40 mg/d), or nonsteroidal anti-inflammatory, antimalarial, or immunosuppressive drugs for at least 30 d before the first study dose.	Severe active LN or CNS lupus; pregnancy; previous treatment with any B-lymphocyte-targeted drug within 3 months.	38.0 ± 11.0	38.1 ± 11.9	(*n* = 563) 539 (95.7)	(*n* = 562) 522 (92.9)	≥4-point reduction in SELENA–SLEDAI score, no new BILAG A organ domain score and no more than 1 new BILAG B score, and no worsening in physician's global assessment score *versus* baseline	In patients with baseline proteinuria ≥ 1 g/24-h equivalent (*n* = 220), renal remission rates were numerically higher and time to first renal remission was numerically shorter in the belimumab-treated groups; had numerically lower renal flare rates.	52 Weeks
William Stohl et al. (2017) (BLISS-SC) [21]	836 (Americas/ Western Europe/ Australia/ Israel/Eastern Europe/Asia)	Belimumab 200 mg or placebo by prefilled syringe in addition to standard SLE therapy for 52 weeks.	Aged ≥ 18 years; diagnosis of SLE; positive ANA and/or anti-dsDNA antibodies; SELENA–SLEDAI score ≥ 8	Severe lupus kidney disease (proteinuria > 6 g/24 h or equivalent according to a spot UPCR or a serum creatinine level > 2.5 mg/ dL) or severe CNS lupus	38.1 ± 12.10	39.6 ± 12.61	(*n* = 563) 521 (93.7)	(*n* = 280) 268 (95.7)	NA	Fewer patients in the belimumab group had a renal flare as compared with placebo, although this difference was not statistically significant (4.7% *versus* 7.5%; HR 0.57 [95% CI 0.32–1.01]; *p* = 0.0532).	52 Weeks
Yoshiya Tanaka et al. (2020) (BLISS-NEA) [22]	60 (Japanese)	Belimumab 10 mg/ kg or placebo by intravenous infusion plus standard of care, on Days 0, 14, and 28, then 4-weekly until Week 48.	Aged ≥ 18 years; diagnosis of SLE; SELENA–SLEDAI score ≥ 8	Severe lupus kidney disease or active nephritis; CNS lupus; any new SLE medications other than corticosteroids within 60 d prior to baseline, and B cell targeted therapy at any time.	38.1 ± 10.23	33.7 ± 10.61	(*n* = 39) 35 (89.7)	(*n* = 21) 20 (95.2)	SELENA–SLEDAI renal domain improvement	The proportion of patients experiencing renal organ system improvement was 60.0% in the belimumab group and 20.0% in the placebo group.	52weeks
Richard Furie et al. (2020) (BLISS-LN) [15]	448 (Asia/ Europe/ United States or Canada and other)	Belimumab 10 mg/ kg or matching by intravenous infusion days 1, 15, and 29 and every 28 d thereafter to week 100.	Aged ≥ 18 years; autoantibody-positive SLE; UPCR ≥ 1; biopsy-proven LN class III or IV with or without coexisting class V, or pure class V LN within 6 months before, or during, screening. Only patients with biopsy specimens showing active lesions or active and chronic lesions.	Dialysis within 1 year; eGFR < 30 mL/min/1.73; previous failures of both CTX and MMF induction; receipt of CTX induction therapy within 3 months; receipt of B-cell–targeted therapy within 1 year.	33.7 ± 10.7	33.1 ± 10.6	(*n* = 223) 197 (88.3)	(*n* = 223) 196 (87.9)	PR: UPCR ≤ 0.7; < 20% of eGFR below pre-flare value; eGFR ≥ 60 mL/min/1.73 m^2; No use of rescue therapy CR: UPCR< 0.5, an eGFR that was no worse than 10% below the pre-flare value or ≥ 90 mL/min/1.73 m^2, and no rescue therapy.	Significantly more patients who received belimumab than those who received placebo had a CRR at week 104; The group of patients who received belimumab had a significantly lower risk of a renal-related event or death during the trial than the group of patients who received placebo.	104 Weeks

(*Continued*)

Table 1. Continued.

Author (years)	Patients (R)	Protocol	Inclusion criteria	Exclusion criteria	Age (years)		Women (%)		Definition of renal response	Outcomes	Follow-up
					Belimumab	Control	Belimumab	Control			
Yemil Atisha-Fregoso et al. (2021) [23]	43 (White/Black/ Asian/ Hispanic or Latino)	Rituximab at a dose of 1000 mg, and CYC at a dose of 750 mg intravenously at weeks 0 and 2 ; Patients in the RCB group received belimumab at a dose of 10 mg/ kg at weeks 4, 6, and 8 and every 4 weeks thereafter through week 48.	Aged ≥ 18 years; diagnosis of SLE; positive ANA and/or an-dsDNA antibodies; SELENA–SLEDAI score ≥ 8; recurrent or refractory LN; had been treated previously with either CYC or MMF.	Prior treatment with rituximab at any time or treatment with another B cell biologic therapy within the prior 12 months.	34.5 ± 9.14	32.3 ± 11.43	(*n* = 21) 19 (90.5)	(*n* = 22) 18 (81.8)	PR: the same criteria as used for the CR, except that the UPCR component of the partial response definition required only > 50% improvement from baseline. CR: UPCR < 0.5; eGFR ≥ 120 mL/ min/1.73 m^2, or if the value was <120 mL/min/1.73 m^2, then >80% of the eGFR recorded at the time of study entry; and adherence to the prednisone dosing provisions.	Overall, renal response was similar between the RC group and the RCB group at all time points.	96 Weeks
Ellen Ginzler et al. (2022) (EMBRACE) [24]	448(in Brazil/ Colombia/ France/South Africa/the UK, and the US)	Belimumab 10 mg/ kg intravenously or placebo, on days 0, 14, and 28 and every 28 d thereafter up to week 48.	Age ≥ 18 years; self-identified Black race; SELENA–SLEDAI score ≥ 8; positivity for ANA (titer ≥ 1:80) and/or anti-dsDNA (≥30 IU/mL).	Previous treatment with belimumab; severe lupus kidney disease or active nephritis, or CNS lupus.	38.6 ± 11.1	39.3 ± 12.2	(*n* = 299) 290 (97.0)	(*n* = 149) 144 (96.6)	SELENA–SLEDAI–SLEDAI-2K renal domain improvement at week 52	SELENA–SLEDAI–SLEDAI-2K renal involvement, more patients in the belimumab group (41.8% [23 of 55]) experienced improvement in this domain compared with those in the placebo group (20.6% [7 of 34]); baseline proteinuria > 0.5 g/24 h was numerically greater with belimumab treatment compared with placebo (65.27% versus 32.89%); 16 patients (42.1%) in the belimumab group and 6 (26.1%) in the placebo group with baseline proteinuria > 0.5 g/24 h experienced a downward shift in proteinuria to ≤ 0.5 g/24 h.	52 Weeks and 6-month open- label extension phase.

SELENA-SLEDAI: Safety of Estrogen in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; ANA: antinuclear antibody; LN: Lupus Nephritis; CNS: central nervous system; SRI: SLE Responder Ind-ex; BILAG: British Isles lupus assessment group; SLE: Systemic lupus erythematosus; anti-dsDNA: anti-double-stranded DNA; UPCR: Urinary protein-to-creatinine ratio from 24-h urine sample collection; NA: denotes not applicable; eGFR: estimated glomerular filtration rate; CYC /CTX: cyclophosphamide; MMF: mycophenolate mofetil; CR: Complete response; PR: Partial response; RC group: participants treated with rituximab and cyclophosphamide but no belimumab infusions; RCB group: participants treated with rituximab, cyclophosphamide, and glucocorticoids followed by weekly belimumab infusions until week 48; SRI–SLEDAI-2K: SLE Disease Activity Index 2000

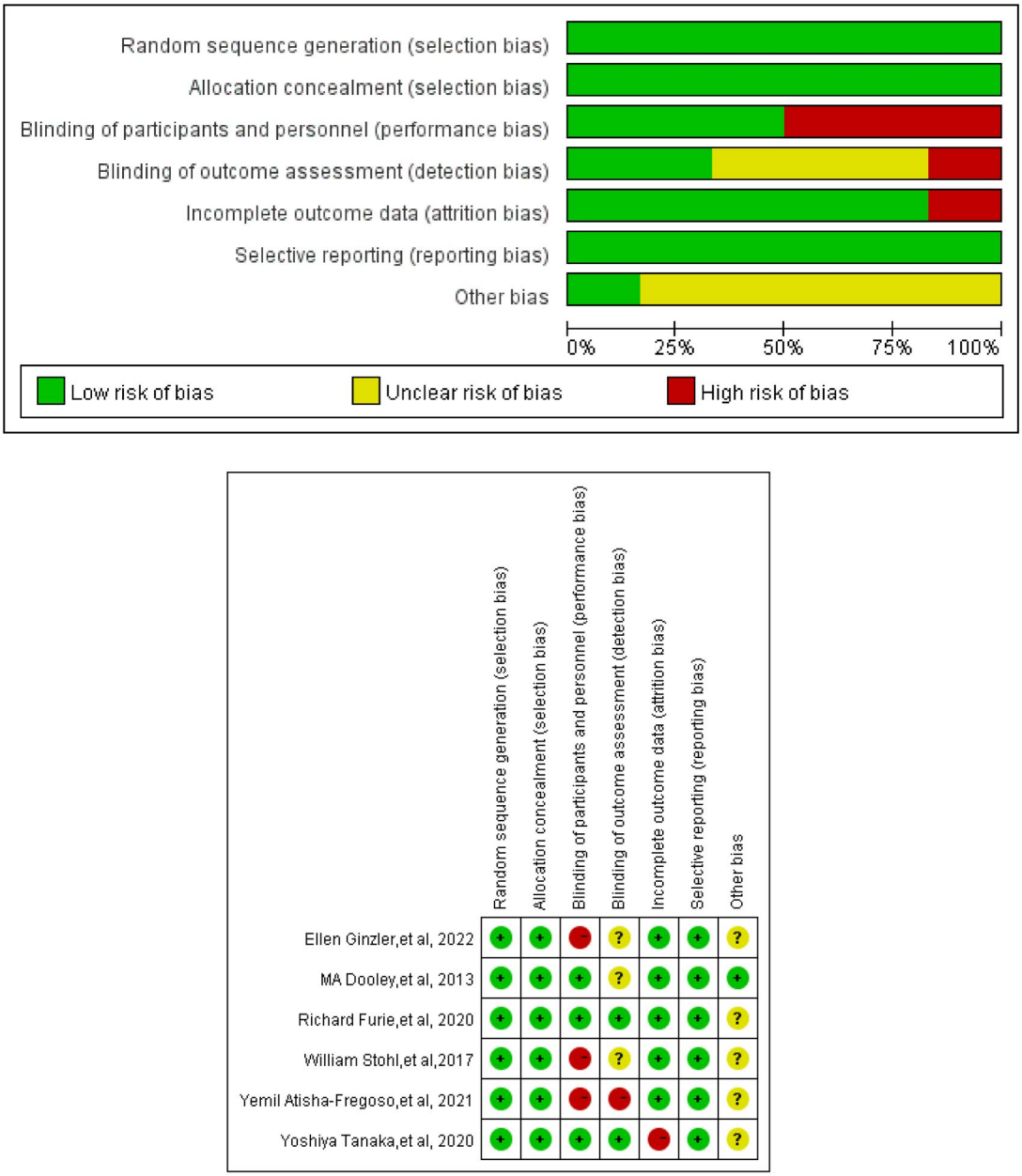

Figure 2. Risk-of-bias summary of randomized controlled trials.

1. The pooling data of these five studies ($n = 712$) showed that the total renal RR in the belimumab group was significantly higher than the control group (RR, 1.31; 95% CI, 1.11–1.53; $p = 0.001$). Similarly, the complete RR in the belimumab group was higher than in the control group (RR, 1.47; 95% CI, 1.07–2.02; $p = 0.02$). There have 366 patients received MMF at baseline, the results showed significantly that the total RR in the belimumab group was significantly higher than in the control group (RR, 1.45; 95% CI, 1.25–1.70; $p < 0.001$). There was no significant heterogeneity among the studies. The pooled RRs for renal response using the fixed-effects model are shown in Figure 3.

Two articles reported changes in proteinuria and serum creatinine. MA Dooley et al. showed that among patients with baseline proteinuria > 0.2 g/24 h ($n = 645$), belimumab lead a numerical or significantly higher median percentage reduction in proteinuria at weeks 12–52 than placebo. Ellen Ginzler et al. showed a 64.85% reduction of proteinuria from baseline in the belimumab group and a 32.33% reduction in the placebo group at week 52 in patients with proteinuria > 0.5 g/24 h at baseline in the double-blind period (mITT).

Renal flare in the belimumab therapy and control groups

Among these included studies, four studies provided data on renal flare with a mean treatment time of 65 weeks and three studies provided data on renal function worsening or progression to ESRD with a mean treatment time of 84 weeks. In the pooled analysis, there was a significantly reduced risk of renal flare in the belimumab group than in the control

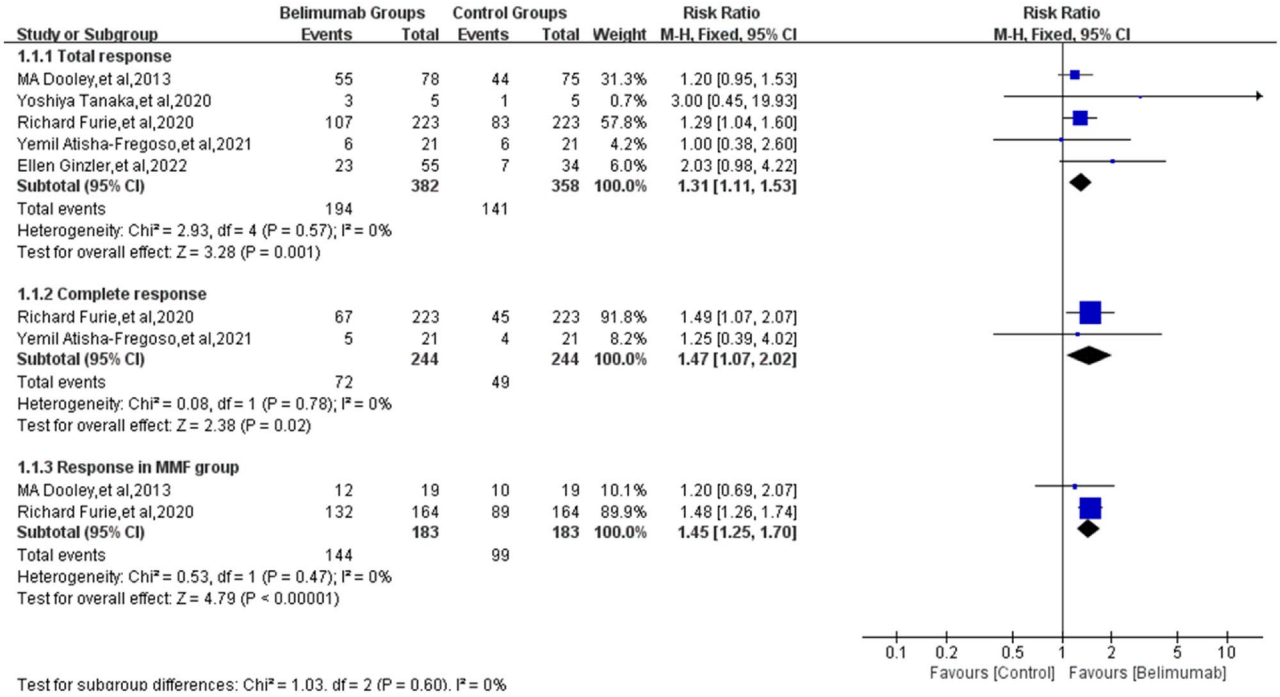

Figure 3. Comparison of renal response between the belimumab and control groups.

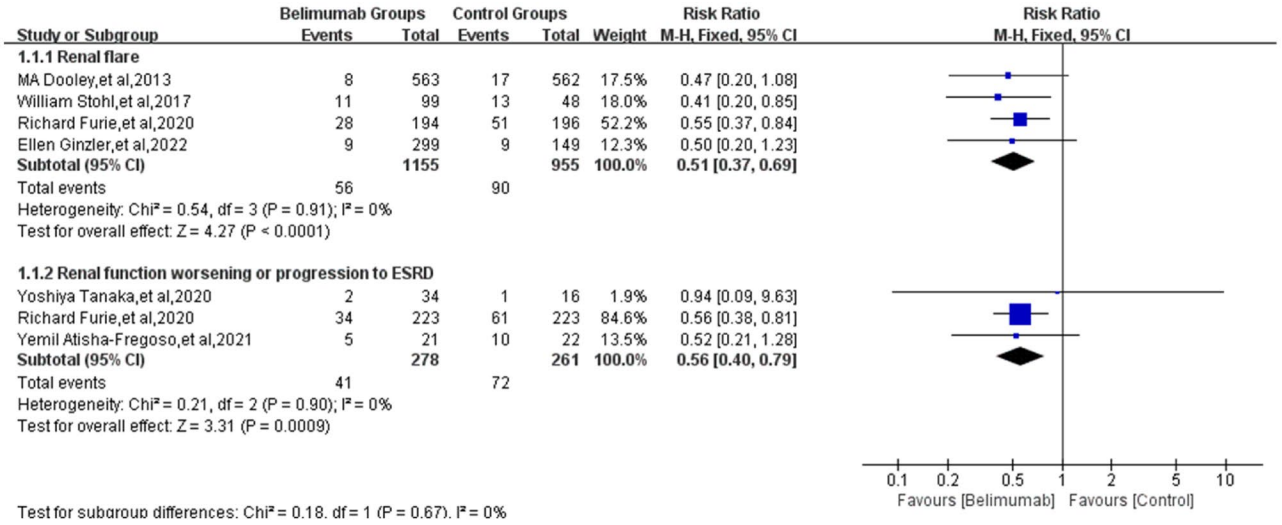

Figure 4. Comparison of renal flare rate between the belimumab and control groups.

group (RR, 0.51; 95% CI, 0.37–0.69; $p < 0.001$). Similarly, the risk of renal function worsening or progression to ESRD was also significantly reduced (RR, 0.56; 95% CI, 0.40–0.79; $p = 0.001$) (Figure 4). There was no significant heterogeneity among the studies.

Safety of the belimumab therapy

There were six articles reporting the incidence of treatment-related adverse, and five of them provided participants with serious adverse events or death. The pooling data on adverse events during treatment using fixed effects model showed no significant differences between the belimumab group and control group for the occurrence of treatment-related adverse events (RR, 1.04; 95% CI, 0.99–1.09; $p = 0.12$). But the serious adverse was reduced in the belimumab group than in the control group (RR, 0.84; 95% CI, 0.71–0.99; $p = 0.04$). The serious adverse reaction study was tested for heterogeneity with $I^2 = 67\%$ and $p = 0.02$, suggesting that the heterogeneity between the studies was statistically significant. We first excluded the study by Yemil Atisha-Fregoso et al. because of its high bias. The test of heterogeneity was $I^2 = 67\%$,

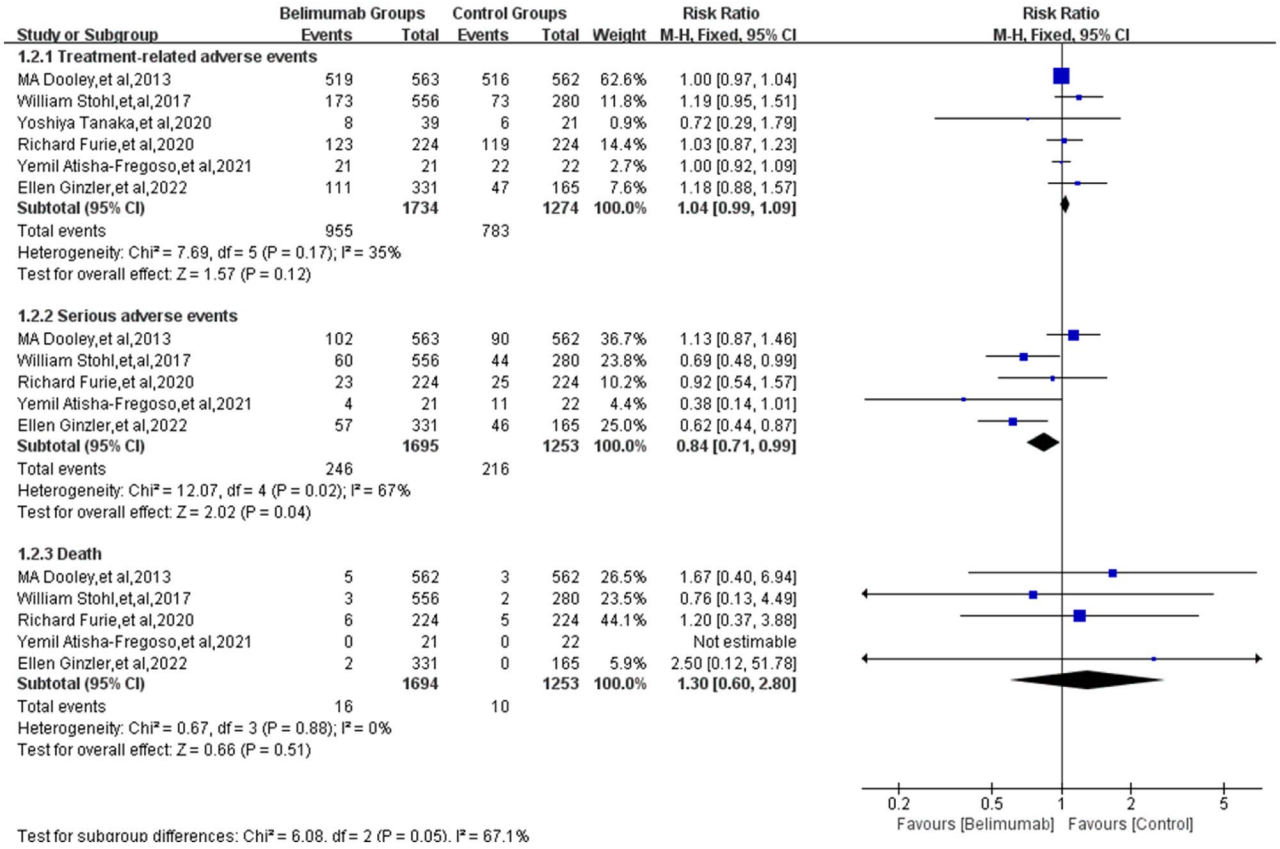

Figure 5. Comparison of treatment-related adverse events between the belimumab and control groups.

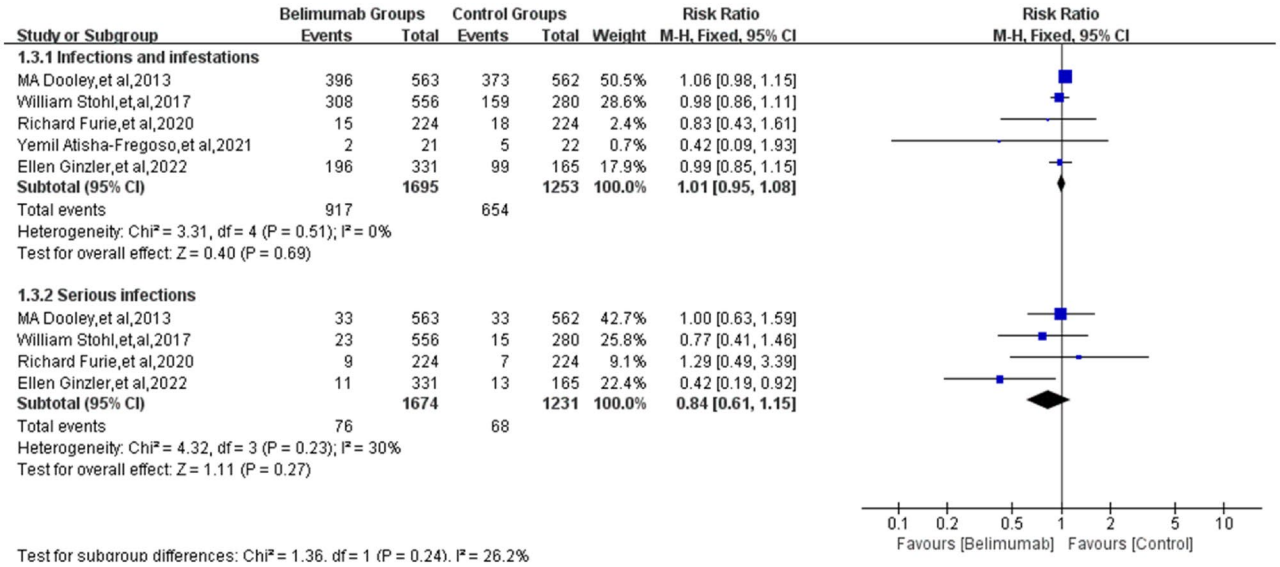

Figure 6. Comparison of infection between the belimumab and control groups.

($p = 0.02$) after exclusion and no significant difference between belimumab group and control group (RR, 0.86; 95% CI, 0.73–1.02; $p = 0.09$). Similarly, we investigated the influence of a single study on the overall risk estimate by excluding one study at a time. The combined RR of overall risk estimates was less stable, with a range from 0.68 (95% CI, 0.54–0.84) to 0.92 (95% CI, 0.76–1.11). The reasons for this heterogeneity may be related to the large sample size of the study by MA Dooley et al. However, belimumab has demonstrated a favorable safety in treatment of LN.

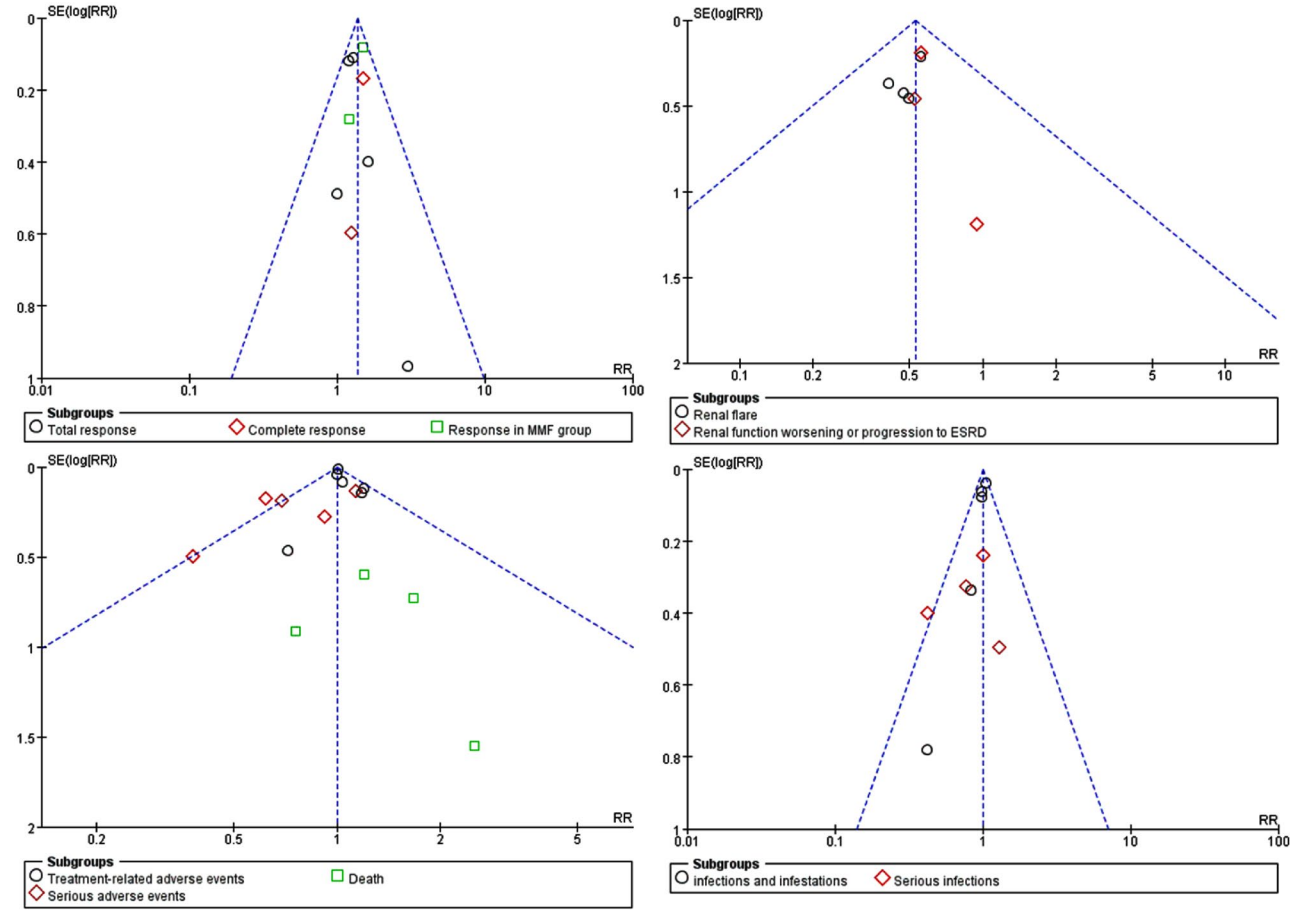

Figure 7. Funnel plots for publication bias detection.

In terms of deaths, based on data from five studies (2947 participants), there was no significant difference in the number of deaths in the belimumab group compared to the control group (RR, 1.30; 95% CI, 0.60–2.80; $p = 0.51$) (Figure 5).

Four studies reported the incidence of infection or infestation. The pooled analysis showed no significant differences between groups for the occurrence of infections and infestations (RR, 1.01; 95% CI, 0.95–1.08; $p = 0.69$), and serious infections (RR, 0.84; 95% CI, 0.61–1.15; $p = 0.27$) (Figure 6).

Publication bias

A visual inspection of the funnel plot of RRs from these studies revealed approximate symmetry (Figure 7).

Discussion

This study was the first meta-analysis of multiple RCTs to assess the efficacy and safety of belimumab therapy in LN and the results showed that the renal response in the belimumab plus standard treatment group was superior to standard treatment group. This was consistent with the results of many observational studies.

Belimumab's mechanism of action is based on the known pathological functions of BAFF, a tumor necrosis factor (TNF) super family ligand. Excess BAFF in kidney tissue induced the formation of renal tertiary lymphoid structures (TLSs), elevated autoantibody levels, and promoted LN [25]. By inhibiting BAFF, belimumab is able to effectively block this pathological pathway, reduced the number of B cells and plasma cells, resulting in the failure of B cell activation and their ability to produce sufficient immunoglobulin [26]. The final result will lead to an immunosuppressed state, which may elucidate to be efficacious in LN patients who have a high degree of autoreactive B cells [27]. Although the potential efficacy of B cell depletion has been demonstrated in several observational open-label studies, RCTs of rituximab in SLE or LN, did not meet their primary endpoints [28,29]. One possible explanation for this is that levels of BAFF rise following B cell depletion [30]. In fact, several case reports highlight that treatment with RTX followed by BEL leads to a reduction in proteinuria and a significant improvement in refractory LN [31–33]. Regarding sequential B-cell targeted therapy in LN, the BEL first/RTX second study is currently recruiting (NCT03747159), some authors also prefer to switch to a different anti-CD20 drug, such as ocrelizumab, ofatumumab, or Obinutuzumab [34]. It is hoped that a clearer understanding of the combination of B-cell targeted therapies will emerge.

In this meta-analysis, we found that the total renal response and complete RR were significantly higher in the belimumab group than in the control group. The pooled-analysis showed that the RR in the belimumab group was significantly higher than in the control group, when MMF were used in SoC at baseline. On the basis of BLISS-LN trial, belimumab may have a role in augmenting induction treatment with MMF in patients with active LN [35].

Renal involvement is a common cause of morbidity in SLE. Most patients with LN have an initial response, but relapses are common and treatment-resistant disease often occurs [36]. The average duration of observation in our included studies was 68 weeks; we found that the risk of renal flare, renal function worsening or progression to ESRD were lower in the belimumab group than in the control group. The high frequency of renal flares is a crucial contributing factor to poor kidney outcomes in patients with LN. They reflect a new immune and inflammatory attack on the kidney that exacerbates glomerulosclerosis and interstitial fibrosis, with subsequent development of ESRD [37]. The combination of age greater than 35 years and greater than 30% of time spent in renal flare showed very high risk [38]. Therefore, timely kidney biopsy or discovery of new biomarkers with better predictive power is necessary for early detection of flare and initiation of appropriate treatment.

Although the patients enrolled in the meta-analysis had active LN, fewer data are available for refractory LN and in patients on KRT. Valentina Binda et al. reported that satisfactory use in a patient on peritoneal dialysis and after kidney transplantation [39]. Liu D et al. included seven patients diagnosed with SLE with renal involvement requiring dialysis. Apart from patient 7 on maintenance dialysis, 5 of 6 patients had increased urine output and were out of dialysis treatment [40]. Zhang C et al. reported similar results [41]. These results showed that belimumab was able to increase urine output and reduce the incidence of dialysis dependence, induce immunologic remission and decrease the disease activity of SLE in patients receiving dialysis treatment. The safety issue is promising, with no documented severe adverse effects [40]. However, the main limitations of these studies included the lack of a control group and the short period of observation.

In our meta-analysis, the safety of treatment in the belimumab group was similar to the control group. The risk of serious adverse events appeared to be lower in the belimumab group, although there was a high heterogeneity of results, suggesting the need to include more studies with larger samples for analysis. For many SLE trials, the belimumab 10 mg/kg group showed greater improvements in GC dose [42]. Prolonged therapy with corticosteroids is associated with the increase in chronic organ damage [43], the use of high doses of GCs may mask the efficacy of the drug and increase adverse effects. Valentina Binda et al. reported that belimumab allowed the achievement of complete response together with the withdrawal or the reduction of corticosteroids in LN patients [39].

Our meta-analysis showed no significant differences between groups for the occurrence of infection or infestations. Opportunistic infections treated with belimumab are rare, and multiple real-world studies further corroborate its safety. Although a greater proportion of patients treated with belimumab had lower than normal IgG or IgM levels, there was no significant increase in the risk of infection in patients with immunoglobulin levels below the lower limit of normal compared to those with normal level [44]. However, the risk of psychiatric and neurological adverse events (e.g., progressive multifocal leukoencephalopathy, severe depression, suicide, etc.) associated with belimumab treatment is high [45], which still needs further attention.

However, there are some limitations in this study: First, the possibility of information and selection bias and unknown confounding factors cannot be completely ruled out. Second, most trials excluded patients with severe active LN. The small number of included studies and the inclusion of few laboratory indicators or clinicopathological indicators, such as serum creatinine and urine protein, made it difficult to perform satisfactory subgroup analyses. Third, the patients included in this meta-analysis differed in terms of race, duration of disease, and previous medication, which may have influenced our findings. This meta-analysis had not been registered online in advance, but the study was carried out and the article was written strictly according to the PRISMA statement.

Conclusions

Despite the limitations of the included studies, belimumab has demonstrated a favorable efficacy and safety profile, and provided selection of treatment regimens for LN. The available published data were promising and the meta-analysis of RCTs supported belimumab for renal response.

Compliance with ethics guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Author contributions

All authors made substantial contributions to all the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the manuscript critically, (3) final approval of the version to be submitted. All authors have read and agreed to the published version of the manuscript.

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Data availability statement

All data generated or analyzed during this study are included in this published article/as Supplementary information files.

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