A SYSTEMATIC REVIEW AND META-ANALYSIS ARTICLE

Systematic Review and Meta-Analysis of the Efficacy and Safety Profile of Belimumab in Combination with Standard Therapy for Adults with Systemic Lupus Erythematosus

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disorder marked by pathogenic autoantibodies, resulting in considerable morbidity and mortality. Despite existing diverse treatment regimens, the need for more effective therapies persists. Recent advancements include monoclonal antibodies, such as belimumab, which can inhibit receptors tied to SLE's pathogenesis. This meta-analysis aimed to evaluate the efficacy and safety of combining belimumab and standard therapy compared to placebo in SLE patients, utilizing as many indicators as possible to comprehensively assess the former's potential.

Methods: This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions. A thorough literature search was performed across various databases, including PubMed, ScienceDirect, ProQuest, and grey literature sources such as MedRxiv and BioRxiv. The data underwent statistical analysis, with $I^2<50\%$ indicating low heterogeneity and $p<0.05$ denoting statistical significance.

Results: The literature search yielded seven records for analysis in this study. All the selected studies were multicenter, phase III/IV, randomized clinical trials published between 2011 and 2019. The selected studies' risk of bias was assessed using Cochrane's Risk of Bias (RoB) 2 tool. The results indicated that belimumab and standard therapy significantly improved disease activity, reduced flare occurrences—particularly severe flares, lowered corticosteroid dosage, and enhanced key biomarkers compared to placebo. The safety profile was favorable, with significantly minimal side effects, infections, and mortality risks.

Conclusion: Belimumab combined with standard therapy demonstrates promising efficacy and safety for SLE treatment, suggesting its potential for broader adoption in clinical practice.

Keywords: Systemic lupus erythematosus; belimumab; placebo; efficacy and safety; disease

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Highlights:

1. This systematic review and meta-analysis provide a thorough and complete analysis of multiple indicators regarding the efficacy and safety of belimumab in the treatment of systemic lupus erythematosus (SLE), which have never been reviewed before.
2. The findings of this study may lead to broader acceptance and adoption of belimumab as the standard treatment for SLE.

Article history: •Received 7 May 2024 •Revised 26 June 2024 •Accepted 4 July 2024 •Published 31 January 2025

INTRODUCTION

Systemic lupus erythematosus (SLE), a multi-systemic autoimmune disease with a complex pathogenesis, is a significant health concern affecting individuals of all ages (Gordon et al., 2018). A key characteristic of SLE is the production of pathogenic autoantibodies that can target various organs. The clinical manifestations of SLE are highly variable, with the most common being arthritis, hematological disorder, and kidney damage (Trilistyoati et al., 2021). In addition, 70–85% of SLE patients suffer from skin-related manifestations. The incidence of SLE is on the rise, with an average of 400,000 new cases reported annually (Tian et al., 2023). An Italian study indicated that the average mortality rate was 18.6 per 1,000 SLE patients,

Available at https://e-journal.unair.ac.id/CIMRJ ; DOI: 10.20473/cimrj.v6i1.66383

with a standardized mortality rate (SMR) of 2.65 from 2012 to 2021, highlighting the severity of the disease (Zen et al., 2023).

The contemporary treatment protocols for systemic lupus erythematosus (SLE) encompass multiple pharmacological agents, notably corticosteroids (e.g., prednisone and methylprednisolone), nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials, azathioprine, methotrexate, and cyclosporine. Corticosteroids have been used in the treatment of SLE for nearly 100 years (Al Sawah et al., 2015). These treatment regimens have led to an increase in the five-year survival rate of SLE patients, reaching 89%, in contrast to a mere 40% during the 1940s. Nevertheless, the often severe and recurring signs and symptoms of SLE continue to impose a significant physical, psychological, and economic burden on SLE patients. A case report showed that even with a routinely administered current multidrug treatment regimen, recurrent flares with severe manifestations persist (Hadisuwarno & Rahmawati, 2023). The treatment of various clinical manifestations in SLE patients may cost up to 71,334 USD per patient each year (Carter et al., 2016). In addition, the current treatment regimen carries unintended hazards, since prolonged use of corticosteroids elevates the risk of infection, heart disease, osteoporosis, and renal failure (Stojan & Petri, 2017).

B cells are pivotal in the development of SLE, contributing to the production of harmful autoantibodies. The activation of B cells leads to an increase in the production of pathological autoantibodies, which in turn cause tissue damage through immune complex deposition, the activation of complement systems and neutrophils, as well as increased apoptosis and cytokine production (Vaillant et al., 2023). This activation occurs when beta-lymphocyte stimulators (BLyS) bind with three receptors on the surface of B cells, i.e., the B cell activating factor receptor (BAFF-R); transmembrane activator-1, calcium modulator, cyclophilin ligand interactor (TACI); and B cell maturation antigen (BCMA). The elevation of BLyS is also observed in the development of several autoimmune disorders, including rheumatoid arthritis and Sjögren's syndrome (Jordan & D'Cruz, 2015). An elevation in apoptosis coincides with diminished clearance of apoptotic debris, frequently resulting from compromised phagocytosis due to immunological tolerance malfunction. This results in autoreactive B cells to produce more autoantigen-antibody complexes (Sutanto & Yuliasih, 2023).

Recent advancements in SLE drug development have focused on the creation of various monoclonal antibodies (Malik & Ghatol, 2023). These antibodies function by recognizing and binding to specific proteins (antigens) on cell surfaces, thereby initiating a variety of immune responses that allow the immune system to eliminate the targeted cells (Bayer, 2019). Belimumab, one of the first monoclonal antibodies developed, has shown high potential in the treatment of SLE (Bruce et al., 2022). It operates by binding to BLyS and inhibiting its attachment to its receptors. This mechanism effectively suppresses the survival of B cells, particularly autoreactive B cells, and reduces their differentiation into plasma cells, which are responsible for producing pathological autoantibodies (Singh et al., 2021).

While several authorities have approved the use of belimumab as a complementary therapy for certain patients, its widespread adoption remains pending. It has yet to become a standard treatment regimen in many countries (Sumariyono et al., 2019). This might be because monoclonal antibodies, such as belimumab, carry several side effects, mainly immunosuppression and an increased risk of infection (Bruce et al., 2022). Several reviews have been conducted to evaluate the efficacy and safety of belimumab for SLE treatment. However, most of these reviews remain insufficient to clearly determine the efficacy and safety of belimumab in the treatment of SLE. As SLE is a complex disease, the treatment must consider various indicators, such as disease activity, flare occurrences, changes in corticosteroid dose, and biomarker fluctuations. Many prior studies only reviewed specific indicators while leaving others unexamined, thereby presenting inadequate assessment of the actual efficacy and safety of the treatment. This meta-analysis aimed to analyze various indicators regarding the efficacy and safety of belimumab in conjunction with standard therapy for SLE, involving as many clinical trials and patients as possible. Reviewing and analyzing these indicators could help provide a more thorough evaluation of belimumab for SLE treatment, enhancing its acceptability for broader adoption and usage.

METHODS

The International Prospective Register of Systematic Reviews (PROSPERO) has recorded this systematic review and meta-analysis under registration number CDR42024591703. Our search strategy and technique were designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Sohrabi et al., 2021). Additionally, we conducted our meta-analysis in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Bias Methods Group, 2019).

We conducted a literature search across multiple databases, including PubMed, ScienceDirect, and ProQuest. Several grey literature databases, including MedRxiv and BioRxiv, were searched as well. We used several keywords and Boolean operators as part of our search strategy (Bramer et al., 2018). Our study imposed no temporal limit on publication and no data exclusion. The inclusion criteria for literature selection were as follows: (1) randomized-controlled trials comparing belimumab and standard therapy with placebo; (2) the availability of full texts in English; (3) the inclusion of adult SLE patients (≥18 years old); (4) the application of the European League Against Rheumatism and American College of Rheumatology (EULAR/ACR) criteria for SLE diagnosis; (5) the inclusion of research outcomes pertaining to treatment efficacy, including changes in disease activity, flare occurrences, corticosteroid dosage, and post-therapy biomarkers; and (6) the inclusion of research outcomes regarding treatment safety, encompassing risks of side effects, infections, and mortality. The exclusion criteria were (1) duplicate records, (2) papers with unavailable complete texts, (3) publications without full texts in English, (4) studies with incomplete data, and (5) studies involving individuals with multiple diseases beside SLE.

We selected the articles used in this study by eliminating duplicates and non-English records, assessing titles and abstracts, and evaluating each full text against the inclusion criteria (Porritt et al., 2014). Decisions were reached by consensus, and disagreements were settled by discussion. The data presented by the selected studies were extracted, synthesized, and arranged in tabular format. We extracted the authors' names, publication date, inclusion and exclusion criteria for patients, total number of patients,

age, sex, SLE-related baseline indicators, dosage and preparation of belimumab therapy, duration of treatment, standard therapy used, control intervention, outcomes, and adverse events.

Due to variability in baseline data across the selected studies, we reported baseline characteristics that were considered relevant to this systematic review, including baseline disease activity indicators such as the Safety of Estrogens in Lupus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) and the British Isles Lupus Assessment Group (BILAG) index, baseline average corticosteroid dosage, and baseline biomarker indicators. In instances where a selected study did not include a particular data point, we denoted it as "NA" (an abbreviation for "not available") in the table. The risk of bias assessment for each study was conducted separately by individual researchers. We discussed the results and reached a consensus on determining the risk of bias (Porritt et al., 2014).

The quality and bias risk assessment for the included studies was performed utilizing Cochrane's Risk of Bias (RoB) 2 tool. Five bias domains—randomization, variations from intended interventions, incomplete outcome data, outcome measurement, and selection of reported results—were employed to measure the score of each study (Cochrane Bias Methods Group, 2019). The outcomes of each study concerning efficacy and safety were extracted and tabularized. Each study included four primary indicators of efficacy and three main indicators of safety, divided into different parameters and methods of measurement. We sorted and selected subvariables from each outcome by identifying the inclusion of identical parameters and methods of measurement in at least two studies.

We analyzed the outcomes related to changes in disease activity using the systemic lupus erythematosus responder index (SRI), a composite endpoint defined by a reduction of ≥4 points in the SELENA-SLEDAI, as well as an absence of the worsening of the BILAG index and the Physician Global Assessment (PGA) results (Ohmura, 2021). For outcomes related to changes in flare occurrences, we analyzed the overall rate of flare occurrences and the specific rate of severe flare occurrences. For outcomes regarding changes in corticosteroid dosage, the analysis included a reduction of ≥25% to ≤7.5 mg/day, an increase from ≤7.5 mg/day to >7.5 mg/day, and a sustained reduction (>12 weeks) from a baseline dose of ≥7.5 mg/day. Except for the risk of mortality, the same subvariable selection process was also applied to outcomes concerning treatment safety. We examined five subvariables for the risk of adverse events, i.e., serious side effects, severe side effects, treatment-related side effects, systemic reactions, and psychological side effects. For outcomes related to the risk of infections, the analysis encompassed severe and serious infections.

We conducted the meta-analysis utilizing Review Manager for Windows, version 5.4 (The Cochrane Collaboration, 2020). The results were assessed for heterogeneity, in which an I^2 lower than 50% was considered to indicate low heterogeneity. Moreover, results with $p<0.05$ were deemed statistically significant. We determined a significant result when the data showed statistical significance and low heterogeneity. Analyses of subgroup differences were conducted among different subvariables of an outcome. Sensitivity analyses were also performed to ascertain whether studies with a small sample size could affect the entire analysis outcome. The publication bias was assessed using the funnel plot analysis available in Review Manager (Higgins et al., 2023).

RESULTS

Figure 1 presents the PRISMA 2020 flow diagram detailing the processes for sorting and selecting studies. In the initial search, we discovered a total of 856 articles. We retrieved these articles from five different search engines, including PubMed (n=110), ScienceDirect (n=71), and ProQuest (n=612), along with grey literature databases MedRxiv (n=35) and BioRxiv (n=28). We removed 50 records before screening due to various reasons, such as duplicate records (n=43) and non-English publications (n=7). The screening identified 806 records that met the criteria. A total of 799 records were excluded during the screening process for various reasons, including inconsistencies with the title and abstract (n=748), lack of accessible full texts (n=28), and incompatibility with the established inclusion criteria for this systematic review (n=23). Thus, seven articles were identified as meeting the inclusion criteria for analysis in this systematic review. Among the seven studies analyzed, only one was determined to possess a low risk of bias (Furie et al., 2011). The remainder were found to have certain biases. The bias domain that raised the most significant concern was the selection of the stated outcomes. Figure 2 illustrates the bias risk scoring for each article.

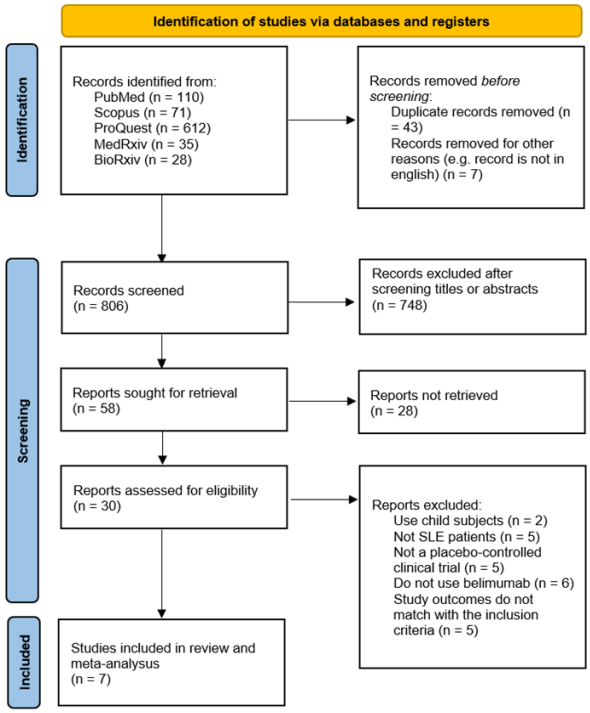


Figure 1. PRISMA 2020 flow diagram for the study selection processes

Table 1 presents the summarized baseline characteristics of each included study. The seven included articles were randomized controlled trials that assessed the effect of belimumab and standard therapy for the treatment of SLE in comparison with placebo. Two of the seven articles comprised subgroup analyses of the preceding randomized controlled trials (Doria et al., 2018; Tanaka et al., 2019). All seven studies were multicenter clinical trials involving a total of 4,089 patients from multiple countries worldwide. These clinical trials used the American College of

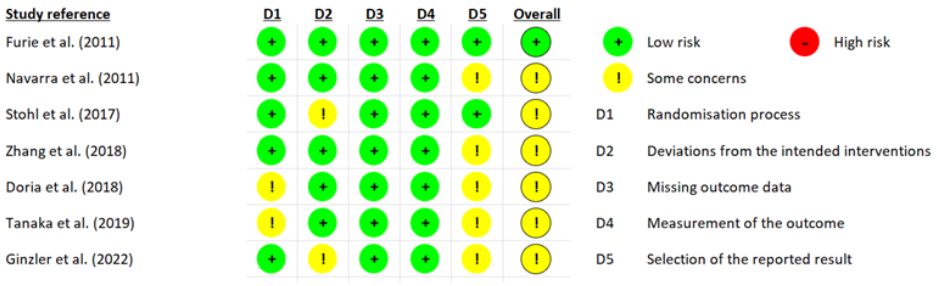


Figure 2. Visualization of the risk of bias scoring

Table 1. Summary of the baseline characteristics of the included studies

Author, year, registration number	Study design	Dosage and preparation	Number of patients	Age, sex	Treatment protocol	Standard therapy	SELENA-SLEDAI score	Patient(s) with BILAG 1A/2B	Average baseline corticosteroid dose (mg/day)	Patient(s) with anti-dsDNA ≥30 IU/mL	Patient(s) with C3 <0.9 g/L
Furie et al. (2011) NCT00424476	Stage III multicenter, double-blind, and placebo-controlled	IV belimumab 1 mg/kg	271	40±11.9 93.4% F	Therapy was provided on days 0, 14, and 29, followed by subsequent treatments every 28 days until week 72. Weeks 52 and 76 were the therapeutic endpoints.	Corticosteroids (prednisone), mycophenolate mofetil, azathioprine, methotrexate, and aminoquinolone.	9.7±3.7	173 (63.8)	8.7±7.6	171 (63.1)	100 (37.0)
		IV belimumab 10 mg/kg	273	40.5±11.1 94.9% F			9.5±3.6	160 (58.6)	8.4±7.9	179 (65.6)	150 (42.0)
		Placebo	275	40±11.9 91.6% F			9.8±4.0	187 (68.0)	9.4±8.9	174 (63.3)	116 (42.0)
Navarra et al. (2011) NCT00410384	Stage III multicenter, double-blind, and placebo-controlled	Belimumab 1 mg/kg IV	288	35±10.6 94.0% F	Therapy was provided on days 0, 14, and 29, followed by subsequent treatments every 28 days until week 48. Week 52 was the therapeutic endpoint.	Corticosteroids (prednisone), mycophenolate mofetil, azathioprine, methotrexate, and aminoquinolone.	9.6±3.8	166 (58)	12.9±8.6	221 (77.0)	148 (51.0)
		Belimumab 10 mg/kg IV	290	35.4±10.8 97.0% F			10±3.9	172 (59)	13.2±9.5	218 (75.0)	147 (51.0)
		Placebo	287	36.2±11.8 94.0% F			9.7±3.6	166 (58)	11.9±7.0	205 (71.0)	132 (46.0)
Stohl et al. (2017) NCT01484496	Stage III multicenter, double-blind, and placebo-controlled	SC belimumab 200 mg	556	38.1±12.61 93.7% F	Therapy was provided once a week from week 1 until week 52.	Corticosteroids (not specified), mycophenolate mofetil, azathioprine, methotrexate, and aminoquinolone.	10.5±3.19	NA	NA	NA	NA
		Placebo	280	39.6±12.61 95.7% F			10.3±3.04				
Zhang et al. (2018) NCT0134523	Stage III multicenter, double-blind, and placebo-controlled	Belimumab 10 mg/kg	470	32.3±9.65 92.9% F	Therapy was provided on days 0, 14, and 28, followed by subsequent treatments every 28 days until week 48. Week 52 was the therapeutic endpoint.	Corticosteroids (not specified), azathioprine, leflunomide, methotrexate, mycophenolic acid, and antimalarial.	9.8±3.83	204 (45.2)	NA	385 (81.9)	344 (73.2)
		Placebo	235	31.7±9.18 92.9% F			10.2±4.11	108 (47.8)		186 (79.1)	163 (69.4)
Doria et al. (2018) NCT01484496	Subgroup analysis of a stage III multicenter, double-blind, and placebo-controlled trial	SC belimumab 200 mg	248	34.6±10.96 95.2% F	Therapy was provided once a week from week 1 until week 52.	Corticosteroids, tacrolimus, methotrexate, azathioprine, mycophenolic acid, and amino quinolone.	11.5±3.31	186 (75)	12.2±8.34	NA	NA
		Placebo	108	34.6±10.38 98.1% F			11.7±3.14	78 (72.2)	11.4±7.39		
Tanaka et al. (2019) NCT01345253	Subgroup analysis of a stage III multicenter, double-blind, and placebo-controlled trial	Belimumab 10 mg/kg	39	38.1±10.23 89.7% F	Therapy was provided on days 0, 14, and 28, followed by subsequent treatments every 28 days until week 48. Week 52 was the therapeutic endpoint.	Corticosteroids, tacrolimus, methotrexate, azathioprine, mycophenolic acid, and amino quinolone.	10.1±2.82	24 (61.5)	NA	32 (82.1)	34 (84.6)
		Placebo	21	33.7±10.61 95.2% F			10.3±3.16	13 (61.9)		19 (90.5)	17 (81.0)
Ginzler et al. (2022) NCT01632241	Stage III/IV multicenter, double-blind, and placebo-controlled	IV belimumab 10 mg/kg	470	38.6±11.1 97.0% F	Therapy was provided on days 0, 14, and 28, followed by subsequent treatments every 28 days until week 48. Week 52 was the therapeutic endpoint.	Corticosteroids (prednisone), immunosuppressants (not specified), NSAID (not specified), and antimalarial (not specified).	10.2±3.68	205 (71.9)	12.1±10.71	181 (60.5)	57 (38.3)
		Placebo	235	39.2±12.2 96.6% F			10.5±3.08	107 (71.8)	12.2±9.95	99 (66.4)	108 (36.1)

Notes: SELENA-SLEDAI=Safety of Estrogens in Lupus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; BILAG=British Isles Lupus Assessment Group; anti-dsDNA=anti-double stranded deoxyribonucleic acid; C3=complement component 3; NSAID=nonsteroidal anti-inflammatory drug.

Table 2. Summary of the pooled analysis and heterogeneity test results

Outcomes	Pooled overall effects				Heterogeneity		
	aOR/MD/RR	95% CI lower limit	95% CI upper limit	Z-score (p)	Df	I^2	p
Efficacy outcomes							
SRI response rate	aOR: 1.63	1.43	1.85	7.51 (<0.00001)	6	0%	0.54
Flare occurrences							
Overall flares	aOR: 0.69	0.53	0.91	2.67 (0.008)	1	64%	0.09
Severe flares	aOR: 0.58	0.48	0.71	5.25 (<0.00001)	5	33%	0.19
Changes in corticosteroid dosage							
Reduction of ≥25% to ≤7.5 mg/day	aOR: 1.69	1.35	2.10	4.64 (<0.00001)	6	0%	0.97
Increase to >7.5 mg/day	aOR: 0.58	0.40	0.82	3.04 (0.002)	2	0%	0.88
Sustained reduction (>12 weeks) from ≥7.5 mg/day	aOR: 1.69	1.26	2.27	3.52 (0.0004)	1	0%	0.37
Changes in biomarkers							
C3 increase above LLN (≥0.9 g/L)	aOR: 2.37	1.51	3.72	3.76 (0.0002)	1	0%	0.97
C4 increase above LLN (≥0.16 g/L)	aOR: 2.93	1.99	4.31	5.43 (<0.00001)	1	0%	0.69
Seroconversion of anti-dsDNA	aOR: 2.55	1.53	4.25	3.61 (0.0003)	1	0%	0.57
Changes in IgG from baseline (%)	MD: -12.57	-16.02	-9.12	7.14 (<0.00001)	1	0%	0.86
Safety outcomes							
Risk of adverse events							
Serious side effects	RR: 0.87	0.74	1.03	1.66 (0.10)	4	79%	0.0007
Severe side effects	RR: 0.80	0.69	0.92	3.07 (0.002)	6	45%	0.09
Treatment-related adverse events	RR: 1.25	1.03	1.51	2.27 (0.02)	2	0%	0.47
Systemic reactions	RR: 1.02	0.84	1.22	0.17 (0.87)	5	16%	0.31
Psychological side effects	RR: 0.93	0.54	1.58	0.28 (0.78)	3	0%	0.71
Risk of infections							
Serious infections	RR: 0.99	0.73	1.35	0.06 (0.95)	4	0%	0.83
Severe infections	RR: 0.80	0.46	1.39	0.79 (0.43)	1	0%	0.58
Mortality	RR: 0.95	0.44	2.07	0.13 (0.90)	5	0%	0.77

Notes: aOR=adjusted odds ratio; MD=mean difference; RR=risk ratio; CI=confidence interval; df=degree of freedom; SRI=systemic lupus erythematosus responder index; LLN=lower limit of normal; C3=complement component 3; anti-dsDNA=anti-double stranded deoxyribonucleic acid; IgG=immunoglobulin G.

Rheumatology (ACR) criteria to determine their patients' SLE diagnosis. Every study only included adults who were 18 years of age or older and had been diagnosed with SLE. Notably, the average percentage of female patients in the seven studies was over 90%. Six out of seven studies reported the ethnic distribution of their patients, of which two studies included ethnic categories of White, Native American, African American, Asian, and Hispanic/Latino; two studies only differentiated between Hispanic and Non-Hispanic; one study focused exclusively on African American patients; and one study categorized patients according to their country of origin. Five out of the seven trials administered intravenous belimumab, two of which employed two dosage groups, namely 1 mg/kg and 10 mg/kg (Furie et al., 2011; Navarra et al., 2011), whereas three studies solely used 10 mg/kg (Zhang et al., 2018; Tanaka et al., 2019; Ginzler et al., 2022). The remaining two studies administered subcutaneous belimumab at a dose of 200 mg (Stohl et al., 2017; Doria et al., 2018).

The standard therapy used generally followed the guidelines for SLE management in the respective countries where the studies were conducted. These typically included corticosteroids, immunosuppressants (including mycophenolate mofetil, azathioprine, and methotrexate), and antimalarials (such as aminoquinoline). Each study reported the baseline average dose of these standard therapy medications. However, no study disclosed the actual dosage or regimen of standard therapy administered to each patient. In this systematic review, we only compared the changes in corticosteroid dosage. We chose to focus on corticosteroids due to their extensive usage in the pharmacological management of SLE and their significant side effects when used chronically, which might affect the patients' prognosis and quality of life (Al Sawah et al., 2015).

Table 2 exhibits the results of the analysis. Figure 3 displays the forest plots for the analyses of efficacy outcomes, divided into (a) changes in disease activity, (b) occurrence rates of flares, (c) changes in corticosteroid dosage, and (d) changes in biomarkers. The forest plot for the SRI response included all studies. Patients treated with belimumab in combination with standard therapy were significantly more likely to exhibit SRI response compared to those on placebo, evidenced by a pooled adjusted odds ratio (OR) of 1.63, a confidence interval (CI) of 1.43 to 1.85, and $p<0.00001$. The analysis showed no heterogeneity among the studies, indicated by an I^2 of 0%.

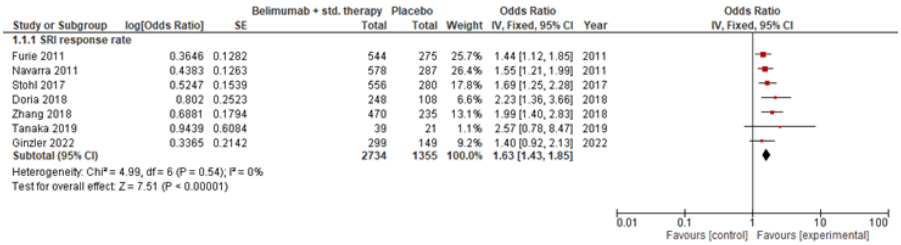
The forest plot for the occurrence rates of flares only included two studies, which exhibited high heterogeneity, with an I^2 value above 50%. Although the data were statistically significant, we determined that belimumab and standard therapy did not have a significant effect on the occurrence of all flares compared to placebo, due to its high heterogeneity (pooled adjusted OR=0.69, 95% CI=0.53–0.91, $p<0.00001$). However, in the forest plot for the occurrence rates of severe flares, we observed that patients treated with belimumab and standard therapy were significantly less likely to experience severe flares in comparison with those receiving placebo (pooled adjusted OR=0.58, 95% CI=0.48–0.71, $p<0.00001$). This forest plot comprised six studies and exhibited low heterogeneity, with an I^2 value below 50%.

According to the analysis of the seven studies, we found that patients treated with belimumab and standard therapy were significantly more likely to achieve a corticosteroid dose reduction of ≥25% to ≤7.5 mg/day compared to those receiving placebo (pooled adjusted OR=1.69, 95% CI=1.35–2.10, $p<0.00001$). The analysis of two studies indicated that patients treated with belimumab and standard therapy had a higher likelihood of attaining a sustained reduction in corticosteroid dosage from ≥7.5 mg/day for more than 12 weeks (pooled adjusted OR=1.69, 95% CI=1.26–2.27, p=0.0004). Meanwhile, the analysis of three studies revealed that patients who received belimumab and standard therapy were significantly less likely to experience an unwanted increase in corticosteroid dosage above 7.5 mg/day (pooled adjusted OR=0.58, 95% CI=0.40 to 0.82, p=0.002). These analyses indicated low heterogeneity among the studies, with $I^2 < 50\%$.

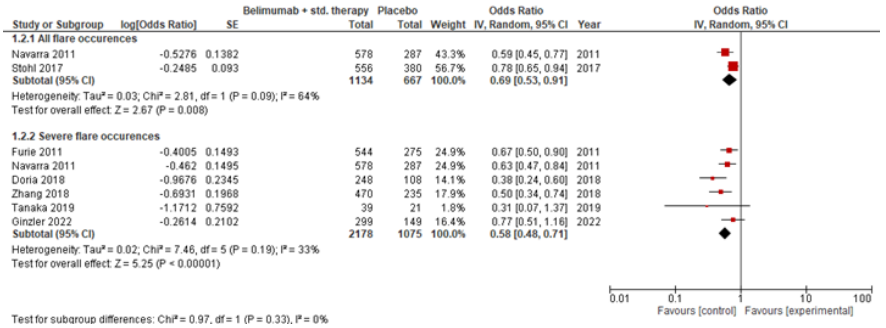
The forest plot for the changes in biomarkers included two studies. The analysis revealed that among patients with complement component 3 (C3) or complement component 4 (C4) levels below the lower limit of normal (LLN)—defined as ≥0.9 g/L for C3 and ≥0.16 g/L for C4—belimumab combined with standard therapy significantly elevated C3 and C4 levels above normal ranges compared to placebo-treated patients (pooled adjusted OR=2.37, 95% CI=1.51–3.72, p=0.0002 for the C3 indicator; pooled adjusted OR=2.93, 95% CI=1.99–4.31, $p<0.00001$ for the C4 indicator). Among patients exhibiting positive anti-double stranded deoxyribonucleic acid (anti-dsDNA), the combination of belimumab and standard therapy demonstrated a significant effect on the seroconversion of anti-dsDNA from positive to negative in comparison with placebo-treated patients (pooled adjusted OR=2.55, 95% CI=1.55–4.25, p=0.0003). Furthermore, the analysis also showed a significant effect of belimumab combined with standard therapy in reducing IgG compared to those receiving placebo (pooled MD=-12.57, 95% CI=-16.02 to -9.12, $p<0.00001$). These analyses indicated low heterogeneity among the studies, with $I^2=0\%$.

Figure 4 displays the forest plots for the analyses of safety outcomes, which were grouped into the risks of (a) side effects, (b) infections, and (c) mortality. We observed no significant difference in the risk of adverse events between patients treated with belimumab and standard therapy compared to placebo-treated patients for two out of the five subvariables. Patients treated with belimumab exhibited a lower risk of experiencing severe side effects than placebo-treated patients (pooled RR=0.80, 95% CI=0.69–0.92, p=0.002). In contrast, placebo-treated patients demonstrated a lower risk of encountering treatment-related adverse events than those treated with belimumab and standard therapy (pooled RR=1.25, 95% CI=1.03–1.51, p=0.02). These two subvariables indicated low heterogeneity among the studies, with $I^2 < 50\%$. No significant differences were observed in other indicators, i.e., the risks of infections and mortality, between patients treated with belimumab and standard therapy compared to placebo-treated patients.

We discovered no notable subgroup differences in the subvariables of flare occurrences (p=0.33; $I^2=0\%$) and changes in biomarkers (p=0.78; $I^2=0\%$). Conversely, we identified significant subgroup differences in the subvariables of changes in corticosteroid dosage. However, the studies showed high heterogeneity, with an I^2 above 50% ($p<0.00001$; $I^2=92.9\%$). In the subgroup analyses of safety outcomes, we found significant differences in the risk of side effects, although with high heterogeneity among the studies (p=0.005; $I^2=73.2\%$). Meanwhile, no significant subgroup differences were detected in the risk of infections (p=0.51; $I^2=0\%$).



(a)



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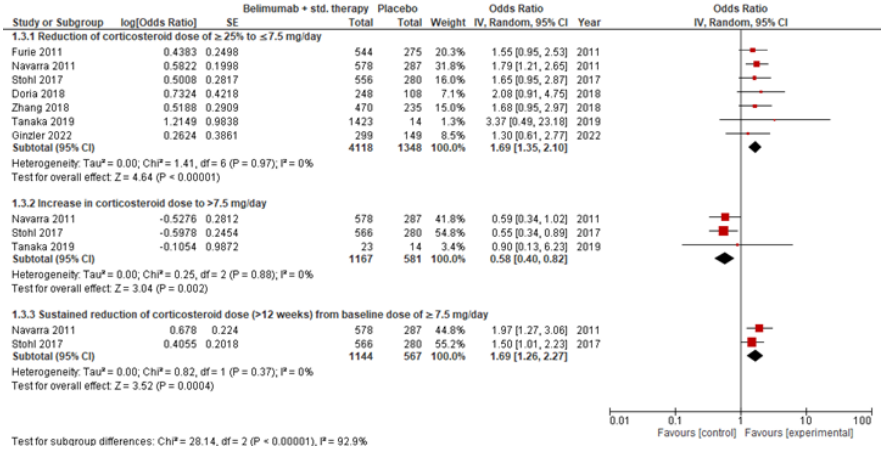

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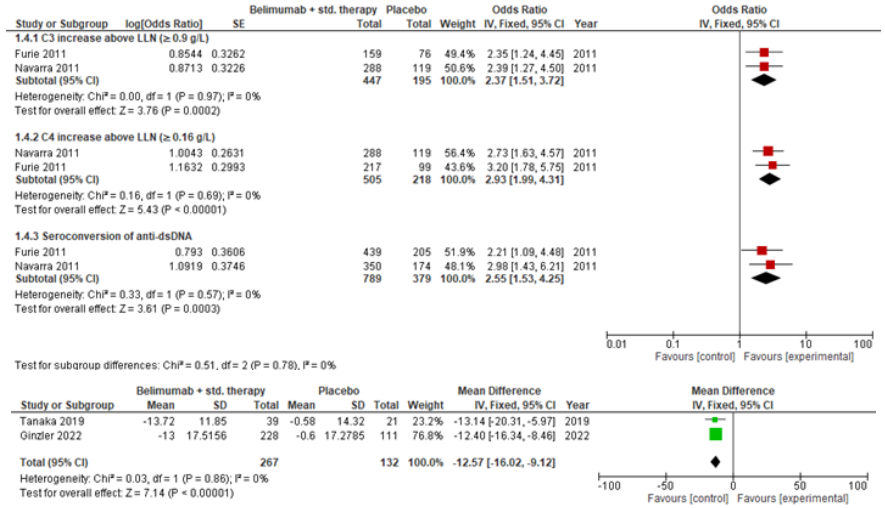
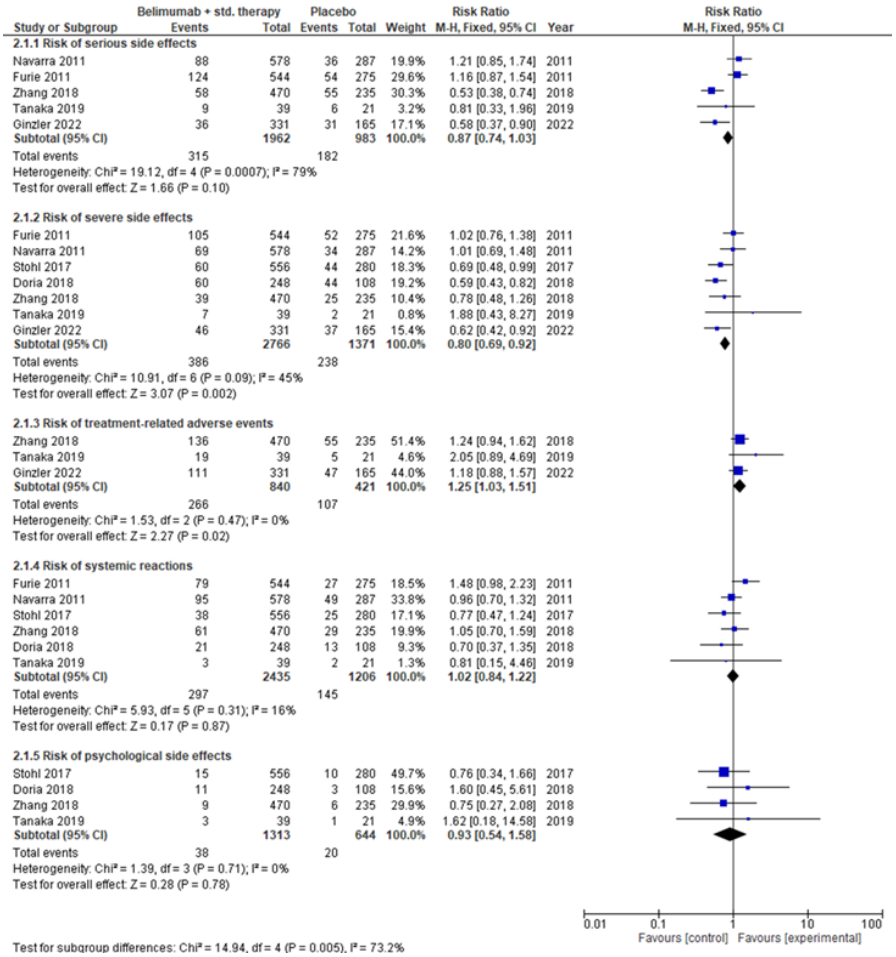
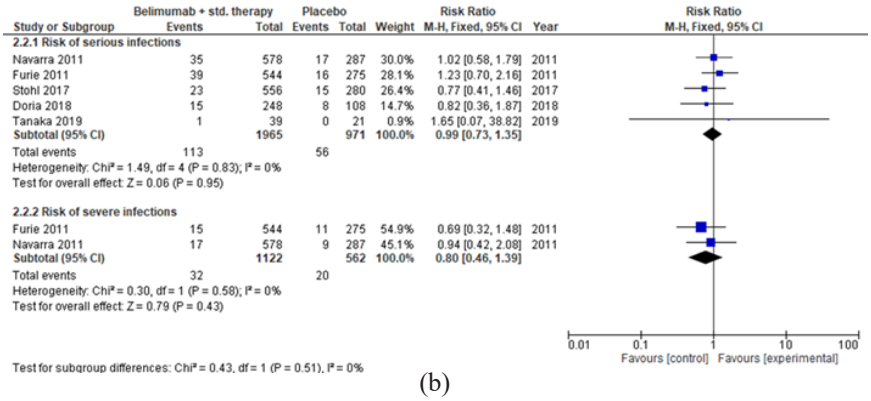


(d)

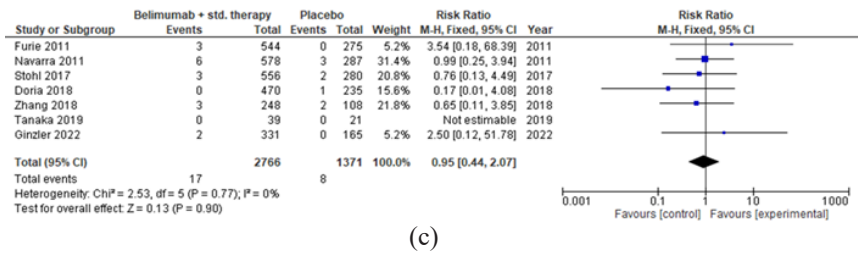
Figure 3. Forest plots showing the analysis results for efficacy outcomes, i.e., (a) changes in disease activity, (b) flare occurrences, (c) changes in corticosteroid dosage, and (d) changes in biomarkers



(a)



(b)



(c)

Figure 4. Forest plots illustrating the analysis results for safety outcomes, i.e., (a) risk of side effects, (b) risk of infections, and (c) risk of mortality

The sensitivity analysis was conducted on each subvariable using the leave-one-out method. No significant changes were found in the sensitivity analysis of the SRI response rate. For flare outcomes, we performed a sensitivity analysis only on the occurrence of severe flares, revealing that excluding the study by Doria et al. (2018) decreased data heterogeneity to 0% (pooled adjusted OR=0.64, 95% CI=0.53–0.74, p<0.00001). The analysis of corticosteroid dosage increase to >7.5 mg/day revealed that excluding the study by Stohl et al. (2017) altered the p-value of the pooled result to above 0.05, rendering it non-significant (pooled adjusted OR=0.61, 95% CI=0.36–1.03, p=0.07). We did not perform sensitivity analyses on the outcomes related to changes in biomarkers.

The sensitivity analyses of safety outcomes also yielded several interesting results. Regarding the two subvariables identified as significant in the risk of severe side effects, the pooled risk ratio moved to the other side of the null effect line upon the exclusion of one article. Nevertheless, excluding the study by Stohl et al. (2017) transformed this finding into significant (pooled RR=0.82, 95% CI=0.70–0.96, p=0.01). In the analysis of the risk of treatment-related adverse events, excluding any single article moved the pooled risk ratio to the other side of the null effect line. However, only by omitting the study by Ginzler et al. (2022) did this result become significant (p=0.04). We also conducted sensitivity analyses on other outcomes deemed as non-significant, revealing that excluding a single study from each outcome moved the risk ratio to the other side of the null effect line. Nonetheless, none indicated statistical significance, as their p-value remained above 0.05. Finally, we did not perform a publication bias assessment in this systematic review and meta-analysis due to the inclusion of only seven papers, which was below the ten-study threshold required for a credible funnel plot analysis (Higgins et al., 2023).

DISCUSSION

Efficacy of belimumab and standard therapy in the treatment of systemic lupus erythematosus

Belimumab demonstrated significant results when combined with standard therapy, as shown by most of the efficacy outcomes. Concerning outcomes related to the changes in disease activity, the combined treatment significantly affected the SRI response rate, demonstrating a favorable clinical response and a reduction in disease activity. Belimumab's mechanism of action prevents the production of pathological autoantibodies by inhibiting the binding of BLyS to its receptors. When combined with standard therapy, this can lead to significant immunosuppressive effects that prevent the occurrence of new clinical manifestations of SLE, hence the decrease in disease activity. An earlier review conducted by Singh et al. (2021) also demonstrated similar outcomes, concluding that belimumab significantly reduces disease activities. However, we identified an earlier outlier study in which belimumab was found to have no significant effect on two disease activity parameters included in our analysis, i.e., SELENA-SLEDAI and PGA (Jordan & D'Cruz, 2015). The phase I clinical trial involved fewer patients and a shorter study duration, possibly limiting its statistical power and generalizability. In contrast, the studies included in our analysis involved a larger cohort of patients with longer follow-up durations, allowing for a more robust assessment of long-term efficacy and safety. Therefore, our findings suggest that while belimumab combined with standard therapy demonstrates a statistically significant effect in reducing disease activity, this outcome may have nuances that depend on the study scale and duration. Further investigations in more extensive, longitudinal trials are warranted to validate the effect of belimumab across diverse SLE populations and determine any variable efficacy linked to baseline patient characteristics.

Belimumab combined with standard therapy demonstrated a significant effect in reducing daily corticosteroid dosage for SLE patients. Corticosteroid remains the mainstay of treatment for most SLE patients (Stojan & Petri, 2017). While this study still included corticosteroids as one of the 'standard therapies' used in combination with belimumab, the reduction in corticosteroid dosage indicated an important clinical achievement. The chronic use of corticosteroids at a baseline dose of ≥7.5 mg/day has been found to correlate with a higher risk of organ damage, including cataracts, osteoporosis, and cardiovascular problems, compared to a baseline dose of <7.5 mg/day, although there is no correlation between long-term corticosteroid use and an increase in blood glucose (Widyanrika et al., 2024). This study also demonstrated that belimumab combined with standard therapy may prevent the increase in corticosteroid dosage. Any increase in corticosteroid dose of 1 mg/day may elevate the risk of new organ damage by 2.8% (Al Sawah et al., 2015).

The previous review conducted by Singh et al. (2021) found that belimumab, administered alongside standard therapy, demonstrated a significant effect in reducing prednisone dosage by 50%. Previous retrospective research by Cortés-Hernández et al. (2023) found that 73.4% of patients experienced a reduction in corticosteroid dosage by ≥20% compared to 3.1% who worsened. In addition, a cohort study carried out by Birt et al. (2020) showed an incremental decrease in average corticosteroid dosage from an average baseline of 14.5 mg/day to 11.9 mg/day, still well above the 7.5 mg/day threshold. They also found that 48.6% of patients continued to receive a corticosteroid dose of ≥7.5 mg/day. Sciascia et al. (2024) demonstrated that steroid-sparing effects may be affected by the study design of the included studies. Corticosteroids, as one of the standard therapy regimens, remain a critical rescue treatment. Therefore, robust steroid supplementation during the early phase of a trial may obscure belimumab's effective and beneficial role in reducing overall corticosteroid dosage. In other words, the heterogeneity of standard therapy protocols in each article included in this study should also be considered and analyzed. However, the analysis was not conducted in this study, although we noted that the standard therapy drugs used in each of the included studies were relatively similar.

Patients with SLE elicit unique biomarkers that may indicate disease activity, such as immunoglobulin G (IgG), anti-dsDNA, and complement proteins, particularly C3 and C4. These patients exhibit a considerable decrease in both complement proteins, resulting in reduced clearance of apoptotic bodies and immune complexes, which is a key to the pathomechanism of SLE (Sandhu & Quan, 2017). An increase in complement proteins correlates with a reduction in disease activity. Anti-dsDNA contributes to the impairment of the kidneys, brain, and skin in SLE. This antibody binds to the DNA antigens or cross-reactive antigens in the renal cells, leading to the formation of immune complexes containing anti-dsDNA in the renal parenchyma. This results in the infiltration of immune cells

and the release of cytokines, accompanied by a complement cascade. These processes induce fibrosis and kidney inflammation (Wang et al., 2022). The seroconversion of anti-dsDNA from positive to negative signifies a reduction in antibodies to levels undetectable by the measurement instrument.

The deregulation of the immune system in SLE patients causes an increase in immunoglobulins, such as immunoglobulin A (IgA) and IgG. IgG, in particular, plays an essential role in forming immune complexes by binding to Fcγ receptors (FcγR), which induces local inflammation that results in multiple tissue and organ damage. A decrease in this immunoglobulin is an essential indicator for controlling disease activity, severity, and prognosis in SLE patients (Qiu et al., 2022). Previous research has found that belimumab-treated patients experience a more significant decrease in key biomarkers, such as IgG, IgA, immunoglobulin M (IgM), anti-dsDNA, and antinuclear antibody (ANA). Belimumab-treated patients have a reduced chance of experiencing seroconversion to positive anti-dsDNA and a decline in C3/C4 levels (Martin et al., 2024). In a recent cohort study, it was also found that belimumab-treated patients, especially those with severe SLE manifestations, exhibited a surge in non-proliferative memory B cells, particularly CD20+CD27+ cells. This rise coincides with the downregulation of lymphocyte migration markers, such as cell adhesion, actin cytoskeleton organization, and cell chemotaxis. However, this means that several CD20+ B cells may persist in specific lymphoid organs (Arends et al., 2024).

While this study demonstrated the significant effects of belimumab on disease activity, corticosteroid dosage, and biomarkers, its effect on flare occurrences was less pronounced compared to the other three variables. Although these outcomes indicated p-values below 0.05, they also revealed I^2 values that were higher than the other outcomes, with the data on the overall occurrence of flares exhibiting $I^2 > 50\%$. These findings might be attributable to the indicator used to measure and stratify flare levels, i.e., the systemic lupus erythematosus flare index (SFI). This index stratifies the flare levels into low/moderate and severe flares (Adamichou & Bertsias, 2017). Simultaneously incorporating data from patients with low/moderate and severe flares might unintentionally create heterogeneity due to the differences in criteria employed to determine flare severity. Otherwise, it is important to note that SLE patients continue to experience active and inactive disease activity periods. Flares might occur more than once in a patient throughout the study period, adding another layer of heterogeneity to the data.

Although this study demonstrated the effect of belimumab in reducing flare occurrences, most patients in all included studies continued to experience flares. In this respect, the effect of belimumab and standard therapy in reducing severe flares, which pose a higher risk of irreversible end organ damage and economic burden, is more important than merely decreasing the overall occurrence of flares (Adamichou & Bertsias, 2017). This rationale explains why more included articles in this study presented data on severe flare recurrences compared to overall flare occurrences. Despite this, a previous cohort study by Iaccarino et al. (2017) found a significant decrease in flare occurrences, with at least one flare observed in 85 (76.6%) out of 111 patients in the 12 months preceding belimumab initiation compared to 38 (34.2%) patients in the 12 months following the initiation. The study also revealed that the occurrence of flares decreased significantly from 1.00±0.81 during the 12 months before belimumab initiation to 0.39±0.56 during the 12 months after the initiation. Thus, we conclude that although belimumab and standard therapy demonstrated a statistically much weaker effect compared to the other outcomes, this combination offers a real benefit in decreasing flare occurrences, particularly severe ones, and improving long-term outcomes.

Safety profile of belimumab and standard therapy in the treatment of systemic lupus erythematosus

This study demonstrated that the combination of belimumab and standard therapy had very little or statistically insignificant safety concerns, at least when compared to placebo. One of two significant safety outcomes (i.e., severe side effects and treatment discontinuation) indicated that patients receiving belimumab alongside standard therapy exhibited a lower safety risk than those on placebo. Meanwhile, patients receiving belimumab and standard therapy consistently faced a relatively higher risk of treatment-related adverse events compared to placebo-controlled patients. A previous study found that the most common treatment-related adverse events of belimumab included nausea, diarrhea, fever, stuffy or runny nose, sore throat (nasopharyngitis), persistent cough (bronchitis), leg or arm pain, headache, as well as redness, itching, or swelling at the site of injection (Levy et al., 2021). However, it is very clear from our analysis that these side effects had no statistical significance when compared to placebo.

One of the two statistically significant indicators clearly indicated the advantage of belimumab in combination with standard therapy compared to placebo. The previous review conducted by Singh et al. (2021) also revealed that belimumab has no significant effect on withdrawals due to adverse events and mortality. Moreover, this analysis discovered that belimumab demonstrated favorable safety outcomes in the treatment of SLE. However, Levy et al. (2021) observed a slight trend toward an increased rate of upper and lower respiratory tract infections and cellulitis with the administration of belimumab. They also identified a slightly increased rate of opportunistic infections and hematological abnormalities. In addition, higher rates of serious depression were observed in patients treated with belimumab compared to those receiving placebo. Despite this, the incidence of these side effects remains rare and insignificant. The research conducted by Levy et al. (2021) demonstrated comparable and non-significant incidence of mortality among belimumab-treated patients in comparison with those on placebo.

This study had several limitations, notably the limited number of clinical trials included, which might restrict the generalizability of the findings and diminish the statistical power to ascertain the actual effects of belimumab. We did not account for several confounding variables in this systematic review and meta-analysis, particularly the dosage and regimen of standard therapy for each patient in this study. This might influence the outcomes of our study, as corticosteroids remain an important immunosuppressant regularly administered to treat SLE patients (Al Sawah et al., 2015). We also did not account for the different racial and baseline demographic characteristics of each patient. Although none were eventually reviewed due to incompatibility with the inclusion criteria, our study identified 65 grey literature publication articles that could change and modify the findings of the meta-analysis in

the future. Nevertheless, this meta-analysis was more thorough and provided more outcomes than previous studies, as we analyzed various indicators of the efficacy and safety of belimumab and standard therapy that had not been investigated. Finally, we used a rigorous method that complies with the Cochrane Handbook for Systematic Reviews of Interventions, thus increasing the likelihood of producing reliable results.

CONCLUSION

Belimumab and standard therapy significantly enhance clinical outcomes for patients with systemic lupus erythematosus (SLE), including reductions in disease activity, flare occurrences—particularly severe flares, corticosteroid dosage, and biomarkers. This combination demonstrates a favorable safety profile, revealing nearly no significant risk of side effects or infections, in addition to no increased risk of mortality. Future reviews and meta-analyses are necessary to assess the efficacy and safety of belimumab, considering variations in standard therapies and demographic baseline characteristics.

ACKNOWLEDGMENT

We thank everyone who contributed to this meta-analysis and the patients who participated in the included studies.

CONFLICT OF INTEREST

None.

FUNDING DISCLOSURE

None.

AUTHOR CONTRIBUTION

MRAD and MR contributed to the conception and design of the article. MRAD, A, and CDKW analyzed and interpreted the data. MRAD, MR, A, and CDKWU contributed to the drafting of the article. MR, A, and CDKW provided critical revision to the article for important intellectual content. MRAD, MR, and CDKW provided the study materials, while MRAD, A, and CDKWU provided statistical expertise. MRAD and MR provided administrative, technical, and logistic support. All authors contributed to the collection and assembly of the data and gave final approval to the article.

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