



Usefulness of Belimumab in Adult Patients With Systemic Lupus Erythematosus Evaluated Using Single Indexes: A Meta-Analysis and Systematic Review

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ABSTRACT

Background: Belimumab is the first antibody drug approved for systemic lupus erythematosus (SLE), and is a fully human monoclonal antibody that inhibits soluble B lymphocyte stimulator protein. In clinical trials, a composite index was used to assess efficacy of belimumab. However, clinical guidelines on SLE treatment currently use single efficacy indexes.

Objective: The main objective of this study was to perform a meta-analysis to evaluate the efficacy of belimumab utilizing single indexes used in routine clinical practice, rather than the composite efficacy index used in clinical trials during the development phase. As a secondary endpoint, safety was also evaluated.

Methods: Several databases were searched to identify reports published up to December 1, 2021 on randomized controlled trials examining the efficacy of belimumab in adult patients with SLE. From the clinical trial data, efficacy was evaluated using single indexes including the SLE Disease Activity Index (SLEDAI), British Isles Lupus Assessment Group Index, and Physician Global Assessment. Safety was also assessed. Data were synthesized and analyzed using Review Manager 5.4. This study protocol was registered in the UMIN Clinical Trials Registry (Registration number: UMIN000052846).

Results: The search identified 12 reports that met the inclusion criteria. Five reports were included in efficacy evaluation and 9 in safety evaluation. The primary endpoint was SLEDAI. Significantly more belimumab-treated patients achieved a ≥ 4 -point reduction in SLEDAI (relative risk 1.28; 95% confidence interval, 1.16–1.40; $P < 0.00001$) compared with placebo. Other efficacy endpoints were also improved significantly in the belimumab group. No difference in safety was found between belimumab and placebo.

Conclusions: The present meta-analysis evaluating clinical trial data using various single indexes recommended by clinical guidelines for SLE verifies that addition of belimumab to standard of care is efficacious for moderate-to-severe SLE.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease. Tissue damage is caused by the deposition of autoantibodies and immune complexes in tissues.¹ Various organs are affected, but the severity and course of disease vary widely from patient to patient.² The goal of treating SLE is to control disease symptoms,

prevent organ damage, and minimize the adverse drug reactions of therapeutic agents.³ Glucocorticoids, antimalarials, non-steroid anti-inflammatory drugs (NSAIDs), and immunosuppressive agents are used to treat SLE.⁴

The intravenous formulation of belimumab is the first new drug approved for the treatment of SLE in more than half a century. The drug is a human immunoglobulin G1 λ monoclonal antibody targeting B lymphocyte-stimulating factor (BLyS). Also known as B cell activating factor (BAFF), BLyS is a cytokine belonging to the tumor necrosis factor superfamily. BLyS is overexpressed in patients with SLE and may be a potential therapeutic target for SLE.^{5,6}

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There is no gold standard to measure disease activity in SLE.⁷ This, coupled with the heterogeneity of disease manifestations, makes the development of therapeutic agents for SLE challenging.⁸ Clinical trials related to the development of belimumab used a composite index; SLE Responder Index (SRI), as the primary endpoint.⁹ SRI defines responder as one that meets the criteria of all 3 of the following single indexes: (1) at least 4-point reduction of SLE Disease Activity Index (SLEDAI) score from baseline, (2) no new increase in British Isles Lupus Assessment Group index (BILAG) organ domain score, and (3) no worsening in Physician Global Assessment (PGA) score (no increase of 0.3 or more points from baseline).⁸ However, SRI is not highly recommended in domestic guidelines. The British Society for Rheumatology guidelines recommend BILAG and SLEDAI for assessing disease activity, and using Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus (SLICC/ACR damage index) for assessing damage.¹⁰ European Alliance of Associations for Rheumatology (EULAR) recommendations and Chinese guidelines recommend SLEDAI, BILAG, PGA, and SLICC/ACR damage index.^{3,11} There is no mention of a composite index such as SRI in the guidelines. The assessment of disease activity with a single validated index is considered reliable.¹⁰ Furthermore, when using composite indicators, the evaluation must first be conducted on individual indexes that make up the composite index. While PGA is relatively simple because it uses a visual analog scale, SLEDAI and BILAG are more complicated since SLEDAI requires evaluation of 24 items and BILAG requires evaluation of each organ.^{12–14} Therefore, it is difficult to use composite index in routine clinical practice.

Meta-analysis is a quantitative, accurate, and reliable method for drawing conclusions and is used as evidence for developing guidelines.¹⁵ Several meta-analyses on the usefulness of belimumab have been reported.^{16,17} However, no meta-analysis on the efficacy of belimumab has examined in detail the use of single indexes to evaluate efficacy.

The purpose of this study was to examine the efficacy of belimumab by performing a meta-analysis analysis to evaluate clinical trial data for efficacy utilizing single indexes used in routine clinical practice, rather than the composite index used in clinical trials during development.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis 2020 (PRISMA 2020).¹⁸ The study protocol was registered in the UMIN Clinical Trials Registry (Registration number: UMIN000052846).

Data sources and search strategy

We searched PubMed, Cochrane Library (CENTRAL), and Japana Centra Revuo Medicina Web for reports on clinical trials of SLE published up to December 1, 2021. The search terms were (belimumab or Benlysta) and (SLE or systemic lupus erythematosus) and (RCT or Randomized controlled trial or (randomized and controlled)).

Furthermore, we searched ClinicalTrials.gov. for randomized clinical trials using belimumab. The ClinicalTrials.gov Identifiers of relevant trials were hand-searched on PubMed. No restrictions were placed on language and year of publication.

Inclusion and exclusion criteria

Clinical studies were included if they met the following criteria: (1) placebo-controlled randomized clinical trial, (2) adult pa-

tients (18 years or older) diagnosed with SLE, (3) belimumab was the intervention drug regardless of the route of administration, (4) improvement in SLE symptoms and safety were evaluated.

We excluded clinical studies that met the following exclusion criteria: (1) not interventional studies; (2) nonoriginal research articles such as reviews, case reports, letters, and research protocols; (3) no data description; (4) studies in children; (5) patients with lupus nephritis; (6) single-dose studies. Single-dose studies were excluded because this meta-analysis aimed to investigate the efficacy of long-term administration.

The control group was expected to receive placebo in addition to standard of care (SoC). We did not specify the drugs used in SoC, because there were many drugs for SLE, including off-label use, but their availability likely varied from country to country, and diverse studies were being conducted.

Outcomes

The primary outcome measure for efficacy was SLEDAI score. The secondary outcome measures were no worsening of BILAG score, no worsening of PGA score, Short Form 36 health survey (SF-36) score, and SLICC/ACR damage index (SDI). Safety was also evaluated as a secondary endpoint. The safety outcomes were the total numbers of adverse events (AEs), serious AEs (SAEs), withdrawals due to AEs, and infections. The definitions of AEs described in each report were used. The numbers of individuals with AEs, SAEs, withdrawals due to AEs, and infections described in each report were used for this analysis.

Screening and data extraction

The reports were independently screened and data were extracted by 2 independent researchers based on inclusion and exclusion criteria. In cases of difference in opinion between the 2 researchers during screening and data extraction, a third researcher resolved the disagreement.

Data were extracted from each report that met the inclusion and exclusion criteria. The extracted data included author, study name, year of publication, national clinical trial number, dosage and route of administration of belimumab, numbers of patients in the belimumab and control groups, patient recruitment criteria, country where study was conducted, study population, study duration, outcome measures, and number of patients achieving the outcome measure. Information about the study design used for quality assessment was also extracted.

Quality assessment

Jadad score was used for quality assessment of the clinical study methodologies.¹⁹ We also used a revised Cochrane risk of bias tool for randomized trials (RoB2) to assess the risk of bias.²⁰ The evaluation results were visualized using Risk-of-bias VISualization (robvis).²¹

Statistical methods

The primary efficacy outcome was evaluated by the number of patients who improved by at least 4 points on SLEDAI. For BILAG and PGA, efficacy was evaluated by the number of patients who achieved that index. Only the results of approved doses; intravenous 10 mg/kg and subcutaneous 200 mg, were analyzed for efficacy endpoints. The safety outcomes were evaluated by the number of adverse events in the belimumab-treated group regardless of the dose.

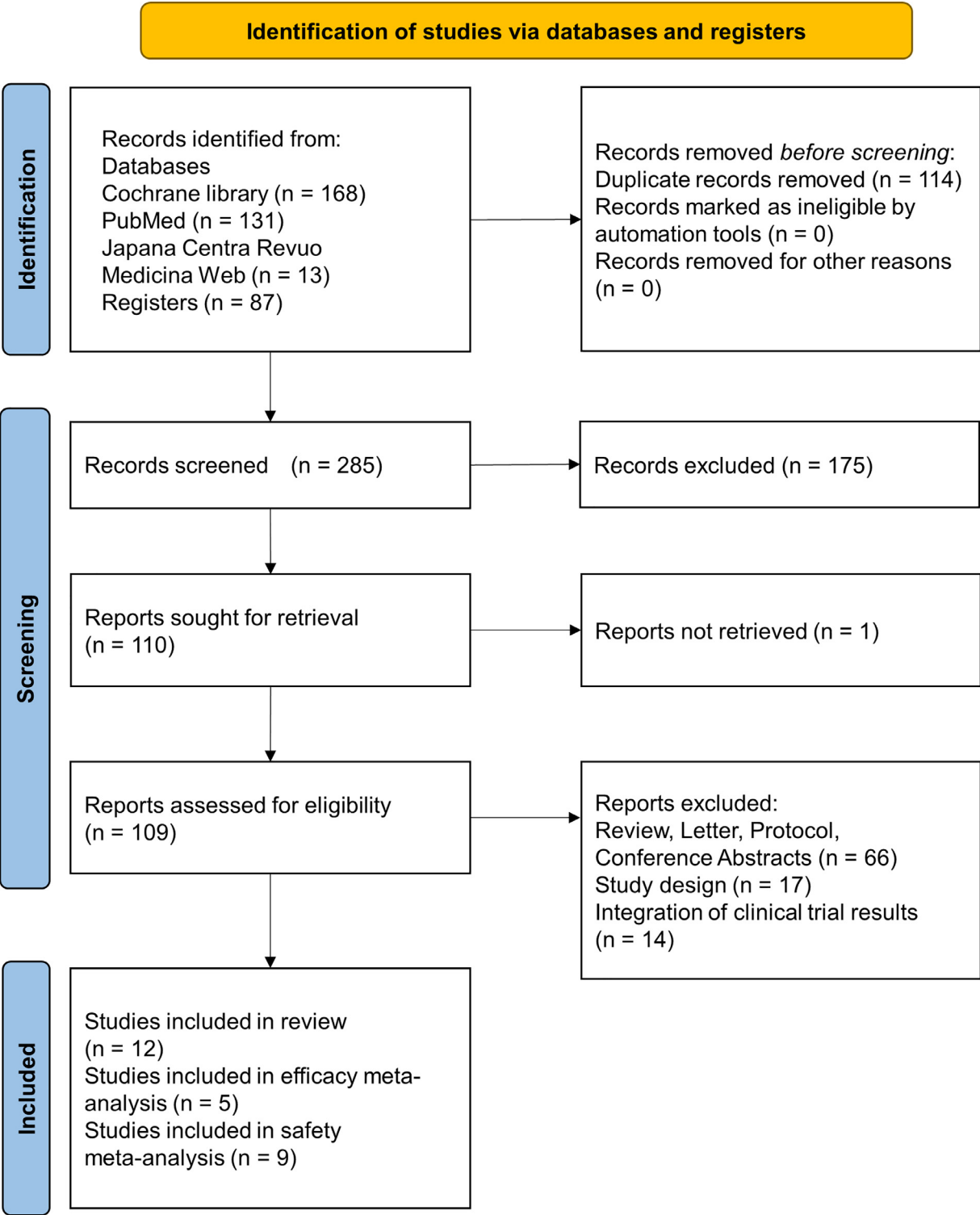


Figure 1. Flow diagram for the identification of clinical trials included in this systematic review and meta-analysis.

Meta-analysis was performed using the Cochrane Collaboration Review Manager software (RevMan 5.4). The statistical method used was Mantel–Haenszel method. Heterogeneity was evaluated based on I^2 value, which determined the analysis method: the fixed effect model was used for I^2 value ≤ 50 as there was no heterogeneity; and the random effect model was used for $50 < I^2$ value to account for heterogeneity.

Results

Search results

A literature search was conducted and 312 reports were found using the search strategy. In addition, 82 clinical trials were found on ClinicalTrials.gov. Of the 82 clinical trials, 20 were RCTs in adult

Table 1
Characteristics of randomized controlled trials included in the review.

NCT number	Study	Author, publication year	Country where study was conducted	Race of study population	Belimumab ^a		Control ^a (n)	Patient selection criteria	Study duration (weeks)	Jadad score
					Dose	(n)				
NCT00071487	Phase II	Wallace, 2009 ³²	US and Canada	Caucasian 70.1% African-American 23.6%	IV 10 mg/kg	111	113	met ACR criteria for SLE and had active disease (score ≥ 4 at screening on SELENA-SLEDAI)	52	4
NCT00424476	BLISS-52	Merrill, 2012 ²⁵	Same as above	Same as above	IV 4 mg/kg	114	287	met ACR criteria for SLE and had active disease (score ≥ 6 at screening on SELENA-SLEDAI)	52	5
		Ginzler, 2014 ²⁴	Same as above	Same as above	IV 1 mg/kg					
NCT00410384	BLISS-76	Navarra, 2011 ²⁶	13 countries [†]	Indigenous American 32.3% Caucasian 26.5% African-American 3.5% Asian 37.8%	IV 10 mg/kg	290	275	met ACR criteria for SLE and had active disease (score ≥ 6 at screening on SELENA-SLEDAI)	76	5
		Furie, 2011 ²²	19 countries [‡]	Indigenous American 12.6% Caucasian 69.5% African-American 14.4% Asian 3.4%	IV 1 mg/kg	271				
NCT01345253	BLISS-NEA	Zhang, 2018 ³³	3 countries (China, Korea, Japan)	No Data [§]	IV 10 mg/kg	451	226	met ACR criteria for SLE and had active disease (score ≥ 8 at screening on SELENA-SLEDAI)	52	5
NCT01484496	BLISS-SC	Tanaka, 2019 ³¹	Japan (subgroup analysis)	Same as above	SC 200 mg/kg	556	280	met ACR criteria for SLE and had active disease (score ≥ 8 at screening on SELENA-SLEDAI)	52	4
		Tanaka, 2020 ³⁰	Same as above	Same as above						
NCT01705977	BASE	Stohl, 2017 ²⁹	30 countries [#]	No Data [§]	IV 10 mg/kg	2001	2002	met ACR criteria for SLE and had active disease (score ≥ 8 at screening on SELENA-SLEDAI)	52	5
		Sheikh, 2021 ²⁷	33 countries ^{**}	No Data [§]						
No registration	BEAT-LUPUS	Shipa, 2021 ²⁸	UK	Caucasian 57.7% African-American 11.5% South Asian 11.5% Chinese 5.8% Other 13.5%	IV 10 mg/kg	26	26	met British Society for Rheumatology criteria, and were due to be treated with rituximab because of failure of conventional therapy according to NHS England guidelines and the British guidelines for management of SLE in adults	52	5
NCT01632241	EMBRACE	Ginzler, 2022 ²³	6 countries (Brazil, Columbia, France, South Africa, UK, US)	Black African ancestry or African American 97.3% Multiple 2.7%	IV 10 mg/kg	331	165	met ACR criteria for SLE and had active disease (score ≥ 8 at screening on SELENA-SLEDAI) and were self-identified black race	52	5

ACR = American College of Rheumatology; IV = intravenous injection; NCT = National Clinical Trial; SC = subcutaneous injection; SELENA-SLEDAI = Safety of Estrogen in Lupus Erythematosus National Assessment SLE Disease Activity Index; SLE = systemic lupus erythematosus; UK = United Kingdom, US = United States of America (USA).

^a In all trials, the intervention group received belimumab in addition to standard of care, and the control group received placebo (e.g., saline) in addition to standard of care. Standard of care included glucocorticoids and/or immunosuppressants and/or antimalarials.

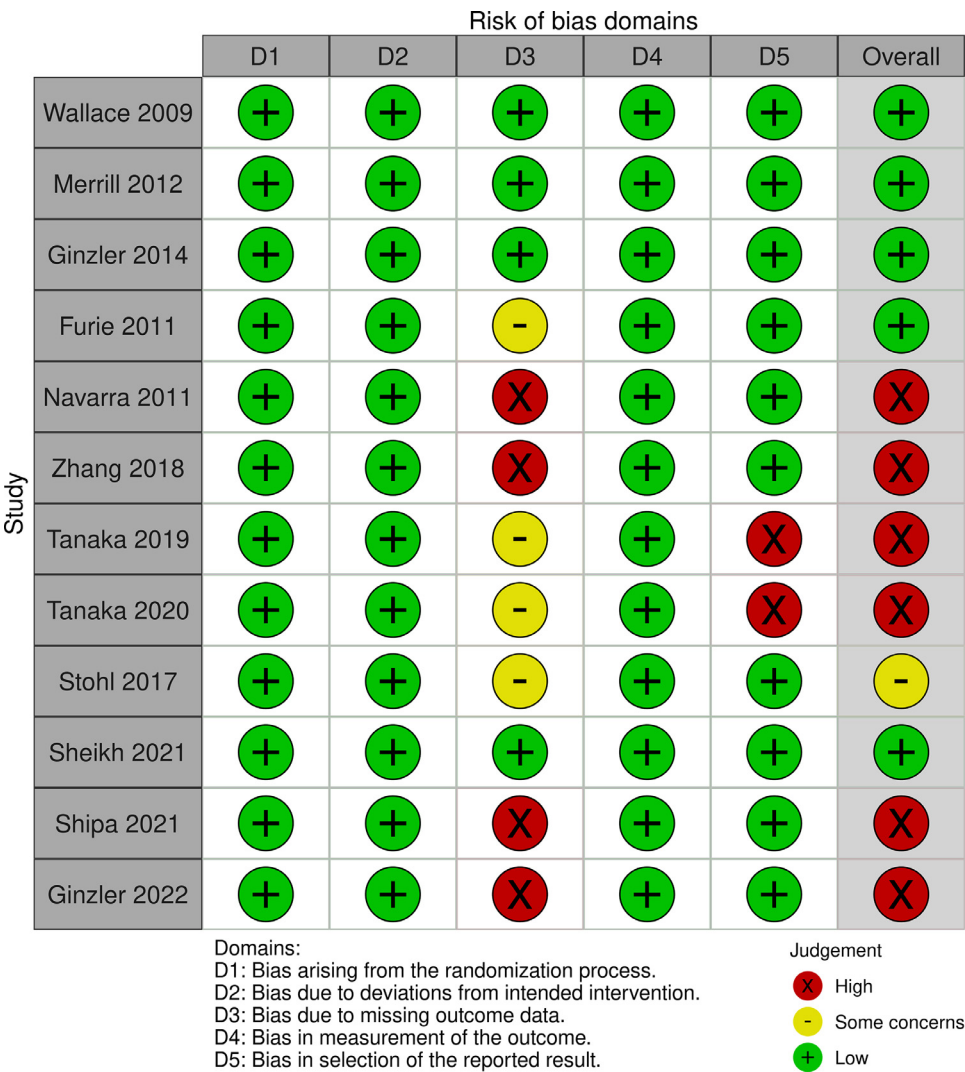
[†] Argentina, Australia, Brazil, Chile, Colombia, Hong Kong, India, Korea, Peru, Philippines, Romania, Russian Federation, Taiwan.

[‡] Austria, Belgium, Canada, Costa Rica, Czech Republic, France, Germany, Israel, Italy, Mexico, Netherlands, Poland, Puerto Rico, Romania, Slovakia, Spain, Sweden, United Kingdom, United States (source: ClinicalTrials.gov ID NCT00410384).

[#] Argentina, Austria, Belgium, Brazil, Bulgaria, Chile, Colombia, Croatia, Czechia, Denmark, France, Germany, Hungary, Italy, Japan, Malaysia, Mexico, Philippines, Poland, Portugal, Romania, Russian Federation, Serbia, Singapore, Spain, Sweden, Taiwan, Thailand, Ukraine, United Kingdom, United States (source: ClinicalTrials.gov ID NCT01484496).

^{**} US, Argentina, Australia, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czechia, Estonia, Hong Kong, Hungary, Indonesia, Italy, Korea, Lithuania, Malaysia, Mexico, New Zealand, Peru, Philippines, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Spain, Switzerland, Taiwan, Thailand, Ukraine.

[§] No mention of race, but the country of registered patients and the number or percentage of patients are stated.



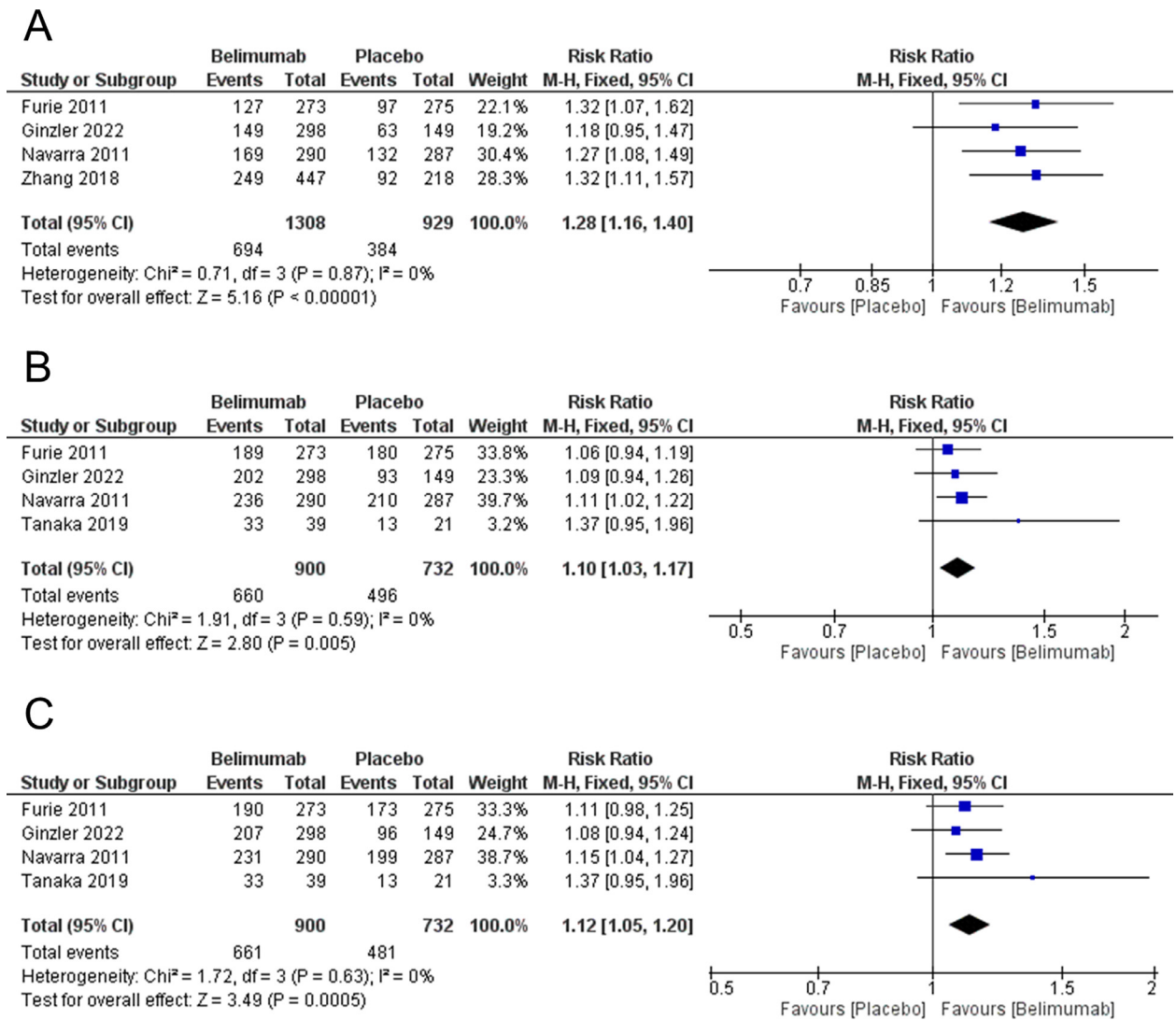


Figure 3. Forest plot of efficacy outcomes for belimumab versus placebo in SLE patients. Primary efficacy outcome: ≥ 4 -point reduction in SLEDAI score (A). Secondary efficacy outcomes: no worsening in BILAG score (B) and no worsening in PGA score (C). BILAG = British Isles Lupus Assessment Group index; CI = confidence interval; M-H = Mantel-Haenszel method; PGA = Physician Global Assessment; SLE = systemic lupus erythematosus; SLEDAI = the SLE Disease Activity Index.

National Assessment SLE Disease Activity Index (SELENA-SLEDAI) score. BEAT-LUPUS was the only study in which patients were treated with rituximab followed by belimumab, and the diagnostic criteria for SLE were also different. Regarding countries and study populations, with the exception of 2 Phase II clinical trials, BLISS-NEA, and EMBRACE, the studies were conducted in multiple countries, and the countries and populations varied among studies. There were 3 reports of Phase II clinical trials, each using a different efficacy index. Two reports by Tanaka et al^{30,31} were a subgroup analysis of data from only Japanese subjects only recruited in the multi-national BLISS-NEA study, and many indexes were reported. These reports were analyzed after confirming no overlapping of results.

Quality assessment

As shown in Table 1, 7 of the 9 clinical studies had a Jadad score of 5, and 2 studies had a score of 4. These high Jadad scores indicate good clinical study methodology in all the studies. On the other hand, assessment using RoB2 suggested risk of bias in several reports (Figure 2). Of the 12 reports analyzed, the overall risk of bias in judgment was high in 6, had some concerns in 1, and

was low in 5. For the domain of bias due to missing outcome data, 4 reports were rated as high risk and 4 reports as some concerns. Missing data was caused by large numbers of patients dropping out of the trial due to the long trial periods. Two reports that extracted Japanese data and hence reported a selected race were rated as high risk of bias in selection of the reported result.

Primary efficacy outcome: SLEDAI

Patients treated with belimumab were significantly in favor of achieving a ≥ 4 -point reduction in SLEDAI score compared with patients receiving placebo (relative risk [RR] 1.28; 95% confidence interval [CI], 1.16–1.40; $P < 0.00001$). There was no significant heterogeneity in this analysis (Figure 3A).

SLEDAI is available in various versions. Among the 4 efficacy studies in this analysis, Ginzler et al²³ used SLEDAI-2K, while the others^{22,26,33} used SELENA-SLEDAI.

Secondary efficacy outcomes: BILAG, PGA

Patients in the belimumab group were significantly in favor of achieving no new BILAG 1A/2B domain score compared with pa-

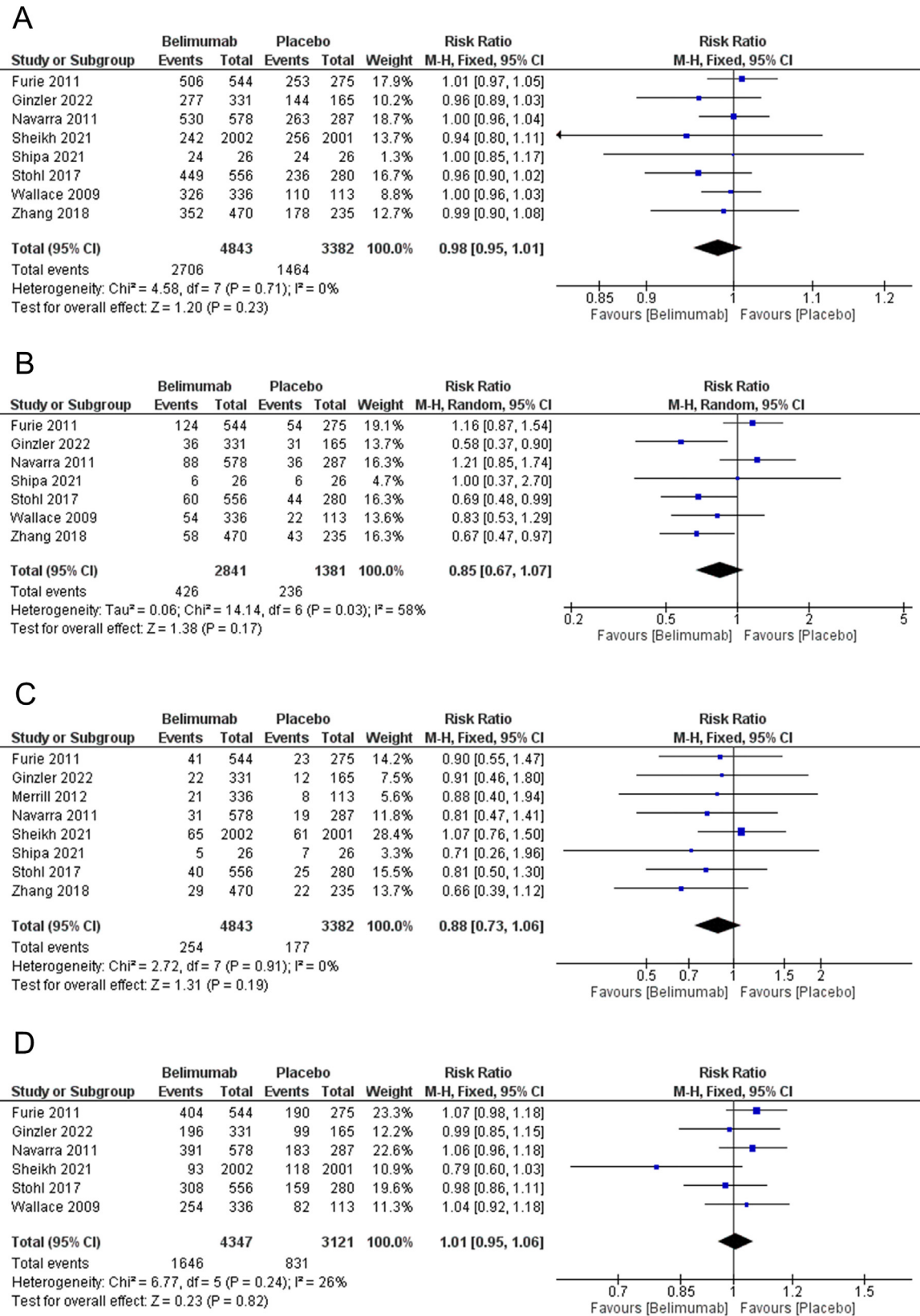


Figure 4. Forest plot of safety outcomes for belimumab versus placebo in SLE patients. (A) AEs, (B) SAEs, (C) withdraw due to AEs, (D) infections. AEs=adverse events; CI=confidence interval; M-H=Mantel-Haenszel method; SAEs=serious AEs; SLE=systemic lupus erythematosus.

tients in placebo group (RR 1.10; 95% CI, 1.03–1.17; $P=0.005$). Likewise, patients treated with belimumab were significantly in favor of showing no worsening in PGA (<0.3 increase from baseline) compared with patients receiving placebo (RR 1.12; 95% CI, 1.05–1.20; $P=0.0005$). No statistical heterogeneity was observed in these analyses (Figure 3B, C). For SF-36 and SDI, it was not possible to perform meta-analysis due to the small number of reports.

Safety outcome

AEs did not differ between the belimumab and placebo groups (RR 0.98; 95% CI, 0.95–1.01; $P=0.23$). There was no statistical heterogeneity in this analysis (Figure 4A). SAEs, withdrawals due to AEs, and infections were not significantly different between the 2 groups (Figure 4B–D). SAEs were moderately heterogeneous with $I^2=58\%$. Therefore, a random effects model was used in the analysis.

Discussion

We examined the efficacy of belimumab by conducting a meta-analysis to evaluate clinical trial data with single indexes used in routine clinical practice, rather than the composite index used in clinical trials during development. This is the first meta-analysis to evaluate the usefulness of belimumab focusing on single indexes such as SLEDAI, BILAG, and PGA, which are used in daily clinical practice. The results of this study also showed that the belimumab group achieved all the efficacy indexes significantly better than the placebo group. This finding is consistent with that of Wei et al¹⁷ who evaluated the usefulness of belimumab in patients with SLE in a meta-analysis using SLE Responder Index 4 (SRI4), a composite index. It is also consistent with the findings of Singh et al¹⁶ in a Cochrane review on the usefulness of belimumab in patients with SLE. Their review examined SELENA-SLEDAI and SF-36 quality of life indexes as well as AEs, rather than the composite index. In the present study, the efficacy of belimumab in patients with SLE was demonstrated not only based on composite indices such as SRI4, but also single indexes. In clinical practice, it is very important to be able to assess treatment efficacy easily using a single indicator.

We should consider the potential impact of synthesizing reported results using different versions of SLEDAI and results derived from subjects with different background on the finding of the meta-analysis. Multiple versions of SLEDAI are used as the primary outcome measure in the reports analyzed in this study. The original version of SLEDAI was developed in 1992,¹³ and subsequently revised and developed into 2 versions; SLEDAI-2K and SELENA-SLEDAI^{34,35}. The 2 revised versions are both evaluated based on disease activity over the past 10 days and are scored on a 105-point scale. SLEDAI-2K and SELENA-SLEDAI assess persistent disease activity in terms of rash, alopecia, and mucosal ulcers.³⁶ SELENA-SLEDAI, on the other hand, differs from SELENA-2K in that the presence of either objective or subjective findings is accepted to score the descriptor.⁷ The 2 revised versions of SLEDAI have been found to correlate with the original SLEDAI and have been treated equally in other studies.³⁷ However, one report using SLEDAI-2K showed no significant difference between belimumab and placebo; hence careful judgment is needed when applying the present results to clinical practice.²³

Differences in patient background in some included studies such as subgroup analysis of a selected ethnic group and study population receiving other biologics prior to belimumab may affect the results of meta-analysis. Two reports used in this meta-analysis were subgroup analyses of Japanese subjects from a multi-national clinical trial population.^{30,31} Racial differences in disease severity and prevalence have been reported for SLE, with a trend of higher prevalence and greater severity in non-Caucasian populations.^{23,31}

Regarding the administration of biologics, patients treated with rituximab were subsequently treated with belimumab in one clinical trial.²⁸ The effect of prior treatment with other biologics on the efficacy of belimumab has not been reported. However, because of the possibility of an effect, the criteria of subject enrollment included no prior use of biologic before study entry in all the clinical trials analyzed, except the above-mentioned study.²⁸ The impact of these reports on the results of this meta-analysis was examined in a sensitivity analysis, but no impact was found (data not shown).

The current study showed that the addition of belimumab to SoC is beneficial in reducing disease activity in patients with SLE. Furthermore, adding belimumab to SoC did not increase the risk of AEs. However, current treatment guidelines for SLE do not strongly recommend belimumab for patients with SLE. EULAR recommends to consider the use of belimumab when disease control with hydroquinone (HCQ), prednisone, and immunosuppressive agents is inadequate or when tapering of glucocorticoid is unacceptable.³ The British Society of Rheumatology guidelines state that belimumab should be used in patients with moderate or severe disease and when they do not respond to other therapies.¹⁰ In other words, belimumab is an option to consider when existing therapies do not provide an adequate response. The above guidelines and recommendations recommend disease management with HCQ and prednisone across a wide range of disease severity, from mild to severe. However, HCQ is toxic to the eye. Ocular toxicity increases markedly with increase in treatment duration, and the incidence has been reported to exceed 1% after 5 to 7 years.³⁸ Routine ophthalmologic examinations are necessary when HCQ is used, and caution should be exercised for long-term use in SLE. Similar risks have been reported for long-term use of prednisone. Gladman et al³⁹ reported that approximately 80% of organ damage at 5 years after diagnosis was associated with glucocorticoids. In the early stages of SLE, organ damage from the disease itself is more common, but in the later stages, damage from glucocorticoid therapy increases. Cumulative doses of glucocorticoids have also been reported to increase the risk of osteoporotic fractures, coronary artery disease, and cataracts.⁴⁰ Reducing both the cumulative dose and duration of glucocorticoid administration is an important issue in the treatment of SLE. To date, observational studies have examined dose reduction of glucocorticoids following belimumab therapy.^{41,42} In an observational study conducted in the USA, 86% of patients were able to discontinue or reduce the dose of prednisone after 6 months of belimumab treatment.⁴¹ Currently, some SLE patients suffer from treatment-related complications despite the availability of therapies that are useful in controlling their disease. We believe that the results of this study evaluating the benefit of the new drug belimumab will provide new insights for these patients.

However, our study has several limitations. First, the dropout rate in each study was high, over 20% in 4 reports. The clinical trials were relatively long, ranging from 52 to 76 weeks, which may have partially contributed to the high dropout rate. Although meta-analysis combines the effect sizes of different studies and generally improves the effect size, some of the individual studies were underpowered due to small sample size. Second, all the studies used in this analysis included patients with moderate-to-severe disease. Therefore, the present results may be difficult to apply to patients with mild disease. Finally, the association between SoC and outcome is unknown. However, since belimumab is currently approved for use in combination with SoC, this may reflect the real-world clinical situation. With regard to SoC, the possibility of dose reduction of glucocorticoids with add-on belimumab has been confirmed in clinical trials used in this analysis and in observational studies.^{41,42} The possibility of dose reduction of other standard therapies should also be clarified.

In conclusion, the present study using a meta-analysis/systematic review approach found that the addition of belimumab to SoC in adult patients with moderate-to-severe SLE is efficacious when evaluated using various guideline-recommended single indexes such as SLEDAI, BILAG, and PGA.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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