



Efficacy and Safety of Belimumab Plus Standard Therapy in Patients With Systemic Lupus Erythematosus: A Meta-analysis

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ABSTRACT

Purpose: The treatment of belimumab plus standard therapy in patients with systemic lupus erythematosus (SLE) has been studied extensively in recent years. Our aim was to estimate the efficacy and safety of this therapy compared with placebo plus standard therapy in patients with SLE.

Methods: PubMed, Web of Science, Embase, Chinese Biomedical Literature Database (CBM, Chinese), and Wanfang Database (Chinese) were searched for all randomized clinical trials that mainly studied the efficacy and safety of belimumab plus standard therapy before June 2015. We extracted or calculated the rate of the SLE Response Index and adverse event rate at 52 weeks in all the included studies. The odds ratio (OR) with 95% CI between the 2 groups in this meta-analysis was conducted by using a random-effects model. Sensitivity and publication bias analyses were also performed. All statistical tests were performed by using Stata software version 12.0 (StataCorp., College Station, Texas).

Findings: In the overall samples (4 studies, N = 4692), a significantly higher SLE Response Index rate at 52 weeks was found in belimumab plus standard therapy group compared with the placebo plus standard therapy group in all studies (OR = 1.49; 95% CI, 1.26–1.77; $P < 0.001$). When assessed with the incidence of serious adverse events, the data revealed that there was no significant difference between the 2 groups, with pooled OR = 1.08; 95% CI, 0.83–1.39; $P = 0.573$; OR = 1.23; 95% CI, 1.02–1.48; $P = 0.029$; and OR = 1.07; 95% CI, 0.88–1.29; $P = 0.506$.

Implications: The results suggest that treatment with belimumab plus standard therapy is more effective than placebo plus standard therapy in SLE patients,

which represents major progress in the treatment of SLE. Regardless of the statistical analyses, further research is necessary to optimize treatment effects. (*Clin Ther.* 2016;38:1134–1140) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: belimumab, adverse event, meta-analysis, systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by an unpredictable course and loss of self-tolerance with hyperactivation of autoreactive T and B cells and autoantibody formation.¹ Currently, conventional treatments including corticosteroids, antimalarial agents, and immunosuppressive agents, either alone or in combination, are the main standard treatments for the SLE patients.² However, the traditional treatments for SLE has been challenged due to the heterogeneity of the disease and various disease activity scales. These SLE therapies are often not effective enough and cause various serious side effects.³ In addition, there have been few drugs that have specifically been approved for to treat SLE, which makes the situation worse.⁴

The current advances in immunology and rheumatology raise the hope of the development of a new treatment for SLE. Biological therapies, which target important pathogenetic disturbances in the immunological system of SLE patients, provide hope for effective

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and safe treatment of SLE. Currently the most advanced clinical trials are being conducted with antilymphocyte B drugs, such as rituximab, belimumab, and epratuzumab.^{4,5} Belimumab is an immunoglobulin G1 monoclonal antibody that targets and inhibits the biological activity of soluble B-lymphocyte stimulator (BLyS). Belimumab, the first biological agent, was registered for treatment of the active seropositive form of SLE. Compared with traditional SLE treatments, belimumab targets specifically the fundamental pathology of SLE and has been widely interpreted as representing an advancement in treatment options.^{6,7} Significantly greater benefits have been shown with belimumab plus standard SLE therapy than those with placebo plus standard therapy in many clinical trials. However, these trials were designed to assess the effects of belimumab on different clinical parameters to track the progression of SLE. These include the Physician's Global Assessment, the Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLE-DAI), the British Isles Lupus Assessment Group (BILAG) Index, and the SLE Response Index (SRI).^{8,9} Therefore, the results of these studies remain inconclusive.

In this meta-analysis, our main aim was to synthesize findings from randomized, controlled trials (RCTs) of belimumab treatment to assess the overall performance of this drug using the SRI and incidence of adverse events (AEs).

METHODS

Study Identification

The relevant studies were identified and selected by searching the databases of PubMed, Cochrane Library, Embase, CINAHL, and the Science Citation Index (updated to June 2015) with the search terms “belimumab” and “SLE” combined with “treatment” and for all study publications; there was no language restriction in the literature search. Additional studies were identified by a hand search of the references of original research, and reviews were also examined in order to find more eligible studies. With regard to published studies by the same authors, with overlapping data, we selected the most recent or complete study only.

Inclusion Criteria

The inclusion criteria of our meta-analysis were as follows: (1) evaluation of the belimumab treatment for SLE; (2) RCTs; (3) provided sufficient SRI or AE

incidence data in order to calculate the odds ratio (OR) with 95% CI. The following were exclusion criteria: (1) not a case-control study, (2) reviews or case reports, (3) no available data reported, and (4) duplicated reports. No language or date limitations were imposed. There was also no limitation on the form of publication.

Data Extraction

We extracted the following data from articles that met criteria: (1) first author's name, (2) patient characteristics, (3) ethnicity, (4) ages, and (5) number of subjects. Any disagreement was resolved by consensus.

Quality Assessment

The quality of the included RCTs was assessed in accordance with the Cochrane Handbook¹⁰ by recording 7 items of bias risk: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data addressed, and free of selective reporting.

Statistical Analyses

Unadjusted ORs were calculated for binary outcomes. The heterogeneity was tested by using a χ^2 -based Q statistic test. The effect of heterogeneity was quantified by using an I^2 value as well as a P value. If the I^2 value was $>50\%$ or $P < 0.10$, ORs were pooled in a random-effects model. Otherwise, a fixed-effects model was used. A sensitivity analysis was carried out to assess whether there was stability of our results. We assessed for publication bias by using Egger's test ($P < 0.05$ indicates that statistically significant publication bias existed) and visual observation of the funnel plot. All statistical tests were conducted by using the Stata software version 12.0 (StataCorp, College Station, Texas).

RESULTS

Our search returned 149 publications and abstracts, of which 135 were clearly not relevant to the study and excluded. Ten studies were excluded because the absence of required data and duplicated studies. Four RCTs were identified for systematic analysis (Figure 1).

Study Selection and Characteristics in the Meta-Analysis

We included a total of 4 articles^{11–14} in our meta-analysis after a careful examination based on the

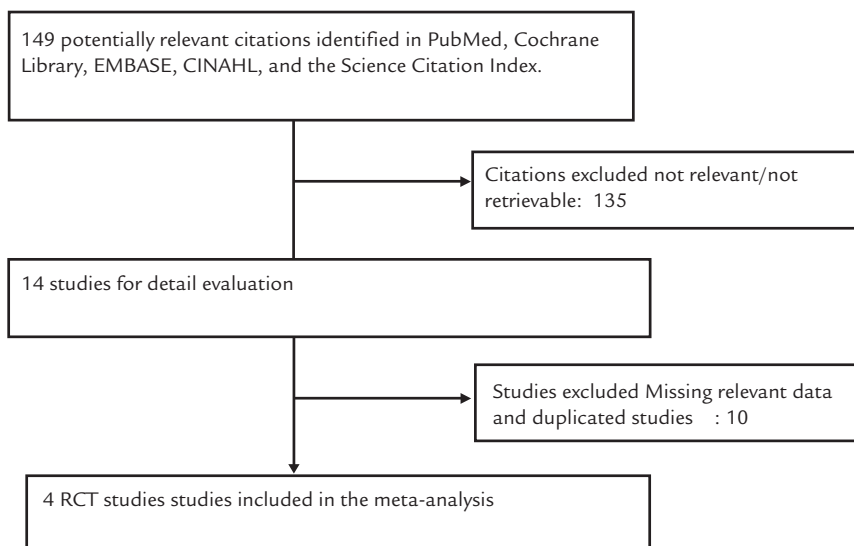


Figure 1. Scheme of selection of articles included in the meta-analysis: MEDLINE, the American College of Rheumatology, and the Europe League against Rheumatology search: process selection.

inclusion criteria. Of these articles, only 2 provided the data regarding both SRI and AEs at 52 weeks in patients treated with belimumab plus standard therapy compared with standard therapy. One article contained only the data of SRI at 52 weeks, and 1 provided incidences of AEs alone. Therefore, 3 articles reported the results of SRI at 52 weeks and 3 reported AE incidence. The general characteristics of studies included in the meta-analysis are listed in the [Table](#). All patients received standard therapy plus belimumab or placebo by intravenous infusion on days 0, 14, and 28, and then every 28 days to week 52 (BLISS-52). The 2 groups did not differ in any of the main baseline characteristics or in the reasons for discontinuation of treatment. Patients with SLE who were receiving standard therapy were randomized to placebo or belimumab.

Effectiveness in the Belimumab Therapy and Placebo Groups

The primary end point in both trials was the SRI rate at week 52. The SRI is a composite responder index that includes 1 measure of disease activity improvement (≥ 4 -point decrease in Safety of Estrogens in Systemic Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index [SELENA-SLE DAI] score). A 4-point reduction is, therefore, considered clinically meaningful. As shown by [Figure 2](#), the I^2 value is $>50\%$ and $P = 0.919$; ORs were calculated by a

fixed-effects model. There was a significantly higher SRI response rate at 52 weeks in the belimumab plus standard therapy group than in the placebo plus standard therapy group, with pooled ORs = 1.49 (95% CI, 1.26–1.77; $P < 0.001$). These findings suggest that belimumab plus standard therapy has greater therapeutic effectiveness than standard therapy alone in patients with SLE.

Safety in the Belimumab Therapy and Placebo Groups

The most common AEs in patients included arthralgia, upper respiratory tract infection, headache, fatigue, and nausea. Because the I^2 value is $>50\%$ and $P < 0.05$, a fixed-effects model was used. In terms of the incidence of AEs and serious AEs ([Figures 3A](#) and [3C](#)), analysis of data revealed no significant difference between the treatment group and placebo group (OR = 1.08; 95% CI, 0.83–1.39; $P = 0.573$ and OR = 1.07; 95% CI, 0.88–1.29; $P = 0.506$). However, when assessed by the incidence of serious AEs, there was a slightly significant difference between the 2 groups with OR = 1.23; 95% CI, 1.02–1.48; $P = 0.029$ ([Figure 3B](#)).

Sensitivity Analysis and Publication Bias

A sensitivity analysis was performed to assess the sensitivity of our meta-analysis. The results revealed no

Table. General characteristics of studies included in the meta-analysis.

First Author	Patient Characteristics	Ethnicity	Age, y (SD)	Sample Size
Wallace ¹¹	Score ≥ 6 on SELENA- SLEDAI who were autoantibody positive, on standard therapy for > 30 days, and without severe active lupus nephritis or central nervous system lupus	White (51.99%), Asian (17.12%), black (11.92%), Hispanic or Latino (31.53%), Alaska Native or Native American from northern, central, southern United States (18.38%), Native Hawaiian or other Pacific Islander (0.2%)	40.2 \pm 10.9	2143
Navarra ¹²	Patients (age ≥ 18 y) who met the American College of Rheumatology criteria for SLE and had active disease (score ≥ 6 on SELENA-SLEDA I)	Native American (33.3%), white (26.5%), black (3.5%), Asian (37.8%), Hispanic or Latino (48.6%)	35.6 (11.5)	865
von Vollenhoven ¹³	All patients had a score ≥ 6 on SELENA-SLEDAI, corticosteroid use in 86% and anti-dsDNA positivity in 69%. In addition, 45% of patients had low C3 levels and 56% had low C4 levels		38.7 (11.4)	865
Furie ¹⁴	Patients with scores > 6 on SELENAI	Native American (12.6%), white (69.5%), black (14.4%), Asian (3.4%), Hispanic or Latino (21.1%)	35.5 (11.1)	819

dsDNA = double-stranded DNA; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE = systemic lupus erythematosus.

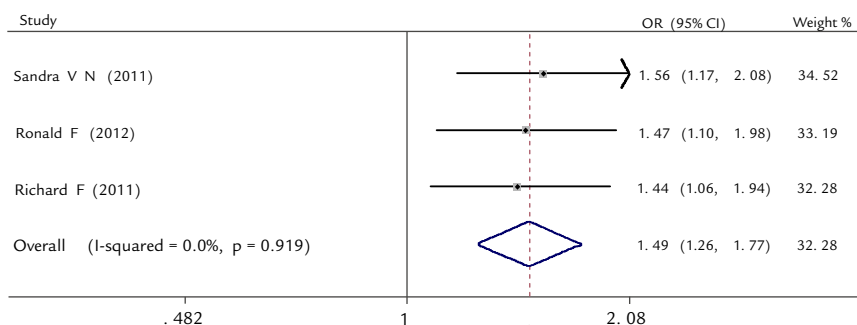


Figure 2. Results of meta-analysis of Systemic Lupus Erythematosus Response Index at week 52 comparing belimumab plus standard therapy with placebo plus standard therapy. OR = odds ratio.

significant differences in the 4 trials (data not shown). Therefore, the results suggested data included in our study was relatively stable and credible. To estimate the publication bias, both funnel plot and Egger's test were conducted. Both the shapes of the funnel plot and Egger's test ($P > 0.05$, data not shown) showed no asymmetry in our meta-analysis, indicating that no publication bias existed in our meta-analysis.

DISCUSSION

The study is a comprehensive meta-analysis of the clinical studies, which was designed to assess the effect of belimumab in combination with standard therapy in patients with SLE. We found that belimumab with standard treatment has a significantly higher SRI at week 52 than placebo with standard treatment. All studies included demonstrated that no significant dose-related increase in SRI rate was observed. These suggest that belimumab with standard therapy is more effective than placebo with standard treatment in patients with SLE. Furthermore, belimumab plus standard therapy had a similar safety effect with placebo plus standard treatment, which had no significant differences in the occurrence of AEs or serious AEs between the 2 groups. Although the rate of serious AEs was somewhat higher with belimumab, there was no excess of AEs within any individual organ system class. Furthermore, the studies of both Wallace et al.¹¹ and Navarra et al.¹² showed that the rates of serious AEs were similar across treatment groups. Therefore, long-term follow-up in larger numbers of patients is needed for a definitive

assessment of serious AEs. In addition, Mosak and Furie¹⁷ found that the rates of renal flare, renal remission, renal organ disease improvement, proteinuria reduction, grade 3/4 proteinuria, and serologic activity favored belimumab. Significant reductions in immunoglobulin G and autoantibodies and improvement in C3/C4 levels were found in belimumab-treated patients, resulting in greater positive-to-negative conversion rates for immunoglobulin G anti-double-stranded DNA, anti-Sm, anticardiolipin, and antiribosomal P autoantibodies, and normalization of hypergammaglobulinemia and low C3/C4 levels.¹⁵ However, there are not enough reports providing the exact data regarding anti-double-stranded DNA and C3/C4 levels for further meta-analysis.

Belimumab is a human immunoglobulin G1 monoclonal antibody. The mechanism of belimumab is to bind soluble human BLyS and inhibit its biological activity.¹⁶ BLyS was overexpressed in patients with SLE and other autoimmune diseases, and its level correlated with increased SLE disease activity and elevated titers of anti-double-stranded DNA antibody.¹⁷ BLyS was initially discovered as a cytokine that induced B-cell proliferation and immunoglobulin secretion. Many studies demonstrated that it plays a critical role in the maturation and survival of peripheral B cells. Therefore, belimumab is able to reduce BLyS concentration, which leads to apoptosis of autoimmune B cells and results in the reduction of new or existing autoimmune B-cell clones.¹⁷⁻¹⁹

The number of published RCTs would affect the results of this study, and the quality of the reported data influenced the power of our meta-analysis; greater statistical reliability would be achieved if

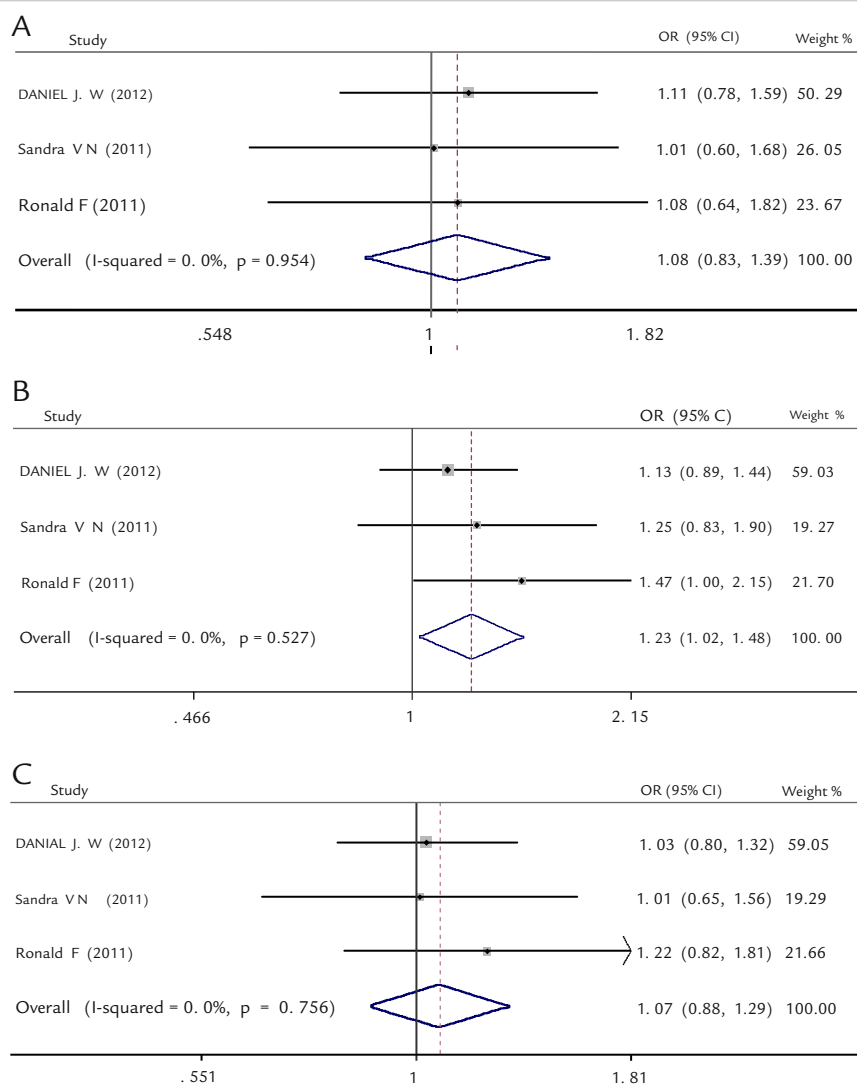


Figure 3. Results of meta-analysis for incidence of adverse events (A), serious adverse events (B, C) at week 52 in the belimumab plus standard therapy group and the placebo plus standard therapy group.

additional and more comprehensive trials including all of the efficacy parameters were included. Nevertheless, a sensitivity analysis supported the conclusions drawn from the overall unstratified analyses. In addition, this study has several potential limitations. First, the possibility of information and selection biases and unidentified confounders cannot be completely excluded. Second, most studies included in this meta-analysis were conducted in Western countries. Thus, our findings may not be generalizable to populations in East Asia. Third, we restricted our search strategy to articles published in English

or Chinese. Articles with potentially high-quality data that were published in other languages were not included.

CONCLUSIONS

Our meta-analysis shows that belimumab with standard therapy is more effective than placebo with standard treatment in controlling progress in patients with SLE. Inhibition of soluble BLyS with belimumab would represent major progress in the treatment of SLE, paving the way for the development of new

biological agents, potentially revolutionizing the treatment of SLE.

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CONFLICTS OF INTEREST

No conflict of interest exists.

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