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Novel Evidence-Based Systemic Lupus Erythematosus Responder Index

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Abstract

Objective—To describe a new systemic lupus erythematosus (SLE) Responder Index (SRI) based on the belimumab phase II SLE trial and demonstrate its potential utility in SLE clinical trials.

Methods—Data from a 449-patient randomized, double-blind, placebo-controlled study of 3 doses of belimumab (1, 4, 10 mg/kg) or placebo plus standard of care therapy (SOC) over a 56-week period were analyzed. SELENA-SLEDAI and BILAG SLE disease activity instruments, SF-36 Health Survey, and biomarker analyses were used to create a novel SRI. Response to treatment in a subset of SLE patients (n=321) who were serologically active (ANA ≥1:80 and/or anti-dsDNA antibody ≥30 IU) at baseline was retrospectively evaluated using the SRI.

Results—SRI response is defined as: 1) ≥4-point reduction in SELENA-SLEDAI score; 2) no new BILAG A or no more than 1 new BILAG B domain score; and 3) no deterioration from baseline in the Physician's Global Assessment (PGA) by ≥0.3 points. In serologically active patients, addition of belimumab to SOC resulted in a response in 46% of patients at week 52 compared with 29% for the placebo patients (P=0.006). SRI responses were independent of baseline autoantibody subtype.

Conclusion—Evidence-based evaluation of a large randomized, placebo-controlled trial in SLE resulted in the ability to define a robust responder index based on improvement in disease activity without worsening of the overall condition or the development of significant disease activity in new organ systems.

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INTRODUCTION

Randomized, controlled trials (RCTs) of patients with systemic lupus erythematosus (SLE) are particularly challenging because of the heterogeneity of disease manifestations (1), the waxing and waning course of the disease, the variety of immunomodulating medications utilized to control disease activity (2,3), and the lack of a standardized method for defining response. The American College of Rheumatology (ACR), the Food and Drug Administration (FDA), Outcome Measures in Rheumatology Trials (OMERACT), European League Against Rheumatism (EULAR), and clinical experts recommend that SLE clinical trials include outcome measures assessing cumulative organ damage, SLE disease activity, health-related quality of life (HRQoL), and adverse events (3–8). In 1987, members of the Systemic Lupus International Collaborating Clinics (SLICC) initiated an effort to develop a consensus for disease activity indices (DAIs) and outcome measures for SLE RCTs. Since that time, numerous instruments have been used in SLE clinical studies, including, but not limited to: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (9), the modifications to the SLEDAI that were developed for the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial (SELENA-SLEDAI) (10), and the British Isles Lupus Assessment Group (BILAG) instrument (11,12), their SLE flare indices (13,14) as well as the SLICC damage index (15).

SLEDAI, Systemic Lupus Activity Measure (SLAM), and BILAG have performed in effective and reliable manners in studies; furthermore, they correlate with one another (6,16,17). SLEDAI, SELENA-SLEDAI, SLEDAI 2000 (18–21), and BILAG (11,12,22) have been successfully used in observational trials and case studies, although baseline DAI scores were not always predictors of subsequent damage or other outcomes (23,24). These DAIs were validated in the context of long-term observational studies and not in RCTs (3,6,7,9,12,22). The few RCTs conducted have shown that improvement in DAI scores correlated with response rates, disease remission, and flare prevention (3,6,25,26). However, a threshold of clinically meaningful change has not been established in studies performed with the investigational agents anti-CD40L antibody (27), dehydroepiandrosterone (DHEA) (28), abetimus sodium (29), mycophenolate mofetil (30), or rituximab (31). A responder index, developed in collaboration with the FDA, defined response as improvement and/or “no deterioration” in patient- and physician-reported outcomes (28).

In 2005, the FDA released draft guidance on the development of drugs for the treatment of SLE that covered the use of DAIs, flares, and organ-specific outcomes (4). Based on the FDA, OMERACT, and EULAR recommendations, the ideal responder index should detect early as well as overall changes in disease activity. It should also be able to simultaneously identify improvement and worsening in the same and/or different organ systems, be validated by a long-term RCT, and be compatible with regulatory requirements of the FDA and European Medicines Agency (EMEA) (4,5,8).

The largest phase II RCT in SLE completed to date examined the efficacy of belimumab in patients with active SLE who were receiving standard of care therapy (32). Belimumab, a fully human monoclonal antibody to B-lymphocyte stimulator (BLyS), was developed to selectively inhibit the biologic activity of soluble BLyS (33). Elevated levels of BLyS (a promoter of B-cell survival, B-cell differentiation, and Ig-class switching) have been shown to correlate with increased SLE disease activity (32,34). In this phase II trial, exploratory analyses identified a major subpopulation of SLE patients who were serologically active, indicative of B-cell hyperactivity, and were more responsive to belimumab therapy than to placebo as determined by SLE DAIs and HRQoL (32,35,36).

Evidence-based exploratory analyses of this RCT led to the creation of a robust individual responder index, which not only could be used as a primary endpoint in SLE trials but could also define a clinically meaningful change. The SLE Responder Index (SRI) utilizes the SELENA-SLEDAI score to determine global improvement; BILAG domain scores to ensure no significant worsening in heretofore unaffected organ systems; and Physician's Global Assessment (PGA) to ensure that improvements in disease activity are not achieved at the expense of the patient's overall condition, which may have been missed by either DAI.

PATIENTS AND METHODS

Study Design and Entry Criteria

The evidence base for the SRI evaluation came from a phase II dose-ranging RCT evaluating the safety, tolerability, biologic activity, and efficacy of belimumab combined with SOC in 449 SLE patients who had SELENA-SLEDAI scores of ≥4 at baseline (32). Patients with a diagnosis of SLE by ACR criteria (37) and a history of measurable autoantibodies who were on a stable SOC regimen (2) for at least 30 days prior to screening were included; patients with active lupus nephritis or central nervous system disease were excluded. Concurrent corticosteroid and immunosuppressive agents could be changed throughout the protocol as clinically indicated. All patients gave informed consent for the study, and there was an independent Data Safety Monitoring Committee (32).

Patient population—A major subset of patients (n=321) identified as serologically active (antinuclear antibodies [ANA] ≥1:80 by HEp-2 cell immunofluorescence and/or anti-dsDNA ≥30 IU/mL) at screening and baseline (Day 0) were found to respond better to belimumab therapy than to placebo (32). Representing 71.5% of the original cohort, these patient were assessed to evaluate components of SLE DAIs in developing the SRI.

SLE disease activity and efficacy measures: DAIs—SELENA-SLEDAI (10), SLE Flare Index (SFI) (13), PGA, BILAG (11,22), and SF-36 (38) were determined every 4 weeks during the first 24 weeks of the study and then at weeks 32, 40, 48, and 52. A reduction of ≥4 points in SELENA-SLEDAI score from baseline is considered to be a clinically meaningful improvement (39). PGA (10,13) scores of 0, 1, 2–2.5 and 3 are benchmarks on a 10-cm visual analog scale (VAS) corresponding to no, mild, moderate or severe life-threatening lupus disease activity, respectively. An increase in ≥1 unit from the last assessment is considered a mild-moderate flare, whereas an increase to >2.5 points is considered a severe flare (13). An increase of ≥0.3 points (>10% on the 3-point VAS) from baseline was considered clinically significant worsening (40). The SFI identifies mild-moderate flares or severe flares based on clinical activity, PGA, or need for additional treatment (13). A severe flare by classic BILAG is defined as a new organ domain score of A, whereas a moderate flare is defined as a new organ domain score of B (14). Biomarkers and laboratory parameters routinely measured with the SLE disease activity scales have been described (32).

SLE Responder Index—The SRI was calculated any time the SLE disease activity scores were measured in individual patients. A responder was defined as having ≥4-point reduction from baseline in SELENA-SLEDAI score AND no new BILAG A organ domain scores or ≥2 new BILAG B organ domain scores compared with baseline AND no worsening in PGA (<0.3-point increase from baseline). If all 3 criteria were met, the patient was considered a responder at that particular point in time; otherwise, the patient was considered a non-responder.

Statistical methods—An exploratory analysis, limited to patients with serologic activity at screening and baseline, was performed on all disease activity scales and efficacy parameters at the week 52 visit. Because of the general lack of a dose response observed in biomarkers, efficacy parameters, or safety measures, the 3 belimumab treatment groups were combined (n=235) and compared with the placebo-treated patients (n=86) (32). The SRI and all other categorical data were analyzed using the likelihood ratio chi-squared test, and the percent change from baseline in PGA was analyzed using a Student *t* test. The absolute change from baseline in SF-36 Physical Component Summary (PCS) was analyzed using the analysis of variance, adjusting for the baseline PCS score. For other study endpoints, discrete variables were analyzed using a likelihood chi-squared test and continuous variables using a Student *t* test.

Missing data in SELENA-SLEDAI, BILAG, and PGA were imputed using a last observation carried forward (LOCF) method. A sensitivity analysis of SRI was also performed in which discontinuation before the week 52 visit was considered to be a treatment failure. Analysis of the selected efficacy endpoints was performed in a modified intention-to-treat (mITT) population, defined as all patients who were randomized and received at least 1 dose of study drug or placebo. The SRI analyses were retrospectively applied to the phase II data of all patients and the serologically active subset. The analyses were not subjected to multiple comparison adjustment.

RESULTS

Demographics and baseline characteristics of serologically active SLE patients

There were no significant differences across treatment groups in any of the parameters, as shown in Table 1. The serologically active patients, representing 71.5% of the enrolled patient population, had similar baseline demographics to the entire cohort (32), except for a higher percentage with anti-dsDNA antibodies (69.5% versus 49.7%), ANA ≥1:80 (95.3% versus 71.2%), a history of immunologic disorder per the ACR SLE criteria (84.4% versus 72.6%), and low C3 (39.3% versus 30.1%) or C4 (50.2% versus 40.1%).

Efficacy

Change from baseline in SELENA-SLEDAI score—Three analyses compared week 52 belimumab treatment responses to placebo in the serologically active population (Figure 1): 1) percentage change in SELENA-SLEDAI scores; 2) percentage of patients achieving a threshold of absolute change in SELENA-SLEDAI score by 1-point increments of improvement or worsening (range −5 to +5, respectively); 3) percentage of patients with ≥4-point improvement. The percent reduction in SELENA-SLEDAI scores at week 52 were statistically greater in the belimumab group than in the placebo group (−28.8% versus −14.2% placebo; P=0.044) (Figure 1A). There were significantly more patients with >0- to ≤2- point improvements in the belimumab group than in the placebo group; a trend to belimumab-treated patients achieving≥3- to ≤5-point improvements without reaching statistical significance was also observed (Figure 1B). Compared with placebo, significantly fewer patients treated with belimumab had worsening of SELENA-SLEDAI scores at all incremental changes >0 to ≤5 points. A larger percentage of patients had a ≥4-point reduction in SELENA-SLEDAI in the belimumab group than in the placebo group at all time points (not significant), with separation beginning at week 16 (Figure 1C and Table 2).

PGA and SF-36 PCS—Among serologically active patients, the PGA scores in belimumab-treated patients were significantly lower than the scores observed in placebo-treated patients, both early (weeks 4, 8, 16) and late (weeks 48, 52) in the study. A 32.7% reduction in PGA score at week 52 in the belimumab group was observed versus a 10.7%

reduction with placebo treatment; *P*=0.001 (Figure 2A). Similarly, the PCS score of the SF-36 improved significantly more in the belimumab group than in the placebo group at weeks 12, 24, 48, and 52 (+3.0 versus +1.2 points with placebo at week 52; *P*=0.041) (Figure 2B). The minimal clinically important difference in SF-36 PCS from baseline is considered a 2.5-point increase (35,36), which was observed only in the belimumab group from week 24 onward.

BILAG organ domain flares—There were no significant differences between the belimumab and placebo groups in the percentages of patients who developed new A or B organ domain scores at week 52 (29.4 versus 39.5% with placebo; *P*=0.087) (34). However, focusing on specific organ domains (Figure 3), significantly fewer belimumab-treated patients than placebo patients had new BILAG A or B flares in the renal (*P*=0.034), neurological (*P*=0.035), and musculoskeletal (*P*=0.008) domains. A favorable trend was seen in the cardiorespiratory (*P*=0.060) organ domain. Incorporating a higher threshold for SLE flare, there were fewer new 1A or ≥2 B organ domain flares at week 52 in the belimumab group (8.5% versus 18.6% with placebo; *P*=0.015) (Table 2).

SLE Responder Index (SRI)—In serologically active patients, the week 52 response rates for the SRI and its 3 components are shown in Table 2. No dose response was evident across the 3 belimumab dosing groups. Higher SRI response rates over time occurred in the belimumab-treated group than in the placebo group, with separation after week 12. Statistical significance was reached at week 52 (belimumab group=46% versus 29% with placebo; *P*=0.006) (Figure 4A) and week 56 (49% versus 35% with placebo; *P*=0.029; data not shown). A greater percentage of patients who received belimumab achieved a ≥4-point improvement in SELENA-SLEDAI score at week 52 than in the placebo group (49.4% versus 39.5% in placebo; *P*=0.117). Patients who received belimumab were more likely to have no worsening (<0.3-point increase) in PGA at week 52 (90.2% versus 76.7% with placebo; *P*=0.003) and have no new A or 2 B BILAG flares (91.5% versus 81.4% with placebo; *P*=0.015) than those in the placebo group. More patients on belimumab treatment achieved sustained SRI responses (weeks 40–52) than those on placebo (26.8% versus 17.4%; *P*=0.076; data not shown).

Sensitivity analyses of a modified SRI were performed in which the minimum requirement for improvement in SELENA-SLEDAI score was 5, 6 or 7 points. At a threshold of ≥5 point improvement, 35.9% (n=206) of those in the belimumab group achieved a response compared with 22.5% in the placebo group (n=71; *P*=0.034). More stringent requirements of 6- or 7-point improvements reduced the number of evaluable patients with higher baseline scores, but the treatment effect remained favorable, although not statistically significant (*P*≤0.242; data not shown). To address the impact of laboratory values on the SRI, analyses were performed following removal of both anti-dsDNA and complement components of the SELENA-SLEDAI score. SRI response rates (all active belimumab 47.3% versus 32.4% placebo; *P*=0.025, Table-2) without the serological components remained statistically different, confirming the clinical relevance of the SRI.

The percentage of patients with ≥4-point improvement inSELENA-SLEDAI score defined as non-responders (not achieving one or both of the other response criteria, PGA or BILAG) in the SRI was over 3-fold greater in the placebo group than in the belimumab group (10.3% placebo versus 3.4% belimumab). Of 34 placebo-treated patients who had a ≥4-point improvement in SELENA-SLEDAI score at week 52, 9 patients (26%) did not meet SRI criteria because of worsening disease activity (2 PGA, 3 BILAG, and 4 PGA+BILAG). In comparison, of 116 belimumab-treated patients with a ≥4-point improvement in SELENA-SLEDAI score at week 52, 8 patients (7%) did not meet SRI criteria because of worsening disease activity (2 PGA, 4 BILAG, and 2 PGA+BILAG). Even if dropouts before week 52

were assumed to be non-responders at 52 weeks, a greater percentage of serologically active patients treated with belimumab achieved a response as defined by the SRI (40.9% versus 27.9% with placebo; *P*=0.031; data not shown).

Analysis of all belimumab-treated patients stratified by autoantibody subtype (anti-dsDNA, anti-RNP, anti-Ro, anti-cardiolipin, and anti-Smith; n=63 to 165 per subgroup) at baseline revealed that the week 52 SRI responses were comparable (40%–51%) across the 5 different autoantibody subtypes and the serologically active (46%) group (n=235) (Figure 4B). Analysis of all patients (N=449), irrespective of baseline autoantibody status, demonstrated a significantly higher SRI response rate at week 52 in the combined belimumab treatment group (45.9% versus 35.4% in placebo; *P*=0.045; data not shown).

DISCUSSION

The lack of a gold standard to measure SLE disease activity or a surrogate marker endorsed by international rheumatology societies or national health authorities has impeded the development of SLE therapies. Several DAIs, such as the SLEDAI, SELENA-SLEDAI, BILAG, SLAM, and European Consensus Lupus Activity Measure (ECLAM) (3,7) have been validated based on the concordance of scores with expert opinion, acceptable inter-observer variability among trained evaluators, correlation between individual patients' scores on different indices, and correlation between increases in scores and clinical decisions to increase therapy. Although each DAI has its unique strengths and weaknesses, all have demonstrated sensitivity to changes (7) in disease activity in cohort studies, and, therefore, are suitable for use in clinical trials. The draft FDA guidance document recommended analyzing the results of clinical trials to verify "that an improvement in a disease activity score represents clinical benefit to the patient and to assess the generalizability of the results" and "that the improvement in disease activity is not accompanied by worsening in other disease manifestations" (4).

A reduction from baseline in SELENA-SLEDAI score by ≥4 points has been defined as clinically meaningful (39). As a validated instrument requiring the unambiguous elimination or normalization of SLE signs, symptoms, or lab abnormalities, the SELENA-SLEDAI sets a high threshold for response. With the exception of laboratory values, it is not easily triggered by normal variations in disease activity. Increased disease activity using the SLEDAI or SELENA-SLEDAI has been defined as an increase of 3 or more points (10,13). The SLEDAI, SLEDAI 2000, and SELENA-SLEDAI scores have been validated in observational studies, large RCTs (3,7,10,41), and across populations with different ethnicities and races (16,17). In addition, recent correlations of BILAG classic and BILAG 2004 (42) with SLEDAI 2000 indicated that a ≥3-point reduction in SELENA-SLEDAI score correlated with a clinically meaningful change in BILAG and an associated reduction in therapy, whereas a ≥3-point increase in score was associated with disease worsening and new or increased therapy (43). In contrast, an ACR expert panel reviewing 15 case vignettes over 2 to 3 visits thought a minimum of a 7-point reduction in SELENA-SLEDAI score to be clinically meaningful (44). The variations in defining a clinically meaningful threshold could be due to dissimilar sample sizes or baseline disease severity.

It is vital that improvement in SLE disease activity is not accompanied by worsening of other disease manifestations. The choice of the BILAG to evaluate worsening provided a sensitive measure of flare, because it assesses changes in organ-specific disease activity between points in time and was specifically developed with the tenet of intention to treat. It is thought that the development of either 1A or ≥2 B organ system scores represents an increase in disease activity sufficient to add new therapy consisting of steroids and/or immunosuppressives (11,14,22), underscoring this definition as an important anchor of

clinically meaningful change. The flare component of the SELENA-SLEDAI was not included in the measure of worsening because it was found to be particularly problematic in situations where patients with high disease activity at baseline triggered a severe flare based on modest increases in SELENA-SLEDAI from scores close to 12 to a score >12.

The PGA component is included in the SRI to ensure that improvement in SELENA-SLEDAI score was not achieved at the expense of worsening of the patient's overall condition, which might not have been detected by BILAG or SELENA-SLEDAI. The PGA has been shown to correlate with SLEDAI or SELENA-SLEDAI scores (9,10) and other DAIs (3,7,10,13,17,20,41). In a study performed by SLICC, SLE experts compared BILAG and SLEDAI scores with a physician-generated VAS in 80 cases evaluated at baseline, 3, and 6 months. The 2 DAIs correlated well over time, but less so with the physician VAS, indicating that the VAS detects factors not reflected in the DAIs (45). In addition, OMERACT and EULAR recommend that outcome measures in clinical trials include disease activity with global and organ system scores, as well as biomarkers, HRQoL, and damage scores (5,8).

In other diseases where manifestations are heterogeneous, combined responder instruments have been used to assess disease activity. In fact, the accepted primary regulatory endpoint for most rheumatoid arthritis RCTs, ACR 20, includes measures of signs, symptoms, and laboratory values. It incorporates several VAS scores that assess physician and patient global status of disease activity (46), as well as patient-reported pain. Furthermore, the primary endpoint for Crohn's disease, the Crohn's Disease Activity Index (CDAI), includes measures of organ involvement, signs, symptoms, laboratory values, an assessment of patient global status, and use of medications (47).

The BILAG composite score or reduction of A and/or B organ domain scores were considered for inclusion in the SRI as measures of assessing improvement. However, in the phase II belimumab trial, both of these BILAG measures failed to show consistent improvement for either belimumab or placebo treatment because new or recurrent C or B scores, especially in the musculoskeletal and mucocutaneous domains, were frequently triggered through minor fluctuations of disease activity or laboratory values. Whereas BILAG scoring, which is anchored with definitions, was more sensitive to change than SELENA-SLEDAI, the variability was so great using the primary outcome definitions that improvement or worsening often was not sustained for more than 1 to 3 months at a time. This suggested that defining 1 new B score as the cutoff for flare is too sensitive if the goal is to restrict flares to those that represent clinically meaningful changes. BILAG is a comparison with the prior month and is not anchored to baseline values; therefore, a patient could improve from the last visit but still be worse than they were at baseline. Conversely, a flare could be triggered despite the patient being better than at baseline.

A >2.5-point improvement in SF-36 PCS (value of the minimum clinically important difference [MCID]) (35,36) was evaluated as an additional response criterion in the SRI. The SF-36 PCS median score was significantly improved in the group treated with belimumab compared with the placebo group. Significant differences were noted as early as 12 weeks, and sustained increases of >2.5 points were observed from weeks 24 through 52. SF-36, a generic measure of HRQoL that has been validated in SLE RCTs, offers the ability to compare SLE with other chronic rheumatic and nonrheumatic conditions (35,36). Incorporating the SF-36 PCS as a fourth component of the SRI reduced the overall percentage of responders but increased the separation between active and placebo treatment (48). Although OMERACT (8), FDA (4), and EULAR (5) guidance recommend that HRQoL be measured in SLE RCTs, SF-36 was not included in the SRI as it is not a measure of SLE disease activity. Therefore, SF-36 data will be a major secondary endpoint in

subsequent RCTs to assess the impact of treatment from the patient's perspective and to correlate responses with the SRI.

Treatment of serologically active SLE patients with belimumab resulted in greater SRI response rates at all time points, especially after week 12, in comparison with patients treated with placebo. Differences became statistically significant at weeks 52 and 56. SRI response detects improvements in both clinical disease manifestations and SLE-related lab abnormalities. Removal of the two serological components of the SELENA-SLEDAI score did not diminish the belimumab treatment effect compared to the unmodified SRI. Interestingly, anti-Smith or anti-RNP antibodies have been associated with poorer responses or quicker times to relapse with rituximab therapy in SLE (49); however, in the belimumab trial, the SRI response rates were similar at 1 year, irrespective of autoantibody subtype at baseline. Reductions in activated or plasmacytoid B cells, a ≥50% reduction in anti-dsDNA antibodies, and/or normalization of low C4 concentrations were predictive of an SRI response in this trial (50).

Serologically active SLE patients who achieved a ≥4-point reduction in SELENA-SLEDAI score on belimumab treatment for 1 year compared with those on placebo were 2- to 3-fold less likely to develop increased SLE disease activity as defined by BILAG (new BILAG A score or ≥2 B scores) or PGA (≥ 0.3-point worsening). These results suggest that belimumab has the ability to improve and stabilize disease activity, as well as reduce flare rates in this population. In serologically active patients, there was a significant reduction in time to new flares between weeks 24 and 52 as defined by the SFI (34), and there were significantly fewer new BILAG flares at week 52. The significant reductions in renal, neurological, and musculoskeletal BILAG flares at week 52 suggest that belimumab may have a greater impact on some SLE disease manifestations than on others.

Retrospective application of the SRI to data from a large phase II RCT of belimumab in patients with active SLE demonstrated that belimumab treatment resulted in a statistically larger percentage of responders than did treatment with placebo. This SRI, based on a responder analysis of a large phase II study, has been accepted as the 52-week primary efficacy endpoint for 2 ongoing global phase III studies. These will be carried out in serologically active SLE patients receiving SOC with baseline SELENA-SLEDAI scores ≥6 points, and will compare treatment with belimumab (1 or 10 mg/kg) with placebo (BLISS 52 and BLISS 76; Clinicaltrials.gov NCT00424476 and NCT00410384).

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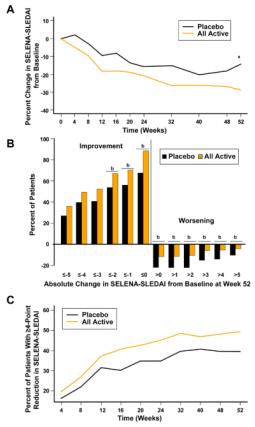

Figure 1. Belimumab effect on SELENA-SLEDAI score at week 52 in serologically active patients (N=321)

(A) Percent change in SELENA-SLEDAI from baseline over time. (B) Absolute changes from baseline in SELENA-SLEDAI score at week 52. (C) Percentage of patients with ≥4-point reduction in SELENA-SLEDAI score.

[a] Statistically significant better response with belimumab all active vs placebo (P=0.04).

[b] Statistically significant better response with belimumab all active vs placebo (P<0.05).

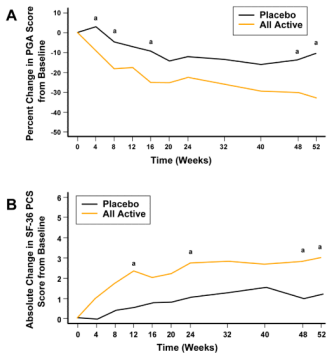

Figure 2. Belimumab effect on PGA and SF-36 scores at week 52 in serologically active patients (N=321)

(A) Percent change in PGA. (B) Absolute point change in SF-36 PCS.

[a] Statistically significant better response with belimumab all active vs placebo ($P<0.05$).

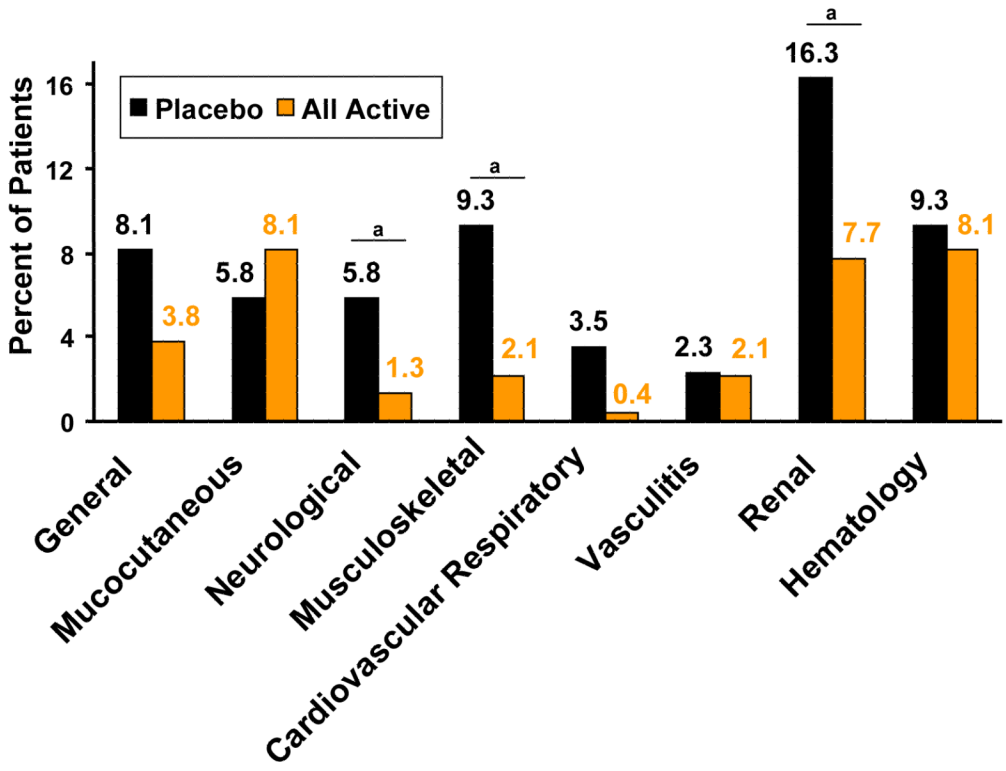

Figure 3. Belimumab effect on BILAG domain scores at week 52 (new A or B scores)

Percent of serologically active patients with new 1A or 1B BILAG organ domain scores at week 52.

[a] Statistically significant better response with belimumab all active vs placebo ($P<0.05$).

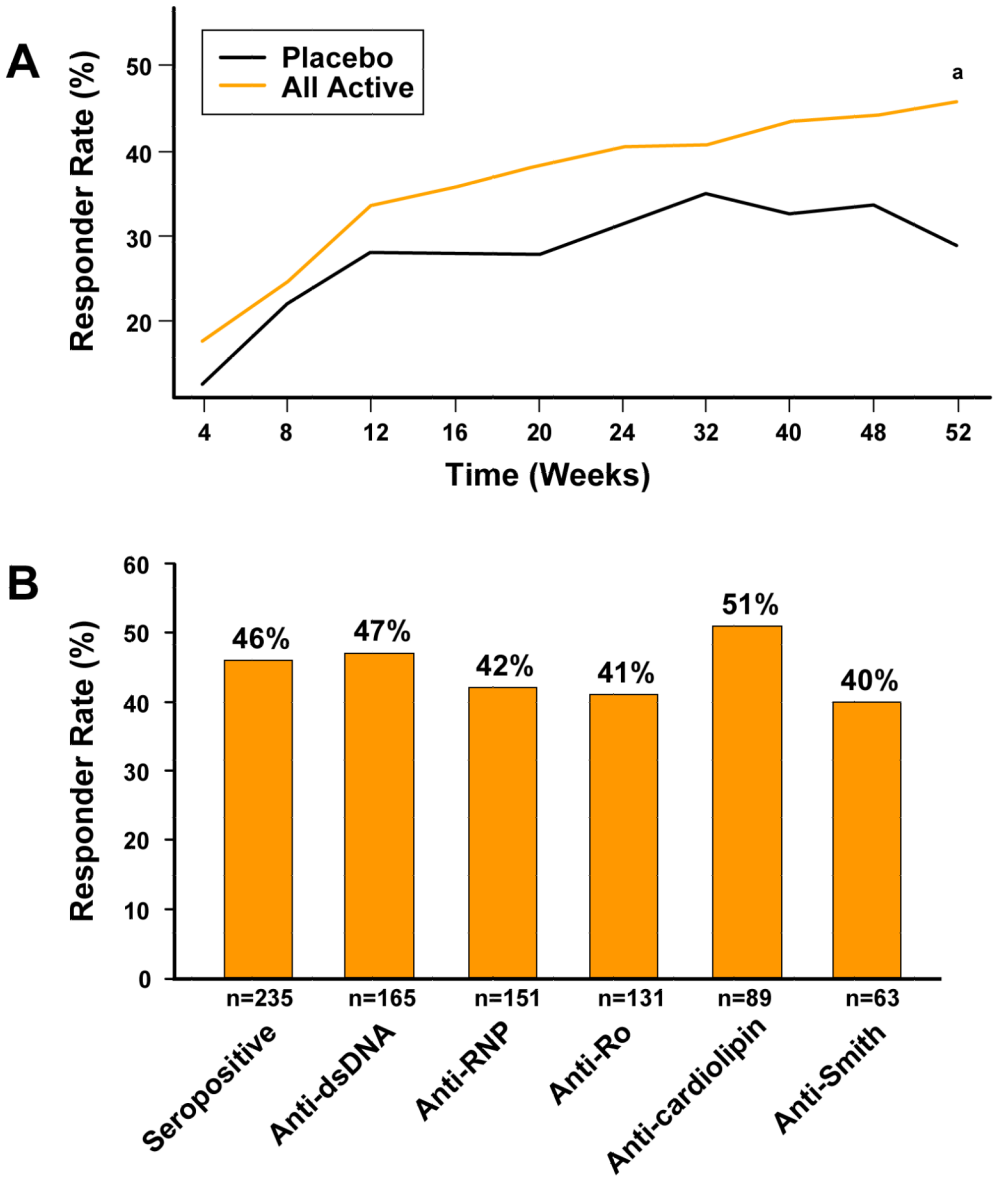

Figure 4. (A) SLE Responder Index over 52 weeks in serologically active patients (N=321). (B) Response rate at week 52 in belimumab-treated patients with different autoantibody subtypes at baseline

[a] Statistically significant better response with belimumab all active vs placebo (*P*=0.006).

Table 1

Baseline demographic and clinical characteristics of serologically active patients (N=321).

	Placebo	Belimumab			
		1.0 mg/kg	4.0 mg/kg	10.0 mg/kg	All Active
	(n=86)	(n=78)	(n=79)	(n=78)	(n=235)
Female, %	93.0	96.2	94.9	97.4	96.2
Race					
Caucasian, %	65.1	69.2	62.0	69.2	66.8
African-American, %	24.4	23.1	31.6	26.9	27.2
Hispanic or Latino origin, %	19.8	15.4	25.3	19.2	20.0
Age, mean y±SD	41.3±11.3	39.8±11.5	41.0±10.5	40.1±10.9	40.3±10.9
Disease duration, mean y±SD	8.1±7.5	9.2±7.8	10.2±9.3	8.5±7.6	9.3±8.3
SELENA-SLEDAI, mean±SE	9.7±0.6	10.4±0.6	9.5±0.5	9.8±0.5	9.9±0.3
≥1 A or 2 B BILAG scores, %	59.3	66.7	67.1	73.1	68.9
PGA, mean±SE	1.3±0.05	1.6±0.06	1.5±0.05	1.5±0.06	1.5±0.03
Daily prednisone use, %	73.3	71.8	73.4	71.8	72.3
> 7.5 mg at baseline, %	45.4	38.5	36.7	43.6	39.6
Immunosuppressive[a] use, %	47.7	46.2	59.5	50.0	51.9
BLyS ALOD, %	47.7	56.4	50.6	50.0	52.3
ANA ≥1:80, %	94.2	97.4	97.5	92.3	95.7
Anti-dsDNA ≥30 IU/mL, %	67.4	75.6	67.1	68.0	70.2
Low C3 (<90 mg/dL), %	30.2	47.4	38.0	42.3	42.6
Low C4 (<16 mg/dL), %	41.9	60.3	46.8	52.6	53.2

[a]Excluding aminoquinolines (hydroxylchloroquine, chloroquine, quinacrine). SD = standard deviation; BILAG = British Isles Lupus Assessment Group; PGA = Physician's Global Assessment; BLyS = B-lymphocyte stimulator; ALOD = above level of detection (0.350 ng/ml); ANA = antinuclear antibodies.

Table 2

Summary of efficacy results for serologically active[a] patients at week 52 (N=321).

	Placebo	Belimumab				
		1.0 mg/kg	4.0 mg/kg	10.0 mg/kg	All Active	
	(n=86)	(n=78)	(n=79)	(n=78)	(n=235)	*P* value[b]
SRI response rate,[c] %	29.1	48.7	43.0	46.2	46.0	0.006
4-point reduction in SELENA-SLEDAI	39.5	52.6	48.1	47.4	49.4	0.117
No worsening by BILAG[d]	81.4	88.5	94.9	91.0	91.5	0.015
No worsening by PGA[e]	76.7	89.7	88.6	92.3	90.2	0.003
Modified SRI [f]	(n=74)	(n=70)	(n=67)	(n=68)	(n=205)	
Baseline SELENA-SLEDAI score, mean	8.2	8.1	8.2	8.1	8.2	
Modified SRI response rate, [f] %	32.4	48.6	46.3	47.1	47.3	0.025

[a] ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL at screening and day 0.

[b] *P* value from likelihood ratio test for pairwise comparison between combined all active vs placebo.

[c] Percent of patients with reduction in SELENA-SLEDAI ≥4 and no worsening by BILAG index (no new A or 2B flares) and no worsening by PGA (<0.3-point increase).

[d] No new A or 2B BILAG flares.

[e] <0.3-point increase in PGA from baseline.

[f] Modified SRI by excluding both anti-dsDNA and low complement (C3/C4) from the determination of the SELENA-SLEDAI score. The number of patients with a minimum score ≥4 at baseline and their mean baseline score is shown for each treatment group.