Clinical, laboratory and health-related quality of life correlates of Systemic Lupus Erythematosus Responder Index response: a post hoc analysis of the phase 3 belimumab trials

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ABSTRACT

Objective: Correlates of systemic lupus erythematosus (SLE) Responder Index (SRI) response with clinical trial end points were examined using pooled data from the Study of Belimumab in Subjects with SLE (BLISS) trials (N=1684).

Methods: Changes in clinical, laboratory and health-related quality of life measures from baseline at 52 weeks were compared between SRI responders (n=761) and non-responders (n=923).

Results: More SRI responders than non-responders had ≥4-point (100% vs 3.8%) and ≥7-point (40.3% vs 1.3%) Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index reductions, no new British Isles Lupus Assessment Group (BILAG) A and ≤1 new B scores (91.9% vs 35.9%), and a 25% reduction in corticosteroid dose decrease of 25% from >7.5 mg/d to ≤7.5 mg/d (25.5% vs 13.9%), and fewer had a corticosteroid increase from ≤7.5 mg/d to >7.5 mg/d (4.1% vs 21.3%; all p<0.001). More responders than non-responders reported improved organ domains: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (mean 1.45 vs 0.40), BILAG (2.00 vs 0.39), and greater improvement in Physician's Global Assessment (all p<0.001). Risks for developing any SLE flare or severe flare were reduced in responders by 42% and 87%, respectively (p<0.001). Responders reported greater improvements in Medical Outcomes Survey Short Form version 2 Physical and Mental Components and all domain scores, and Functional Assessment of Chronic Illness Therapy-Fatigue score compared with non-responders (all p<0.001).

Conclusion: Overall, SRI response in patients with active, autoantibody-positive SLE was associated with improvements in clinical, laboratory and patient-reported outcome measures, indicating that SRI response was associated with a global benefit.

Trial registration number: NCT00424476; NCT00410384.

KEY MESSAGES

- SRI responders reported greater improvements from baseline in a range of clinical, laboratory and health-related quality of life measures, compared with non-responders.
- SRI responses, irrespective of therapy, were associated with global benefits in patients with active, autoantibody-positive SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease associated with considerable morbidity, increased mortality and poor health-related quality of life (HRQoL). Belimumab is a human immunoglobulin (Ig)-G1 monoclonal antibody that inhibits the biological activity of soluble B lymphocyte stimulator, an immunomodulatory cytokine involved in B cell selection and survival that is over-expressed in SLE. In two placebo-controlled trials conducted in patients with active, autoantibody-positive SLE (Study of Belimumab in Subjects with SLE (BLISS)-52 and BLISS-76), belimumab plus standard SLE therapy resulted in significantly higher SLE Responder Index (SRI) response rates at 1 year compared with standard therapy (placebo), indicating greater reductions in SLE disease activity with treatment and improvements in HRQoL measures.

The SRI is a novel composite end point that requires improvement in SLE disease activity without worsening in specific organ domains or global disease activity consistent with US Food and Drug Administration guidance for development of products for
treatment of SLE. A SRI response requires clinically meaningful improvement in the Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) and no worsening of disease, as measured by British Isles Lupus Assessment Group (BILAG) organ domain score and Physician’s Global Assessment (PGA). The present post hoc analysis examined the association of SRI response at Week 52, irrespective of treatment assignment, with individual clinical and laboratory measures, and patient-reported HRQoL and fatigue among SRI responders and non-responders.

MATERIALS AND METHODS

Patients with SLE (n=1684) who were autoantibody-positive (nuclear antibody titre ≥1:80 and/or antidouble-stranded DNA (anti-dsDNA) ≥50 IU/mL) with a SELENA-SLEDAI score ≥6 received placebo, belimumab 1 mg/kg or 10 mg/kg in addition to standard SLE therapy for 52 weeks (BLISS 52; NCT00424476) or 76 weeks (BLISS 76; NCT00410384). Doses of standard therapy were required to be stable for ≥30 days prior to enrolment. Patients could not have severe active lupus nephritis or severe active central nervous system SLE. Progressive restrictions on immunosuppressives and antimalarials began at treatment Week 16, and restrictions on corticosteroids began at treatment Week 24. Patients were stratified at screening by SELENA-SLEDAI score (0–9 vs ≥10), proteinuria (<2 g/24 h vs ≥2 g/24 h), and race (African descent or indigenous American vs other). SRI response rate at Week 52 was the primary end point, defined as a decrease of ≥4 points in SELENA-SLEDAI score, no new BILAG A score and ≤1 new B score, and no worsening (<0.3-point increase) in PGA score. Patients were considered non-responders if they did not meet SRI response criteria, withdrew before Week 52 or received protocol-prohibited medications.

The BLISS trials were conducted according to the principles of the Declaration of Helsinki and the appropriate ethical approvals were obtained. Of the 1684 patients enrolled, 761 were SRI responders and 923 were non-responders at Week 52. Clinical and serological measures of disease activity, less serological activity (based on anti-dsDNA titre (p<0.001) and percentage of patients with C3 or C4 levels less than the lower limits of normal (p<0.001 and p<0.0001, respectively)), and were more likely to have received a corticosteroid dose >7.5 mg/d (p<0.01), but not an immunosuppressant (p<0.0001). At baseline, there were no statistically significant differences in B cell subsets or plasma cell subsets (data not shown). Clinical and laboratory measures of disease activity at Week 52 are shown in table 2.

RESULTS

SRI responses in patients receiving placebo, and belimumab 1 and 10 mg/kg plus standard therapy were 38.8%, 46.2% (p=0.006) and 50.6% (p<0.001), respectively, at Week 52. Baseline characteristics were balanced across treatment groups (table 1) and were generally similar between SRI responders and non-responders. Responders were more likely to have higher disease activity, less serological activity (based on anti-dsDNA titre (p<0.001) and percentage of patients with C3 or C4 levels less than the lower limits of normal (p<0.001 and p<0.0001, respectively)), and were more likely to have received a corticosteroid dose >7.5 mg/d (p<0.01), but not an immunosuppressant (p<0.0001). At baseline, there were no statistically significant differences in B cell subsets or plasma cell subsets (data not shown). Clinical and laboratory measures of disease activity at Week 52 are shown in table 2.

SRI components: SELENA-SLEDAI, BILAG and PGA

More responders than non-responders achieved a ≥4-point reduction in SELENA-SLEDAI score, with only 3.8% of non-responders meeting this SRI criterion versus 100% of responders (p<0.001) (table 2). A reduction of ≥7 in SELENA-SLEDAI score occurred in 40.3% of responders versus 1.3% of non-responders (p<0.001) at Week 52. Mean numbers of improved organ domains per patient were higher among responders as assessed by SELENA-SLEDAI and BILAG (all p<0.001). Mean
improvements in PGA scores in all patients as well as those with no worsening of PGA scores at Week 52 were greater among responders versus non-responders (both p<0.001; 49.3% of non-responders had no worsening at Week 52). Responders had greater improvements in PGA than non-responders as early as Week 4 and this continued through Week 52 (figure 1A).

SRI response as a predictor of BILAG response
To evaluate whether a SRI response at Week 52 predicted improvement in BILAG items present at baseline, an analysis was performed that required a responder to have met SRI response criteria and to have had ≤1 BILAG B score present at Week 52. At baseline 64.8% of SRI responders and 57.5% of non-responders had >1 BILAG B or ≥1 A score. At Week 52 91.9% of SRI responders had ≤1 BILAG B score (table 2) compared with 35.9% of SRI non-responders (p<0.001).

SLE flare index
The risks of any flare and severe flare were lower in SRI responders (42% (HR 0.58; 95% CI 0.52 to 0.65; p<0.001) and 87% (0.13; 0.09 to 0.17; p<0.001), respectively: figure 1B).

Corticosteroid use
Approximately 62% of SRI responders and 55% of non-responders received a prednisone (or equivalent) dose >7.5 mg/d at baseline (table 1). Of these patients, more responders than non-responders had dose reductions ≥25% to <7.5 mg/d at Week 52 (25.5% vs 16.4%; p<0.001), and fewer responders who received prednisone ≤7.5 mg/d at baseline had dose increases to >7.5 mg/d at Week 52 (4.1% vs 21.3%). Over time, fewer SRI responders than non-responders had increases in prednisone dose >7.5 mg/d, with a difference beginning at Week 12 (figure 1C). The proportion of non-
<table>
<thead>
<tr>
<th>Clinical measures</th>
<th>SRI responders (n=761)</th>
<th>SRI non-responders (n=923)</th>
<th>p Value</th>
<th>Adjusted p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SELENA-SLEDAI, n (%)</td>
<td>761 (100)</td>
<td>35 (3.8)</td>
<td>&lt;0.001†</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>≥4-point reduction</td>
<td>307 (40.3)</td>
<td>12 (1.3)</td>
<td>&lt;0.001†</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Mean no. of organ domains with improvement, per patient (SE)§</td>
<td>1.45 (0.03)</td>
<td>0.40 (0.02)</td>
<td>&lt;0.001†</td>
<td>&lt;0.001**(§)</td>
</tr>
<tr>
<td>BILAG</td>
<td>699 (91.9)</td>
<td>331 (35.9)</td>
<td>&lt;0.001†</td>
<td>&lt;0.001**(§)</td>
</tr>
<tr>
<td>Mean % change in PGA score from baseline in all patients (SE)</td>
<td>-58.3 (1.17)</td>
<td>-34.9 (1.75)</td>
<td>0.001†</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>No new BILAG A score and ≤1 new B score, n (%)</td>
<td>699 (91.9)</td>
<td>331 (35.9)</td>
<td>&lt;0.001†</td>
<td>&lt;0.001**(§)</td>
</tr>
<tr>
<td>Mean % change in PGA score from baseline in patients with no worsening (SE)</td>
<td>-58.3 (1.17)</td>
<td>-34.9 (1.75)</td>
<td>0.001†</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Corticosteroid dose, n (%)</td>
<td>120/471 (25.5)</td>
<td>70/505 (13.9)</td>
<td>&lt;0.001†</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Dose decrease to ≤7.5 mg/d from &gt;7.5 mg/d at baseline††</td>
<td>122/290 (4.1)</td>
<td>89/418 (21.3)</td>
<td>&lt;0.001†</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>SFI flare, n (%)</td>
<td>532 (69.9)</td>
<td>763 (82.7)</td>
<td>HR 0.58 95% CI 0.52 to 6.5 to 0.001†††</td>
<td>&lt;0.001†††</td>
</tr>
<tr>
<td>Any</td>
<td>47 (6.2)</td>
<td>269 (29.1)</td>
<td>HR 0.13 95% CI 0.09 to 0.17 &lt;0.001†††</td>
<td>&lt;0.001†††</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA antibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median % change in patients positive (≥30 IU/L) at baseline (Q1, Q3)¶¶</td>
<td>-34.2 (−57.04, −0.50)</td>
<td>-26.1 (−50.81, 6.76)</td>
<td>0.01***</td>
<td>0.129**</td>
</tr>
<tr>
<td>Normalisation in patients positive at baseline, n (%)¶¶</td>
<td>69/479 (14.4)</td>
<td>47/434 (10.8)</td>
<td>0.10†</td>
<td>0.243‡</td>
</tr>
<tr>
<td>Normalisation in patients with low C3 (&lt;90 mg/dL) at baseline (Q1, Q3)¶¶</td>
<td>14.5 (1.25, 35.46)</td>
<td>9.0 (−4.88, 26.51)</td>
<td>0.001***</td>
<td>0.009**</td>
</tr>
<tr>
<td>Normalisation in patients with low C4 at baseline, n (%)¶¶</td>
<td>89/292 (30.5)</td>
<td>74/293 (25.3)</td>
<td>0.16†</td>
<td>0.044‡</td>
</tr>
<tr>
<td>Normalisation in patients with low C4 at baseline, n (%)¶¶</td>
<td>40.0 (13.33, 81.82)</td>
<td>28.6 (0.00, 63.64)</td>
<td>0.003***</td>
<td>0.049**</td>
</tr>
<tr>
<td>Normalisation in patients with low C4 at baseline, n (%)¶¶</td>
<td>134/361 (37.1)</td>
<td>112/379 (29.6)</td>
<td>0.03†</td>
<td>0.013‡</td>
</tr>
</tbody>
</table>

*The analysis was adjusted for the baseline value for each listed parameter using the following methods of analysis.
†Likelihood ratio test.
‡logistic regression test.
§Improved from British Isles Lupus Assessment Group (BILAG) A to B score or better, or from B to C score or better; dropout=failure.
¶2-sample t test.
**Analysis of covariance test.
††Last observation carried forward.
***Dropout=failure.
†††Log-rank test.
¶¶Based on modified Systemic Lupus Erythematosus (SLE) Responder Index (SRI) analysis that excluded anti-dsDNA and complement items from determination of 4-point decrease in Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) component of SRI; includes patients with data available at Week 52/primary visit.
***Wilcoxon test.
†††Cox test.

anti-dsDNA, antidouble-stranded DNA; C, complement; PGA, Physician’s Global Assessment; Q, quartile; SFI, SLE Flare Index.
responders with increases in corticosteroid doses rose continually over the study period, whereas the proportion of responders did not rise after Week 4.

Serological measures
In all, 913 patients were anti-dsDNA-positive, 585 had low C3 levels (<90 mg/dL) and 740 had low C4 levels (<16 mg/dL) at baseline. Median anti-dsDNA antibody levels were lower in SRI responders than in non-responders at Week 52 (−34.2% vs −26.1%). Of patients with hypocomplementaemia at baseline, median percent increases from baseline C3 and C4 levels were greater in responders than non-responders (C3: 14.5% vs 9.0%; C4: 40.0% vs 28.6%). More responders than non-responders exhibited normalisation of anti-dsDNA levels (14.4% vs 10.8%). Similarly, normalisation of low complement levels occurred more often in responders than in non-responders (C3: 30.5% vs 25.3%; C4: 37.1% vs 29.6%). Of 542 patients with measurements of circulating CD20 B cell subsets and plasma cell subsets at baseline and Week 52 in BLISS-76, the per cent reductions in these cell types at Week 52 were numerically greater in responders (data not shown). This finding was driven primarily by the SRI responders in the belimumab treatment groups who experienced greater reductions in B cell and plasma cell subsets than patients treated with standard therapy alone.13

Baseline covariate adjusted multivariate analysis of clinical and serological parameters
Overall results from the baseline adjusted analysis were similar to the univariate analysis. There was a greater response in SRI responders compared with non-responders, with similar p values for all the disease activity measures, including SELENA-SLEDAI, BILAG, PGA and SFI flare, as well as reduced corticosteroid use and
improvement in complement levels. The only differences observed were in the serological parameters. The % median change and % normalisation of anti-dsDNA were not significantly different between SRI responders and non-responders; the normalisation of low C3 was significantly greater for SRI responders.

**Patient-reported measures: HRQoL and fatigue**

SRI responders were more likely to have higher baseline PCS scores than non-responders (p<0.05; table 1). Thresholds for minimum clinically important differences (MCIDs) from baseline are 2.5 points for the SF-36 PCS and MCS scores, and are generally considered 5 points for each of the eight domain scores. At Week 52, mean improvements in SF-36 PCS and MCS scores were greater in SRI responders versus non-responders (4.9 vs 2.6 and 4.4 vs 1.7, respectively; p<0.001) and exceeded MCID. A higher percentage of responders reported improvements ≥MCID than non-responders in PCS (59% vs 49%) and MCS (56% vs 44%). Similarly, improvements in individual domain scores were greater in SRI responders and exceeded MCID (all p<0.001). Improvements in non-responders exceeded MCID for PCS and role-physical, bodily pain and vitality domain scores. Mean improvements were ≥two-fold greater in responders versus non-responders in six of eight domains (figure 2 and see online supplementary figure S1); a consistently higher percentage of responders reported changes ≥MCID than non-responders in all domain scores (ranging from 54% vs 42%, respectively, for the role-emotional domain to 65% vs 53%, respectively, for the general health domain). At Week 52, more than twice as many responders versus non-responders reported feeling ‘somewhat better’ (76.1% vs 33.5%) and ‘much better’ (33.8% vs 14.6%) than 1 year ago.

Mean improvements in FACIT-Fatigue scores were higher in SRI responders than non-responders at Week 52 (5.2 vs 3.0). Improvement in the responder group exceeded MCID of 4 points as defined in patients with rheumatoid arthritis. Greater improvements in FACIT-Fatigue scores were observed by Week 8 in responders and were sustained through 52 weeks (figure 3). These findings are supported by improvements reported by responders in the SF-36 vitality domain (10.4 vs 6.5).

**DISCUSSION**

Although the lupus research community has become comfortable with SELENA-SLEDAI, BILAG and PGA as efficacy measures, the same level of understanding does not exist for the SRI. Therefore, we examined the clinical meaningfulness of SRI response in patients with active, autoantibody-positive SLE, irrespective of therapy. Improvements in a variety of clinical, serological and clinically meaningful changes in patient-reported outcome measures indicated that a SRI response was associated with global benefit beyond that measured by the components of the SRI. Overall, reductions in severe flares and corticosteroid use as well as clinically meaningful and statistically significant improvement in patient-reported outcomes correlated with SRI responder status.

While SRI responders would be expected to more frequently meet the SRI criteria (≥4-point improvement) for SELENA-SLEDAI than non-responders, 40% of responders in this analysis had improvement of ≥7 points on the SELENA-SLEDAI compared with 1% of non-responders. The improvement in PGA score in responders was greater than that achieved in non-responders, as well as in the subgroup of non-responders with no worsening in PGA scores, suggesting that SRI response is associated with a marked improvement in overall health. This finding is supported by clinically meaningful improvements in patient-reported HRQoL and fatigue, including PCS, MCS and all domain scores of SF-36, FACIT-Fatigue scores and the SF-36 transition question. In addition, SRI response was correlated with higher mean numbers of organ domains with improvement on SELENA-SLEDAI (2.00 vs 0.39) and BILAG (1.45 vs 0.40), as well as greater reductions in risk of any
Serum C3/C4 and anti-dsDNA.

The SRI response was recommended by the American College of Rheumatology and European League Against Rheumatism for monitoring SLE activity. More severe disease and reduced HRQoL were associated with higher complement levels, anti-dsDNA-positivity, and low complement levels.13 25 Overall, SRI responders were more likely to have baseline high disease activity similar to the predictors of a belimumab SRI response. However, corticosteroid treatment was not predictive of a SRI response, whereas patients receiving prednisone >7.5 mg at baseline were more likely to have achieved a SRI response. Baseline serological activity was not associated with an overall greater likelihood of a SRI response, irrespective of therapy. This differential response can be partially explained by patients in the placebo and belimumab 1 mg/kg groups with high serological activity having lower rates of SRI response (31.7% and 41.5%, respectively) than the overall placebo and 1 mg/kg groups (38.8% and 46.2%, respectively), whereas the SRI responses in the 10 mg/kg group were similar in serologically active (51.5%) and all patients in that treatment group (50.6%).25

The HRQoL benefits in SRI responders support the association of a SRI response with broad improvements in SLE disease activity. The impact of SLE on HRQoL is comparable with or worse than other chronic diseases (eg, AIDS, rheumatoid arthritis, diabetes, congestive heart failure).1 21 22 26 Baseline SF-36 PCS and MCS scores in the BLISS trials reflected this high impact of SLE on HRQoL: compared with mean normative values of 50 in SF-36 summary scores, mean baseline scores were 39.1 for PCS and 40.8 for MCS. At Week 52, improvements from baseline in SF-36 PCS, MCS and all domain scores were greater in SRI responders and exceeded MCID for all scores.

Fatigue is one of the most common clinical manifestations of SLE and is associated with poor physical and mental functioning.27 Mean improvements in FACIT-Fatigue scores reported by SRI responders were greater than in non-responders, with changes from baseline exceeding MCID from Weeks 12 to 52 in those achieving a SRI response at Week 52. However, it should be noted that a MCID of 4, while valid in patients with rheumatoid arthritis, has not yet been validated in patients with SLE. However the MCIDs for SF-36 summary and domain scores were independently validated in SLE and correspond closely to those determined in rheumatoid arthritis. Reductions in fatigue were confirmed by a greater increase in SF-36 vitality domain score, consistent with other published data indicating a high correlation between these measurements.15 28 Finally, three-quarters of responders indicated that they felt ‘somewhat’ or ‘much better’ than 1 year before compared with a third of non-responders.

Interpretation of these study results is limited by the post hoc nature of the analyses. In addition, examining a clinical trial population based on achievement of the primary end point (SRI at Week 52) eliminates the randomised balance of baseline characteristics in the treatment groups. Baseline characteristics were, however,
CONCLUSIONS

Our results indicate that SRI responses, irrespective of therapy, are associated with global, clinically meaningful benefits in patients with active, autoantibody-positive SLE.

REFERENCES


Figure S1. Spydergram of SF-36 domain scores at baseline and Week 52.

#P<0.001. A/G, age-/gender-matched; BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; VT, vitality.