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SF-36v2 and FACIT-Fatigue quality of life improvements with organ-specific SELENA-SLEDAI response and belimumab treatment in patients with systemic lupus erythematosus

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ABSTRACT

Objective Explore organ-specific SLE burden by assessing health-related quality of life (HRQoL) and fatigue changes associated with Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) organ system response (score improvement) and belimumab treatment.

Methods Data from four phase III belimumab trials were pooled for post hoc analysis (GSK Study 217382): BLISS-52 (NCT00424476), BLISS-76 (NCT00410384), BLISS-SC (NCT01484496) and EMBRACE (NCT01632241). Patients with baseline organ system involvement were classed as organ system responders if SELENA-SLEDAI scores for that organ system decreased at any post-baseline visit. HRQoL (36-Item Short Form Health Survey version 2 (SF-36v2)) and fatigue (Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue)) changes over 52 weeks were compared between organ system responders and non-responders, and separately between belimumab versus placebo treatment arms among organ system responders. Group-level differences were compared using analysis of variance; differences were interpreted using published group-level minimal important difference (MID).

Results In these post hoc analyses, musculoskeletal and mucocutaneous organ system responders had greater SF-36v2 improvements than non-responders across most SF-36v2 domains, but differences were largely <MID. Most organ system responders had improved FACIT-Fatigue scores versus non-responders, with cardiovascular and respiratory responders having improvements ≥MID. Musculoskeletal and renal responders receiving belimumab had greater improvements in several SF-36v2 domains than responders receiving placebo (>MID), with FACIT-Fatigue also improving >MID for renal responders receiving belimumab.

Conclusions SLE disease burden differs with the organ system(s) involved. While these analyses are limited by mutual inclusivity of organ system groupings, differing patient numbers between groups and small numbers in some groups, they suggest that mucocutaneous and musculoskeletal organ system response improves SF-36v2 domain scores; cardiovascular and respiratory organ system response may meaningfully improve fatigue; and belimumab may offer additional HRQoL or fatigue benefits beyond standard therapy for musculoskeletal and renal responders.

INTRODUCTION

SLE significantly impairs patients' health-related quality of life (HRQoL), with fatigue being one of the most burdensome symptoms.[1] Reduction in SLE disease activity improves clinical and HRQoL outcomes.[2] The specific organs involved may impact the benefit felt by the patient with disease activity reduction.[3] Belimumab is a treatment option that improves disease activity, fatigue and HRQoL in patients with SLE.[4–7] Given the heterogeneity of SLE, understanding which organ system improvements are associated with meaningful HRQoL improvement is important; however, data are limited.

This post hoc analysis of four phase III belimumab trials explores the associations between Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)[8] organ system disease activity and HRQoL, including fatigue, as well as assessing HRQoL and fatigue changes with belimumab versus placebo among patients with improvement in specific organ systems.

METHODS

Study design

This post hoc analysis (GSK Study 217382) used data from four phase III belimumab trials: BLISS-52 (NCT00424476),[6] BLISS-76 (NCT00410384),[5] BLISS-SC (NCT01484496)[7] and EMBRACE (NCT01632241).[9]

HRQoL was assessed using the 36-Item Short Form Health Survey version 2 (SF-36v2)[10] and fatigue by the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue).[11] SF-36v2 scores were available for BLISS-52 and BLISS-76; FACIT-Fatigue scores were available for BLISS-52, BLISS-76, BLISS-SC and EMBRACE.

SELENA-SLEDAI items were grouped into organ systems.[12] Organ system response was defined as the SELENA-SLEDAI score for that organ system decreasing by any amount at any post-baseline visit, indicating organ system disease activity improvement. Only patients with a baseline score >0 could be classified as responders/non-responders for the corresponding organ system.

Patients

Full inclusion and exclusion criteria for the four trials have been published previously.[5–7 9]

Treatment

In each trial, adults with SLE received standard therapy plus the following belimumab dosage, or placebo: belimumab 1 or 10 mg/kg intravenous on days 0, 14 and 28, and then every 28 days through either 52 weeks (BLISS-52) or 76 weeks (BLISS-76); belimumab 10 mg/kg intravenous on days 0, 14 and 28, and then every 28 days through 52 weeks (EMBRACE); or belimumab 200 mg subcutaneous weekly through 52 weeks (BLISS-SC).

Endpoints

To understand and compare the HRQoL burden experienced across SLE organ system involvement groups, this post hoc analysis evaluated the differences in SF-36v2 scores of patients with SLE organ system involvement relative to the US general population. It explored the effect of organ system involvement on HRQoL and fatigue by comparing the mean SF-36v2 and FACIT-Fatigue score changes from baseline to week 52 between specific organ system responders and non-responders. Lastly, it compared the differences in mean SF-36v2 and FACIT-Fatigue score changes from baseline to week 52 between belimumab and placebo treatment arms (approved belimumab dose (10 mg/kg intravenous or 200 mg subcutaneous)) among organ system responders.

Statistical analysis

To compare the SF-36v2 scores of organ involvement groups with age-adjusted and gender-adjusted US population norms, separate multiple linear regression models were used to adjust the norms sample to match the age and gender distribution of the organ involvement group. Statistical significance of differences between mean scores was calculated using an F-test. Cohen's effect sizes were calculated to interpret the magnitude of differences between patients and US population norms. For alignment with other analyses, only patients with non-missing data for change from baseline to week 52 in all SF-36v2 domains were included in comparison with the US general population norm.

Analysis of variance was used to compare the mean change for all available SF-36v2 and FACIT-Fatigue scores from baseline to week 52 between organ system responders and non-responders, and between belimumab 10 mg/kg intravenous or 200 mg subcutaneous and placebo treatment arms, among organ system responders. Belimumab 1 mg/kg intravenous groups were excluded because this is not an approved treatment dose. Cohen's effect sizes were calculated to interpret the magnitude of differences between groups. Group differences were interpreted using published group-level minimal important difference (MID).[13]

No adjustments were made for multiplicity as the study's objectives rely primarily on interpretations of overall patterns of exploratory post hoc analyses rather than statistical hypothesis testing.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

HRQoL for patients with SLE and organ system involvement at baseline compared with the US general population

Immunological (n=1041), mucocutaneous (n=1066) and musculoskeletal (n=846) system involvements were most prevalent at baseline (figure 1; online supplemental table 1). Central nervous involvement was least common, with only 34 patients. Most baseline SF-36v2 domain scores across organ system groups were ≥10 points (1 SD) below those of age-adjusted and gender-adjusted US general population norms (figure 1; online supplemental table 1). Only vitality scores for patients with renal, vascular or immunological system involvement were ≤5 points (0.5 SD) below the US general population norms.

HRQoL and fatigue differences between organ system responders and non-responders

Mucocutaneous or musculoskeletal responders had significantly greater improvements in most SF-36v2 domains compared with non-responders from baseline to week 52, but only bodily pain and role limitations due to emotional problems (role emotional) among musculoskeletal responders were improved >MID (table 1). Haematological and vascular responders had significant improvements >MID in general health perceptions versus non-responders. All organ system responder groups had significantly improved FACIT-Fatigue scores compared with non-responders (1.1–5.5 points) except central nervous system responders, which was a group with few patients (responders n=27, non-responders n=29). Cardiovascular and respiratory responders had significant FACIT-Fatigue improvement over non-responders that was also >MID (5.5 points).

HRQoL and fatigue differences between belimumab and placebo groups among organ system responders

Differences in HRQoL and fatigue between those receiving approved belimumab doses versus placebo were

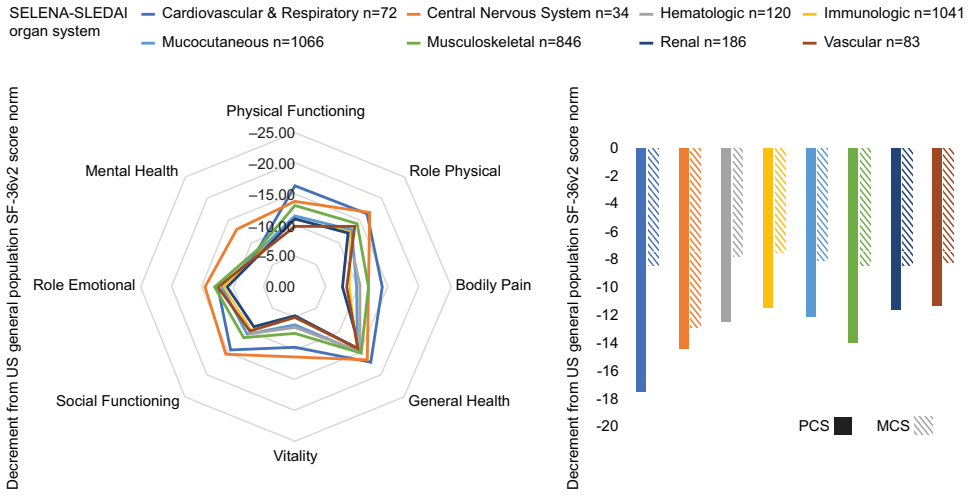

Figure 1 Baseline SF-36v2 domain and summary component score decrements from age-adjusted and gender-adjusted US general population norm among patients with organ system involvement at baseline (only patients with non-missing data for change from baseline to week 52 in all SF-36v2 domains were included in comparison to the US general population norm). MCS, mental component summary; PCS, physical component summary; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; SF-36v2, 36-Item Short Form Health Survey version 2.

inconsistent across organ system responders; however, only the mucocutaneous and musculoskeletal groups had at least 100 patients in each treatment arm (table 2). Musculoskeletal responders who received belimumab had greater improvements in six of the eight SF-36v2 domains and the mental component summary (MCS) compared with those receiving placebo, with vitality (5.6 points), role emotional (6.4 points) and MCS (2.9 points) >MID. Renal responders receiving belimumab also had significantly greater improvements compared with placebo that were >MID for vitality (14.7 points), as well as general health perceptions (8.3 points). FACIT-Fatigue was improved with belimumab versus placebo for mucocutaneous, musculoskeletal and renal responders, >MID among renal responders.

DISCUSSION

These post hoc analyses demonstrate a considerable disease burden for patients with SLE that varies by organ system involvement. Compared with age-adjusted and gender-adjusted US general population norms, patients with active SLE had significantly reduced HRQoL, with baseline SF-36v2 scores often ≥10 points below the norm.

SF-36v2 domain improvements may be more common in SELENA-SLEDAI mucocutaneous and musculoskeletal system responders, with a potential additional benefit of belimumab versus placebo on HRQoL or fatigue for musculoskeletal and renal responders. Mucocutaneous and musculoskeletal responders had greater improvement in several SF-36v2 domains compared with non-responders in the same organ systems. The smaller sample sizes in other organ systems may have contributed to the absence of significant difference between organ system responder and non-responder SF-36v2 scores. A previous analysis of the effect of British Isles Lupus Assessment Group (BILAG) organ domain involvement on HRQoL using data from BLISS-52 also reported that musculoskeletal domain activity had a significant effect on HRQoL and fatigue, alongside the constitutional and haematological BILAG domains.[3] The consistently greater improvement in fatigue among most organ system responders compared with non-responders in the present study is notable given that fatigue is one of the most burdensome symptoms of SLE.[1]

The impact of belimumab on HRQoL, including fatigue, has been demonstrated across several studies.[4] Our analyses provide further insight into the potential for additional HRQoL and fatigue benefits over standard therapy in specific organ system responders. Musculoskeletal responders had greater improvements with belimumab than placebo (>MID) for vitality, role emotional and MCS, while renal responders receiving belimumab had improved vitality, general health perceptions and fatigue, suggesting additional treatment benefit not captured by organ system disease activity scoring alone.

Limitations of this analysis include small sample size in some groups, which would make individual-level meaningful change analyses underpowered, and the potential for patients to have involvement in more than one organ system. FACIT-Fatigue and SF-36v2 are generic instruments, and although both are adequate for use in SLE,[14 15] disease-specific tools could be more relevant. Additionally, only BLISS-52 and BLISS-76 used SF-36v2, whereas all trials used FACIT-Fatigue; increased patient numbers for FACIT-Fatigue versus SF-36v2 data may have contributed to the greater consistency in fatigue improvements across organ system responders compared with SF-36v2 improvements. No adjustments were made for multiplicity and caution is warranted in the interpretation of these results.

Table 1 Difference in mean HRQoL† and fatigue score change from baseline to week 52 between SELENA-SLEDAI organ system responders and non-responders in each organ system

	Organ system							
SF-36v2	**Cardiovascular and respiratory n=54 (R), n=19 (NR)**	**Central nervous system n=21 (R), n=13 (NR)**	**Haematological n=68 (R), n=53 (NR)**	**Immunological n=252 (R), n=810 (NR)**	**Mucocutaneous n=673 (R), n=416 (NR)**	**Musculoskeletal n=583 (R), n=282 (NR)**	**Renal n=118 (R), n=70 (NR)**	**Vascular n=61 (R), n=22 (NR)**
Physical functioning (MID=5)	−3.7	9.7	1.4	0.9	4.0**	3.9*	−1.5	6.2
Role limitations due to physical health (MID=5)	2.6	3.8	5.6	0.1	2.4	3.2	3.3	1.8
Bodily pain (MID=5)	4.2	−2.9	6.9	0.8	4.2**	6.6***	−4.7	10.9
General health perceptions (MID=5)	−2.5	−3.5	6.7*	1.6	3.7***	4.0***	2.1	10.8*
Vitality (MID=5)	2.1	6.6	5.5	−0.2	2.6*	1.2	1.9	3.1
Social functioning (MID=5)	−3.6	5.1	−1.1	−0.0	4.1*	3.5	−0.5	6.8
Role limitations due to emotional problems (MID=5)	4.2	−3.2	6.9	2.4	4.4**	5.4**	5.0	0.0
Mental health (MID=5)	1.7	10.8	3.6	−0.4	3.4**	3.6**	4.8	4.2
Physical component summary (MID=2.5)	0.3	−0.2	1.9	0.5	1.2*	1.5**	−1.5	3.4
Mental component summary (MID=2.5)	1.0	3.9	2.4	0.2	2.0**	1.8*	3.0*	1.5
FACIT-Fatigue (MID=3)	**n=114 (R), n=94 (NR)**	**n=27 (R), n= 29 (NR)**	**n=124 (R), n=170 (NR)**	**n=468 (R), n=1813 (NR)**	**n=1360 (R), n=1197 (NR)**	**n=1148 (R), n=987 (NR)**	**n=186 (R), n=234 (NR)**	**n=108 (R), n=98 (NR)**
	5.5***	4.5	3.8**	1.1*	2.9***	2.7***	2.5*	2.9*

p≤0.05 for responders (R) vs non-responders (NR); Difference in mean score change ≥MID for R
p≤0.05 for R vs NR; Difference in mean score change <MID for R

*p≤0.05; **p≤0.01; ***p≤0.001; no footnote symbol, p>0.05.
†SF-36v2 domain scores used 0–100 scoring and summary components used norm-based scoring.
FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; HRQoL, health-related quality of life; MID, minimal important difference; NR, non-responder; R, responder; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SF-36v2, 36-Item Short Form Health Survey version 2.

Table 2 Difference in mean HRQoL† and fatigue score change from baseline to week 52 between belimumab and placebo treatment arms among SELENA-SLEDAI organ system responders

	Organ system responders							
SF-36v2	**Cardiovascular and respiratory n=20 (BEL), n=17 (PBO)**	**Central nervous system n=11 (BEL), n=1 (PBO)**	**Haematological n=18 (BEL), n=22 (PBO)**	**Immunological n=122 (BEL), n=41 (PBO)**	**Mucocutaneous n=243 (BEL), n=204 (PBO)**	**Musculoskeletal n=203 (BEL), n=180 (PBO)**	**Renal n=39 (BEL), n=38 (PBO)**	**Vascular n=27 (BEL), n=15 (PBO)**
Physical functioning (MID=5)	–3.1	–9.5	6.4	4.8	2.9	5.5*	8.4	6.6
Role limitations due to physical health (MID=5)	1.8	10.2	–1.9	–0.6	–2.3	–2.6	4.7	–10.5
Bodily pain (MID=5)	4.6	15.8	6.8	0.7	2.0	5.3*	2.2	7.6
General health perceptions (MID=5)	–3.4	–3.9	4.6	–1.1	1.1	4.2*	8.3*	3.0
Vitality (MID=5)	–1.0	16.9	7.4	1.1	3.5	5.6**	14.7***	1.4
Social functioning (MID=5)	–1.2	–21.6	3.4	6.8	2.2	4.0	2.8	5.9
Role limitations due to emotional problems (MID=5)	13.4	–24.2	5.3	6.3	2.3	6.4*	4.4	–5.8
Mental health (MID=5)	0.6	1.4	8.5	2.3	2.0	4.6*	6.2	1.1
Physical component summary (MID=2.5)	–1.4	3.7	0.9	–0.5	0.1	0.7	2.1	1.5
Mental component summary (MID=2.5)	2.7	–5.3	3.8	2.2	1.4	2.9**	3.4	–0.5
FACIT-Fatigue (MID=3)	**n=60 (BEL), n=37 (PBO)**	**n=16 (BEL), n=2 (PBO)**	**n=58 (BEL), n=37 (PBO)**	**n=287 (BEL), n=92 (PBO)**	**n=713 (BEL), n=416 (PBO)**	**n=595 (BEL), n=345 (PBO)**	**n=84 (BEL), n=60 (PBO)**	**n=68 (BEL), n=21 (PBO)**
	2.6	5.7	2.7	0.1	1.7**	2.4***	4.3**	1.9

p≤0.05 for belimumab (BEL) vs placebo (PBO); Difference in mean score change ≥MID favouring BEL

p≤0.05 for BEL vs PBO; Difference in mean score change <MID favouring BEL

*p≤0.05; **p≤0.01; ***p≤0.001; no footnote symbol, p>0.05.
†SF-36v2 domain scores used 0–100 scoring and summary components used norm-based scoring.
BEL, belimumab; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; HRQoL, health-related quality of life; MID, minimal important difference; PBO, placebo; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SF-36v2, 36-Item Short Form Health Survey version 2.

Overall, these exploratory analyses aid understanding of organ-specific disease burden and may suggest that improvements in certain organ systems have a greater effect on HRQoL, including fatigue. They also suggest that belimumab may offer additional benefits beyond standard therapy to improve HRQoL and fatigue among patients with musculoskeletal and renal disease activity; further studies could help inform personalised treatment regimens better tailored to each individual's manifestations.

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Contributors All authors contributed to the conception or design of the study, data analysis and interpretation, and drafting, and critically revised the article. AH additionally contributed to data acquisition. W-HC was responsible for the overall content of this work and accepts full responsibility for the work as guarantor, had access to the data and controlled the decision to publish.

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Competing interests RR-B and MK are employees of QualityMetric, which received consulting fees from GSK for this analysis. W-HC, SA, CH and AH are employees of GSK and hold stocks and shares in the company. KG is a former employee of GSK and holds stocks and shares in the company.

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Anonymised individual participant data and study documents can be requested for further research from https://www.gsk-studyregister.com/en/

Author note KG's affiliation is at the time of study.

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