Validation of the Functional Assessment of Chronic Illness Therapy-Fatigue Scale in Patients with Moderately to Severely Active Systemic Lupus Erythematosus, Participating in a Clinical Trial

JIN-SHEI LAI, JENNIFER L. BEAUMONT, SARIKA OGALE, PAUL BRUNETTA, and DAVID CELLA

ABSTRACT. ***Objective.*** Fatigue is a common symptom of systemic lupus erythematosus (SLE). Our objective was to validate the 13-item Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale in patients with SLE.

Methods. The FACIT-Fatigue, Medical Outcomes Study Short-Form-36 (SF-36) questionnaire, Brief Pain Inventory (BPI), and Patient Global Assessment Visual Analog Scale (Patient-GA) were completed at baseline and at Weeks 12, 24, and 52 by patients with moderately to severely active extrarenal SLE. The patients were participating in a rituximab clinical trial. The British Isles Lupus Assessment Group (BILAG) disease activity index and the Physician Global Assessment Visual Analog Scale (Physician-GA) were completed by physicians at the same visits.

Results. At baseline, 254 patients completed the FACIT-Fatigue scale. Cronbach's α was > 0.95 at all visits. In cross-sectional analyses, FACIT-Fatigue scores differentiated between groups defined by BILAG General domain ratings. FACIT-Fatigue had moderate-high correlations (r = 0.5–0.8) with SF-36, BPI, and Patient-GA, but poor correlations with BILAG total score and Physician-GA (r = 0.1–0.3). At Weeks 12, 24, and 52, mean FACIT-Fatigue scale improvement was higher in patients who improved versus those who remained unchanged on the BILAG General domain. FACIT-Fatigue scale scores remained stable for patients with worsened BILAG General domain ratings compared to baseline. Distribution and anchor-based estimates suggested a minimally important difference (MID) range of 3–6 points.

Conclusion. The FACIT-Fatigue scale is a valid and responsive measure of fatigue in patients with SLE. MID in this SLE sample is similar to that derived previously in other populations. Since few patients experienced worsening BILAG General and Musculoskeletal domains in this study, further research is warranted to evaluate the responsiveness of FACIT-Fatigue to worsening of these domains. (J Rheumatol First Release Jan 15 2011; doi:10.3899/jrheum.100799)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease that can affect multiple organs and cause severe organ damage[1,2]. SLE predominantly affects women of reproductive age, and the prevalence is higher among people of African or Asian background[3]. Fatigue is one of the most common symptoms of SLE and can affect up to 81% of patients[4]. It is associated with impaired physical function and is a predictor of work disability in patients with SLE[5]. Fatigue is defined as an overwhelming and sustained sense of exhaustion that decreases one's capacity for physical and mental work[6] and is commonly seen in people with various diseases. Yet few instruments have been validated for measurement of fatigue in SLE clinical trials.

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue scale) is a 13-item questionnaire that assesses self-reported fatigue and its effect upon daily activities and function[7]. It was developed in 1994-95 to meet a growing demand for the precise evaluation of fatigue associated with anemia in patients who have cancer. Subsequently, it has been employed in more than 70 published studies with over 20,000 people, including patients with cancer who are receiving chemotherapy[8,9], patients

From the Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and Genentech Inc., South San Francisco, California, USA.

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J-S. Lai, PhD, OTR/L, Research Associate Professor; J.L. Beaumont, MS, Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine; S. Ogale, Senior Health Economist; P. Brunetta, MD, Genentech Inc.; D. Cella, PhD, Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine.

Address correspondence to Dr. J-S. Lai, Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, 710 North Lake Shore Drive, Suite 724, Chicago, IL 60611, USA. E-mail: js-lai@northwestern.edu

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with cancer who are not receiving chemotherapy[9,10], longterm cancer survivors[11], childhood cancer survivors[12], and patients with rheumatoid arthritis (RA)[13,14,15], psoriatic arthritis[16], paroxysmal nocturnal hemoglobinuria[17] and Parkinson's disease[18]. It has also been validated in the general US population[19,20]. In all cases, the FACIT-Fatigue scale has been found to be reliable and valid. The FACIT-Fatigue is formatted for self-administration on 1 page, and uses a 5-point Likert-type response scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much).

Item content was determined by combined expert and patient input, ensuring that clinically important issues relevant to patients are included. The FACIT-Fatigue scale has been incorporated into the US National Institutes of Health (NIH) initiative Patient Reported Outcomes Measurement Information System (PROMIS; www.nihpromis.org). The primary aim of PROMIS is to develop item banks measuring domains commonly seen in people with chronic illness. Fatigue has been included in the first wave of this effort. Being incorporated into the PROMIS fatigue item bank, a link between PROMIS and FACIT-Fatigue has been created[21], such that scores on the FACIT-Fatigue can be converted to scores on the PROMIS questionnaire. Subsequently, clinicians can easily understand the degree of fatigue experienced by their patients compared to the US general population based on the FACIT-Fatigue scores. In order to do so, validation of the FACIT-Fatigue scale in the disease of interest is required.

We report here the psychometric properties of the FACIT-Fatigue scale for patients with SLE participating in a randomized clinical trial.

MATERIALS AND METHODS

We used data from the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial[22], a 52-week, placebo-controlled, multicenter study of rituximab in patients with moderately to severely active extrarenal SLE who were receiving background immunosuppressants and prednisone. Inclusion criteria included age between 16 and 75 years, a history of meeting 4 American College of Rheumatology criteria for SLE, and active disease at screening, defined as at least 1 organ system with a British Isles Lupus Assessment Group (BILAG) A score (severe disease activity) or at least 2 organ systems with a BILAG B score (moderate disease activity)[22].

Patients were asked to complete the following assessments at baseline, 12 weeks, 24 weeks, and 52 weeks: (1) FACIT-Fatigue scale[7]: a 13-item measure; scores range from 0 to 52, and higher scores indicate less fatigue; (2) Medical Outcomes Study Short-Form 36 (SF-36) version 2[23]: a 36-item health survey; yields 2 summary scores: physical component score (PCS) and mental component score (MCS), which range from 0 to 100; higher scores indicate better health-related quality of life; (3) Brief Pain Inventory (BPI)[24]: pain severity and pain interference scores range from 0 to 10 and higher scores indicate worse pain; and (4) patient global assessment of disease activity (Patient-GA): 100 mm visual analog scale (VAS); higher scores indicate higher disease activity.

The recall period for the FACIT-Fatigue and other patient-reported questionnaires was 4 weeks. The standard recall period for the FACIT-Fatigue is 1 week. Lai, *et al* have shown that both timeframes are well comprehended by patients and are equally appropriate[25] and therefore results from these 2 timeframes are considered comparable from a measurement perspective.

At the same timepoints, physicians completed (1) the Physician global assessment of disease activity (Physician-GA): a 100 mm VAS; higher scores indicate higher disease activity; and (2) the BILAG disease activity index[26]: a transitional ordinal scale index that assesses 8 systems (general, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, vasculitis, renal, and hematologic). Disease activity for each system is categorized into 5 different levels: Grade A (very active disease; 9 points), Grade B (moderately active disease; 3 points), Grade C (mild stable disease; 1 point), Grade D (no current disease activity but system had previously been affected; 0 points) or Grade E (no current or previous disease activity; 0 points).

Statistical analyses. The rituximab and placebo treatment arms were combined to form a single cohort for all analyses. Descriptive statistics (mean, SD, median, minimum, maximum) were summarized for each scale at each timepoint. Internal consistency reliability was evaluated using Cronbach's α coefficients. Convergent validity was assessed using Spearman correlation coefficients between FACIT-Fatigue score and the Patient-GA, Physician-GA, SF-36 PCS, SF-36 MCS, BPI scores, and BILAG total score. Cross-sectional known group validity was assessed by comparing mean FACIT-Fatigue scores across values of clinical disease activity measures (BILAG) at each assessment. Patients were grouped according to BILAG General domain and BILAG Musculoskeletal domain scores (A, B, or C/D/E). ANOVA was used to test the differences in FACIT-Fatigue scores between groups. Effect sizes (mean difference/SD) were calculated for the differences between adjacent groups.

Responsiveness was determined as the extent to which important longitudinal changes in Patient-GA and BILAG grade are measured by changes in the FACIT-Fatigue score. Patient-GA score changes were classified as better, worse, or unchanged, with a 30% increase or decrease used as the criterion for classifying meaningful change. BILAG grade change between consecutive assessments was categorized as more active, stable, or less active. Moving from a BILAG score of D/E to C or vice versa was classified as stable, since those changes were not considered clinically meaningful. ANOVA was used to compare mean FACIT-Fatigue score change between groups.

For both cross-sectional and longitudinal analyses, the General and Musculoskeletal BILAG domains were selected as anchors from the 8 BILAG domains because of their *a priori* hypothesized relationship with fatigue. The General domain includes a physician assessment of fatigue and malaise, while the Musculoskeletal domain includes an assessment of pain, which is known to be associated with fatigue. Additionally, the same grouping (i.e., A, B, or C/D/E) and analytic methods were applied to the other 6 domains included in the BILAG (mucocutaneous, neuropsychiatric, cardiorespiratory, vasculitis, renal, and hematologic) with an attempt to have a better understanding of fatigue experienced by patients with SLE.

Distribution and anchor-based methods were used to identify minimally important difference (MID) for the FACIT-Fatigue in this sample. Anchor-based methods included examining the effect sizes calculated in the cross-sectional and longitudinal analyses described above. Distribution-based methods included 1/3 SD, 1/2 SD, and 1 SE of measurement (SEM). The SEM is computed as follows:

$$SEM = \sigma_x \sqrt{1 - r_{xx}}$$

where r_{xx} = the reliability of the measure (i.e., the Cronbach's α) and σ_x = the SD of the measure.

RESULTS

Two hundred fifty-four patients with moderately to severely active extrarenal SLE were enrolled in the clinical trial. The average age was 40.3 years (SD 11.9) and 90.9% were women (Table 1). Descriptive statistics for FACIT-Fatigue

Table 1. Demographic characteristics of the study population (n = 254).

Characteristics	
Age, yrs, mean ± SD (range)	40.3 ± 11.9 (17–71)
Women, n (%)	231 (90.9)
White, n (%)	143 (56.3)
Black, n (%)	64 (25.2)
Hispanic, n (%)	30 (11.8)
Other, n (%)	17 (6.7)

and other patient-reported and physician-reported outcomes at baseline and Week 12 are presented in Table 2. Descriptive statistics for Week 24 and 52 assessments are not presented but were very similar to Week 12 scores. At baseline, the mean FACIT-Fatigue score was 19.1 (SD 11.5). This is substantially lower than the US population average of 40.1 as reported by Cella, *et al*[27]. When we converted this score to a T score distribution defined by the NIH PROMIS fatigue item bank, where mean = 50 and SD = 10, it is 1.4 SD worse than the US general population mean[21]. Cronbach's α coefficient was > 0.95 for the FACIT-Fatigue scale at all timepoints.

Correlations between the FACIT-Fatigue scores and the clinical measures and other patient-reported measures are presented separately for each timepoint in Table 3. The FACIT-Fatigue was significantly correlated with SF-36 Vitality, PCS and MCS, Pain Intensity, Pain Interference, and Patient-GA across all timepoints. Physician-GA showed little to no correlation with the FACIT-Fatigue at baseline and small correlations at the later assessments. Correlations with BILAG total scores were inconsistent. Correlations between the FACIT-Fatigue score change and changes in the clinical measures and other patient-reported measures are presented in the last 3 columns of Table 3. The FACIT-Fatigue score change was moderately to highly correlated with changes in SF-36 Vitality, PCS and MCS, Pain Intensity, Pain Interference, and Patient-GA. Physician-GA changes showed little to no correlation with the FACIT-Fatigue change scores. Correlations with changes in BILAG total score are also limited.

FACIT-Fatigue scores by BILAG groups are presented in Table 4. The FACIT-Fatigue scale successfully differentiated between groups defined by BILAG General and Musculoskeletal ratings at nearly all timepoints. Effect sizes for these significant differences were generally in the range of 0.4–0.6. Changes in FACIT-Fatigue scale scores by change in Patient-GA and BILAG ratings are presented in Table 5. In most instances, patients with improved or unchanged status compared to baseline experienced a statistically significant improvement in scores with effect sizes in the range of 0.3 to 0.8. FACIT-Fatigue scale scores worsened for patients with worsened Patient-GA, with an effect size of –0.5; scores remained stable for patients with worsened BILAG General and Musculoskeletal ratings compared to baseline, with effect sizes generally < 0.3. Distribution and anchor-based estimates of the MID derived from the analyses above are summarized in Table 6.

Appendix 1 shows the means and effect sizes for

Table 2. Descriptive statistics for FACIT-Fatigue and other outcome measures.

	N	Mean (SD)	Median (range)	Cronbach's α
FACIT-Fatigue scale				
Baseline	254	19.1 (11.5)	17 (0–50)	0.94
Week 12	231	24.8 (13.0)	22 (0–52)	0.95
SF-36 physical component score				
Baseline	250	30.0 (10.0)	28 (6–59)	NA
Week 12	227	34.1 (10.3)	34 (6–59)	
SF-36 mental component score				
Baseline	250	39.8 (12.9)	40 (2–70)	NA
Week 12	227	42.0 (12.9)	43 (8–66)	
BPI pain intensity				
Baseline	253	5.4 (2.4)	5.5 (0–10)	0.88
Week 12	231	4.6 (2.6)	4.5 (0–10)	0.91
BPI pain interference				
Baseline	254	6.0 (2.4)	6.3 (0–10)	0.91
Week 12	231	4.8 (2.7)	5 (0–10)	0.94
Patient global assessment				
Baseline	254	63.8 (21.8)	68 (2–100)	NA
Week 12	231	47.4 (28.3)	50 (0–100)	
Physician global assessment				
Baseline	250	59.6 (15.0)	63 (9–92)	NA
Week 12	229	34.7 (21.5)	34 (0–91)	

FACIT: Functional Assessment of Chronic Illness Therapy; SF-36: Medical Outcomes Study Short-Form-36; BPI: Brief Pain Inventory; NA: not applicable.

Table 3. Relationship between the FACIT-Fatigue and convergent validity measures (Spearman correlation coefficients).

Measures	Cross-sectional				Change from Baseline		
	Baseline	Week 12	Week 24	Week 52	Week 12 – baseline	Week 24 – baseline	Week 52 – baseline
SF-36 Vitality	0.68	0.81	0.81	0.87	0.63	0.67	0.70
SF-36 PCS	0.59	0.64	0.64	0.74	0.38	0.28	0.47
SF-36 MCS	0.52	0.61	0.66	0.69	0.50	0.28	0.42
BILAG total	–0.26	–0.29	–0.13	–0.25	–0.19	–0.13	–0.15
Pain intensity	–0.60	–0.61	–0.68	–0.72	–0.41	–0.50	–0.47
Pain interference	–0.72	–0.70	–0.79	–0.82	–0.53	–0.68	–0.62
Patient-GA	–0.58	–0.65	–0.70	–0.76	–0.46	–0.55	–0.56
Physician-GA	–0.09	–0.29	–0.25	–0.21	–0.22	–0.12	–0.12

SF-36 PCS: Medical Outcomes Study Short-Form 36 physical component score; SF-36 MCS: mental component score; BILAG: British Isles Lupus Assessment Group; Patient-GA: patient global assessment; Physician-GA: physician global assessment.

Table 4. FACIT-Fatigue scale scores by BILAG groups.

Group		Mean (SD)	Effect Size	p*
BILAG General group				
Baseline	C/D/E (n = 149)	21.9 (12.0)	C/D/E vs B: 0.52	< 0.001
	B (n = 80)	15.8 (9.7)	B vs A: 0.24	
	A (n = 25)	13.1 (9.0)		
Week 12	C/D/E (n = 201)	25.9 (13.0)	0.65	0.001
	A/B (n = 29)	17.5 (10.3)		
BILAG Musculoskeletal group				
Baseline	C/D/E (n = 46)	25.1 (13.4)	C/D/E vs B: 0.53	< 0.001
	B (n = 138)	18.9 (11.1)	B vs A: 0.30	
	A (n = 70)	15.7 (9.7)		
Week 12	C/D/E (n = 157)	26.8 (13.2)	C/D/E vs B: 0.42	0.003
	B (n = 53)	21.4 (11.5)	B vs A: 0.22	
	A (n = 20)	18.8 (12.5)		

* ANOVA p value. FACIT: Functional Assessment of Chronic Illness Therapy; BILAG: British Isles Lupus Assessment Group.

Table 5. Change in FACIT-Fatigue scale vs change in Patient-GA and BILAG General and Musculoskeletal ratings.

	Baseline to Week 12 Change	Mean (SD)	Effect Size*	p**
Patient-GA change	Improved (n = 90)	10.5 (12.9)	0.82	< 0.001
	Unchanged (n = 114)	3.1 (7.8)	0.40	< 0.001
	Worsened (n = 24)	–3.6 (6.7)	–0.53	0.016
BILAG General change	Improved (n = 80)	8.2 (11.9)	0.69	< 0.001
	Unchanged (n = 136)	4.2 (10.2)	0.41	< 0.001
	Worsened (n = 11)	0.0 (9.1)	0.00	1.00
BILAG Musculoskeletal change	Improved (n = 126)	7.1 (10.7)	0.66	< 0.001
	Unchanged (n = 95)	3.3 (11.0)	0.30	0.004
	Worsened (n = 6)	2.5 (11.6)	0.22	0.617

* Mean change/SD of change in that group. ** T test of null hypothesis that change is equal to zero. FACIT: Functional Assessment of Chronic Illness Therapy; BILAG: British Isles Lupus Assessment Group; Patient-GA: patient global assessment.

cross-sectional comparisons across groups defined by the remaining 6 BILAG domains (cardiorespiratory, hematologic, mucocutaneous, musculoskeletal, neurological, renal, and vasculitis). In cross-sectional analyses, there was no clear association between FACIT-Fatigue scores and disease activity in the BILAG mucocutaneous, cardiorespiratory, or

Table 6. Summary of distribution and anchor-based estimates of FACIT-Fatigue minimally important difference (MID).

	1/3 SD	1/2 SD	SEM	Anchor-based Differences and Change Scores Based on Responsiveness Analyses*	Estimated MID
Baseline	3.8	5.8	2.8	2.5, 2.6, 2.7, 3.2, 5.4, 6.1, 6.2, 7.1, 8.2, 8.4	3 to 7 points
Week 12	4.3	6.5	2.9		
Week 24	4.1	6.2	2.8		
Week 52	4.6	6.8	2.7		

* Statistically significant differences corresponding to effect sizes between sizes between 0.20 and 0.70. FACIT: Functional Assessment of Chronic Illness Therapy; SEM: standard error of measurement.

hematologic groups. Meaningful differences were observed among patients with no/mild activity versus moderate activity in the BILAG neurological domain. In contrast, patients with a baseline BILAG vasculitis rating of B reported better baseline fatigue scores than those patients with a baseline BILAG vascular rating of C/D/E. The mean changes and effect sizes for groups defined by change from baseline in these BILAG domains are presented in Appendix 2. Patients with improvement in the hematologic domain, which includes hemoglobin, white blood cell counts, and platelet counts, had a greater improvement in fatigue scores than patients who remained unchanged or worsened on this BILAG domain. For the remaining BILAG domains, effect sizes were similar in patients with improved and unchanged disease activity.

DISCUSSION

The goal of this study was to validate the 13-item FACIT-Fatigue scale in patients with extrarenal SLE. Fatigue is a common complaint for people with and without illness. Although the FACIT-Fatigue scale was originally developed for assessment of fatigue in patients with cancer, it has been validated in other populations, including a sample of patients with RA. In this clinical trial population with moderately to severely active SLE, the FACIT-Fatigue scale exhibited excellent internal consistency reliability, as measured by Cronbach's coefficient α. Known group validity was demonstrated by the ability of FACIT-Fatigue scores to successfully differentiate between groups defined by BILAG general and musculoskeletal domain grades. Good convergent validity was supported by moderate to high correlations with other scales, as shown in Table 3. However, we were unable to make the same conclusion with regard to physician-rated disease activity scales, the Physician-GA, and BILAG total scores. A similar finding has been made by others[28,29], where a lack of correlation was observed between patient-reported fatigue, as measured by the Fatigue Severity Score, and physician-reported composite measures of overall disease activity as measured by the SLE Disease Activity Index (SLEDAI) or the Systemic Lupus Activity Measure–revised (SLAM-R). Given the self-referenced nature of fatigue and empirical evidence, it is therefore important to measure fatigue through patient self-report, in addition to physicians' assessment of disease activity.

In longitudinal analyses, the FACIT-Fatigue scale was responsive to changes in the measures that were selected as anchors. Patients with meaningful changes in Patient-GA from baseline to 12 weeks experienced a corresponding improvement or worsening in scores with effect sizes in the meaningful range (0.5–0.8). FACIT-Fatigue scores improved for patients who had improved BILAG grades as well as for patients who had unchanged BILAG grade. However, the magnitude of FACIT-Fatigue score improvements was larger in patients with improved BILAG grade than in patients with unchanged BILAG grade. Very few patients experienced worsening of BILAG General and Musculoskeletal domains, and FACIT-Fatigue scores remained stable for these patients.

Distribution and anchor-based MID for the FACIT-Fatigue scale derived from these analyses were estimated to be 3–7 points. It is important to note that the anchor-based differences represent meaningful differences but they are not necessarily minimally important. Using a cross-sectional approach, Goligher, *et al*[30] derived 5.9 points as the minimal clinically important difference (MCID) for the FACIT-Fatigue scale in patients with SLE. The literature[13,31,32] suggests 3–4 points as the MID for patients with RA or cancer. Discrepancy in anchor-based MID estimates is likely a result of choice of anchors selected for estimation. Based on these results, we conclude that the MCID for the FACIT-Fatigue scale in patients with SLE is 3–4 points. Further studies using different anchors are warranted.

The availability of normative values for the FACIT-Fatigue scale in a variety of populations allows for comparison with the current study. At baseline, the mean FACIT-Fatigue scale score in this study of patients with SLE enrolled in the EXPLORER trial was 19.1 (SD 11.5). This score was over 2.5 SD lower than the general US population, in which data were collected through telephone interviews using random-digit dialing[20]. When it was compared to the PROMIS-based FACIT-F scores, where FACIT-F was

calibrated together with 82 other fatigue items using an Item Response Theory model and data were collected by Internet, current patients with SLE showed 1.4 SD worse than the PROMIS-based norms. In either case, patients with SLE reported significant fatigue relative to the US general population. The patients with SLE in our study scored closer to, but still slightly worse than, the mean of 23.9 for a reference group of anemic patients with cancer[20] but much lower than a sample of patients with RA at the start of a clinical trial (FACIT-F mean = 28.8)[13].

The FDA guidance document (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf) about clinical development programs for SLE acknowledges the importance of using a specific instrument for measuring fatigue. Our study presents the first in-depth analysis of the validity of the FACIT-Fatigue in patients with SLE. However, further assessment of content validity in the specific patient population may be required. An ad hoc committee for SLE response criteria for fatigue[33] recommended the Fatigue Severity Scale (FSS) for measurement of fatigue in SLE clinical trials. This recommendation was based on a systematic literature review of the fatigue instruments that had been used in SLE between 1970 and 2006. The FSS was the most commonly used instrument, while the FACIT-Fatigue was not assessed because it had not been used in SLE at that time. Goligher, *et al*[30] compared 7 fatigue questionnaires, including FACIT-Fatigue, FSS, and the SF-36 Vitality domain, and found the FACIT-Fatigue demonstrated greater sensitivity to subjectively detectable differences in fatigue levels compared to the FSS and SF-36 Vitality domain.

Our study has some limitations. Since very few patients experienced worsening of the 2 BILAG domains in our study (11 patients for the General domain and 6 patients for the Musculoskeletal domain), we could not assess the responsiveness of the FACIT-Fatigue to worsening of these clinical domains. However, a substantial number of patients (24) experienced worsening of their SLE disease activity as measured by the Patient-GA from baseline to 12 weeks. Thus, using the Patient-GA as an anchor, we were able to demonstrate the responsiveness of the FACIT-Fatigue to improvement as well as worsening of SLE disease activity. Data on confounding factors for the association between SLE disease activity and fatigue, such as sleep disorders, depression, or fibromyalgia, were not collected in this clinical trial; therefore we could not assess their contribution to fatigue levels in our SLE study population. Because we used data collected from the EXPLORER study, which limited participation to moderate-severe extrarenal SLE, the results of our study may not be generalizable to patients with inactive or mildly active disease, with or without fatigue. Future studies should examine whether the results could be duplicated in patients with inactive or mildly active disease with or without fatigue.

The FACIT-Fatigue scale is a valid and responsive instrument to measure fatigue experienced by patients with SLE. MID for SLE populations are similar to those derived previously. Since very little worsening of the BILAG domains was observed in our study, further research is warranted to evaluate responsiveness of the FACIT-Fatigue to worsening of physician-assessed disease activity.

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APPENDIX 1. FACIT-Fatigue scale scores by BILAG groups.

		Mean (SD)	Effect Size	p
BILAG Cardiorespiratory Group				
Baseline	C/D/E (n = 195)	19.2 (11.4)	C/D/E vs B: –0.07	0.410
	B (n = 45)	20.0 (11.7)	B vs A: 0.39	
	A (n = 14)	15.3 (12.6)		
Week 12	C/D/E (n = 213)	25.0 (13.1)	C/D/E vs B: 0.02	NC
	B (n = 16)	24.8 (12.0)	B vs A: NC	
	A (n = 1)	2.0 (NA)		
BILAG Hematologic Group				
Baseline	C/D/E (n = 194)	18.5 (11.2)	C/D/E vs B: –0.26	NC
	B (n = 56)	21.4 (12.8)	B vs A: NC	
	A (n = 4)	17.5 (9.3)		
Week 12	C/D/E (n = 200)	24.6 (13.0)	–0.16	0.403
	B (n = 30)	26.7 (13.4)		
BILAG Mucocutaneous Group				
Baseline	C/D/E (n = 71)	16.9 (9.7)	C/D/E vs B: –0.26	0.144
	B (n = 144)	19.8 (12.3)	B vs A: –0.06	
	A (n = 39)	20.5 (11.3)		
Week 12	C/D/E (n = 158)	25.5 (12.9)	C/D/E vs B: 0.14	0.452
	B (n = 57)	23.7 (13.6)	B vs A: 0.12	
	A (n = 15)	22.1 (12.4)		
BILAG Neurological Group				
Baseline	C/D/E (n = 222)	19.7 (11.7)	C/D/E vs B: 0.52	NC
	B (n = 26)	13.8 (9.6)	B vs A: NC	
	A (n = 6)	19.5 (9.3)		
Week 12	C/D/E (n = 215)	25.4 (13.0)	C/D/E vs B: 0.80	NC
	B (n = 13)	15.2 (11.5)	B vs A: NC	
	A (n = 2)	23.5 (7.8)		
BILAG Renal Group				
Baseline	C/D/E (n = 251)	19.2 (11.6)	NC	NC
	B (n = 3)	15.3 (10.5)	C/D/E vs B: NC	NC
Week 12	C/D/E (n = 218)	24.7 (13.1)	B vs A: NC	
	B (n = 9)	26.6 (10.9)		
	A (n = 3)	33.6 (17.0)		
BILAG Vasculitis Group				
Baseline	C/D/E (n = 216)	18.5 (11.0)	C/D/E vs B: –0.55	NC
	B (n = 30)	24.8 (14.4)	B vs A: NC	
	A (n = 8)	13.6 (6.6)		
Week 12	C/D/E (n = 216)	24.8 (12.8)	C/D/E vs B: –0.13	NC
	B (n = 11)	26.5 (16.4)	B vs A: NC	
	A (n = 3)	23.0 (18.2)		

FACIT: Functional Assessment of Chronic Illness Therapy; BILAG: British Isles Lupus Assessment Group; NC: not calculated (when group sample size < 10).

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APPENDIX 2. Change in FACIT-Fatigue scale versus change in BILAG ratings.

	Baseline to Week 12 Change (n)	Mean (SD)	Effect Size*	p**
BILAG Cardiorespiratory change	Improved (40)	4.4 (9.3)	0.47	0.005
	Unchanged (182)	5.8 (11.4)	0.51	< 0.001
	Worsened (5)	–1.8 (5.9)	–0.31	0.532
BILAG Hematologic change	Improved (33)	9.5 (14.5)	0.66	< 0.001
	Unchanged (188)	4.7 (10.2)	0.46	< 0.001
	Worsened (6)	5.6 (7.8)	0.71	0.142
BILAG Mucocutaneous change	Improved (101)	4.5 (11.2)	0.40	< 0.001
	Unchanged (121)	6.4 (10.8)	0.59	< 0.001
	Worsened (5)	–0.6 (9.8)	–0.06	0.898
BILAG Neurological change	Improved (23)	6.2 (10.6)	0.59	0.010
	Unchanged (198)	5.2 (11.0)	0.48	< 0.001
	Worsened (6)	7.5 (12.6)	0.60	0.204
BILAG Renal change	Improved (1)	5.0 (—)	—	—
	Unchanged (217)	5.3 (11.0)	0.48	< 0.001
	Worsened (9)	7.5 (11.4)	0.66	0.084
BILAG Vasculitis change	Improved (25)	1.2 (10.9)	0.11	0.600
	Unchanged (200)	6.0 (11.1)	0.55	< 0.001
	Worsened (2)	1.0 (2.8)	0.35	0.705

* Mean change/SD of change in that group, ** t-test of null hypothesis that change is equal to zero. FACIT: Functional Assessment of Chronic Illness Therapy; BILAG: British Isles Lupus Assessment Group.