Impaired Health Status and the Effect of Pain and Fatigue on Functioning in Clinical Trial Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective***. Our study evaluated the impaired health status of clinical trial patients with systemic lupus erythematosus (SLE) and explored the relationship between changes in fatigue and pain and their effect on overall health status.

Methods. Pooled treatment and placebo data from a phase Ib clinical trial of adults with moderate/severe SLE were analyzed. Measures included patient-reported Medical Outcome Study Short Form-36 Survey, Version 2 (SF-36v2), Fatigue Severity Scale, and numeric rating scales (NRS) for pain and global health assessment and clinician-reported global assessment of disease activity (MDGA). Disease burden was compared to the US general population. Health status of responders and nonresponders on pain or fatigue were compared.

Results. The sample included 161 patients with SLE, predominantly female (96%) and white (72%), with average age of 43 ± 11 years. Mean SF-36v2 component summary scores reflected overall problems with physical [physical component summary (PCS); 35.2 ± 9.7] and mental health (mental component summary; 40.9 ± 12.9). Patients with SLE had worse health status on all SF-36v2 subscales than the US general population and comparable age and sex norms (effect size –0.51 to –2.15). Pain and fatigue responders had greater improvements on SF-36v2 scores (bodily pain, physical functioning, social functioning, PCS), patient global health assessment NRS, and MDGA than nonresponders. There was moderate agreement in responder status, based on global assessments by patients and clinicians (68.1%), with some discrepancy between patients who were MDGA responders but patient assessment nonresponders (27.7%).

Conclusion. Improvements in patient-reported pain or fatigue correlated with improvements in overall health. Patient assessments offer a unique perspective on treatment outcomes. Patient-reported outcomes add value in understanding clinical trial treatment benefits. (J Rheumatol First Release Oct 1 2013; doi:10.3899/jrheum.130046)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease that can affect almost any organ system, with heterogeneous clinical manifestations that can vary over time. Commonly used measures of SLE disease activity assess manifestations in constitutional, mucocutaneous, musculoskeletal, neurological, pulmonary, cardiovascular, abdominal, and renal systems[1]. The disease affects primarily women in their reproductive years, and has changed in recent years from life-threatening with high rates of early mortality to a chronic disease with longer life expectancy[2,3].

Studies have demonstrated a multidimensional effect of SLE on health-related quality of life (HRQOL)[4] and posited that the overall effect of SLE may actually be as much or more severe than other more prevalent and better-recognized chronic diseases (e.g., hypertension, diabetes, myocardial infarction)[5]. In comparing health status of

patients with SLE to those with rheumatoid arthritis and other noninflammatory conditions, patients with SLE had better physical function but were more impaired in general health (GH), vitality (VT), social function, role-emotional, and mental health (MH) domains[6]. Also, HRQOL was predicted by organ damage, comorbidity, income, education, and age[6,7,8]. Similarly, a review highlighted the importance of HRQOL as an outcome measure in SLE, concluding that age, fatigue, and other psychosocial factors influence HRQOL in a complex way[9].

Fatigue, the most common constitutional symptom associated with SLE, affects over 50% of patients with SLE[10,11,12]. Although common, fatigue is often not associated with SLE disease activity levels or with chronic organ damage. A study investigating relationships between psychosocial factors and fatigue in SLE found that pain and perceived social support, but not disease activity, predicted fatigue levels[13]. Medications, lifestyle habits, concomitant fibromyalgia, or affective disorders have also been associated with fatigue[14]. Although chronic fatigue may not be related to SLE disease activity or organ damage, presence of fatigue influences HRQOL, even in the absence of comorbid fibromyalgia[15]. A conceptual model of HRQOL for SLE based on qualitative research highlighted the relevance of pain, fatigue/tiredness, and skin problems, the relationships between symptoms and burden, and the broad influence of SLE on patient HRQOL from the patient perspective[16]. Research has suggested that SLE patients with fatigue may be physically compromised[11], and that fatigue may be the most debilitating symptom in patients with SLE[17,18].

The multisystemic nature of SLE is often a challenge for evaluating treatment benefit because a unidimensional approach may not be appropriate. SLE treatments have been evaluated based on their effects on disease activity, organ damage, and quality of life[19]. Outcome measures in clinical trials have included disease activity indices, HRQOL measures, global assessments (patient- and physician-assessed), and measures of organ damage and responder indices[20]. Evaluation of clinical trial treatment benefit has traditionally focused on clinical endpoints, because patient-reported outcome (PRO) measures are often not correlated with disease activity, but rather reflect different aspects of the disease[21]. The benefit of using PRO measures is that they can provide valuable information on the patient experience and perspective that is different from and supplements traditional clinical outcomes[22,23]. Patient report of fatigue has been accepted as an important concept to evaluate benefits of SLE treatments[22].

Exploring PRO data from SLE trials can help us better understand disease burden and effect on HRQOL and functioning. This information can identify unmet medical needs and help develop strategies for PRO data collection that ensure better assessment of disease activity and detection of change, from the patients' perspective. The objectives of our study were to evaluate HRQOL of patients with SLE in a clinical trial by comparing their health status to the US population, and exploring relationships between changes in pain and fatigue with changes in overall health status over time.

MATERIALS AND METHODS

Clinical trial study design. Data came from a phase Ib, randomized, double-blind, placebo-controlled, dose-escalation study (n = 161) evaluating safety and tolerability of multiple intravenous doses of sifalimumab (formerly MEDI-545), a fully human anti-interferon (IFN)-α monoclonal antibody, in adult patients with SLE (MI-CP152; clinical trial no. NCT00482989)[24]. The clinical trial started in March 2008 and was completed in July 2010. Thirty rheumatology centers in 5 countries (Argentina, Brazil, Canada, Chile, and United States) participated.

Study design and subject disposition are described elsewhere[24]. Subjects were enrolled if they were aged ≥ 18 years with moderate to severe SLE and met at least 4 of the 11 revised American College of Rheumatology classification criteria for SLE[25]. Eligible subjects also had a positive antinuclear antibody test (at least 1:80 serum dilution in the past or at screening), and met at least 1 of the 2 criteria for disease activity: Safety of Estrogens in Lupus Erythematosus (SELENA)–Systematic Lupus Erythematosus Disease Activity Index (SLEDAI)[26] score ≥ 6, or at least 1 system with a score of A, or 2 systems with a score of B on the British Isles Lupus Assessment Group (BILAG) index[27] at screening. Patients with infections or recent high (> 20 mg/day) or fluctuating doses of oral corticosteroids, antimalarials, or immunosuppressives; B-cell depleting therapies within the past 12 months, leflunomide in the past 6 months or any other biologic agent in the past 30 days were excluded.

The study was conducted in accordance with the International Conference on Harmonization Guidance for Good Clinical Practice and Declaration of Helsinki. Recruitment procedures were approved by an institutional review board/independent ethics committee prior to study initiation and were performed in accordance with US Health Insurance Portability and Accountability Act requirements and all applicable state and federal laws and regulations. Written informed consent was obtained from subjects before study entry or any study-specific activities.

SF-36v2. The Medical Outcome Study Short Form-36 Health Survey, Version 2 (SF-36v2) is a generic health status measure shown to be reliable and valid in diverse patient groups and healthy populations[28,29,30,31]. It is one of the most widely used HRQOL instruments among many different disease populations[28,29,32,33]. The standard SF-36v2 with a 4-week recall period was used.

SF-36v2 contains 8 subscale and 2 summary scores. The subscales are Bodily Pain (BP), GH, MH, Physical Functioning (PF), Role-Emotional (RE), Role-Physical (RP), Social Functioning (SF), and Vitality (VT). Subscale scores range from 0–100, with higher scores reflecting better health status. Mental Component Summary (MCS) and Physical Component Summary (PCS) scores are generated using a weighted combination of the subscale scores. Scores were generated using norm-based methods that standardize scores to have a mean = 50 and SD = 10 in the normative general US population, where scores > 50 are above average and < 50 are below average[31]. Responder criteria values proposed for SF-36 subscales range from 3.2 (RP) to 5.7 (GH), and 3.1 (PCS) and 3.8 (MCS) for component scores[34]. Disease-specific estimates of meaningful change in SF-36 scores have also been developed; improvement of 5-10 points for individual SF-36 domains and 2.5–5 points for PCS and MCS summary scores have been considered indicative of important improvement[20,35,36]. In addition, there is also evidence that minimally important differences vary for improvement versus deterioration, with lower thresholds for worsening, as evidenced by decreases ranging from 1.7 to –14.7 for domains and –0.8 to –2.1 for summary scores seen among SLE clinical trial patients[35].

Fatigue Severity Scale. The Fatigue Severity Scale (FSS) assesses severity of fatigue and interference with daily activities, physical function, exercise, work, family, or social life in the past week[37,38]. FSS includes 9 items rated on a 1 (strongly disagree) to 7 (strongly agree) scale. The total score is calculated as the mean of the items and ranges from 1–7, where higher scores indicate greater fatigue. In this study, if > 2 item responses were missing, FSS was not calculated and the score was set to missing.

Clinical fatigue has been defined as an FSS total score ≥ 4[39]. Important improvement in fatigue has been described as a 10% decrease (95% CI 4.9–14.6) based on the patient perspective[40] and a 15% decrease on FSS based on clinical experts[41]. These decrease estimates using patient[40] and clinician[41] input correspond closely to a 1-point change in total FSS score, which was used to assess potentially relevant improvement in fatigue.

Patient numeric rating scales for pain and global health assessment. Numeric rating scales (NRS) assessed pain and global health. Each included a single question on a 0–100 scale in 5-point increments. The pain item asked "How much pain have you had because of your illness in the past week?" with response anchors 0 (no pain) and 100 (pain as bad as it can be). The patient global health assessment asked "Considering all of the ways that your illness affects you, rate how you are doing;" with response anchors 0 (very well) and 100 (very poorly).

A 2-point change in 0–10 point pain NRS scores has been considered clinically meaningful[42,43]. Multiple anchor-based analyses have also confirmed that patients considered pain intensity reductions on NRS or visual analog scales (VAS) of 1 point or 10–20% as minimally important change, and reduction of at least 2 points or 30% to be moderately clinically meaningful[44,45]. In addition, change thresholds of up to 30% have been used in SLE as a criterion for meaningful change in patient global assessment[46]. A 2-point change on a 0–10 scale[42,43] equates to a 20% change on the 0–100 NRS for pain and global health adopted in this study, where higher scores represent more pain or worse health, respectively. For each measure, a ≥ 20% increase in NRS score was considered worsening.

Physician global assessment of disease. Clinicians rated SLE disease activity using the physician global assessment of disease (MDGA), a VAS ranging from 0–3.0 measured to 1 decimal place. MDGA score could be interpreted as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. No imputation was performed for missing data. For MDGA, an increase from baseline ≥ 0.3 was considered worsening[20,47].

Analytical sample. This was an exploratory analysis evaluating health status and PRO measures in patients with SLE within the context of a controlled clinical trial. The modified intent-to-treat (mITT) population comprised 161 randomized subjects who received at least 1 dose of study medication; 122 of them (75.8%) completed the trial. The mITT population was pooled across treatment groups and analyses were conducted blinded to treatment; the objective of this study was to describe overall burden of SLE and explore relationships between fatigue and other outcomes, regardless of treatment assignment or efficacy. Treatment effects are described elsewhere[24].

Baseline and end of study (EOS) clinical trial data were used in this analysis. Baseline for PRO was defined as the last valid assessment prior to first administration of study drug; this timepoint for outcome measures evaluated in the current study coincided with Study Day 0. EOS was identified as Study Day 196.

SAS statistical software version 9.2 (SAS Institute Inc.) was used to conduct analyses. All statistical tests were 2-sided with a significance level of 0.05. No adjustments for multiple comparisons were performed.

Exploring the HRQOL burden of SLE. To characterize the overall burden of SLE, mean baseline SF-36v2 subscale scores for the clinical trial sample were compared to US general population means using groups stratified by age and sex[31]. In the absence of individual patient level data for general population norms that would allow us to precisely estimate the norms by matching with the age and sex distribution of the trial sample, we used an indirect approach to evaluate burden. We compared mean trial sample scores by age and sex to the appropriate general population age and sex cohorts for whom normative scores have been reported. One-sample t tests evaluated the hypothesis that mean baseline study sample scores are equal to published reference scores. Effect sizes (ES) were computed as the difference between study sample mean and the reference mean, divided by the pooled SD for both samples (i.e., Cohen's d). ES can be interpreted as small (0.20), moderate (0.50), or large (0.80)[48].

The clinical trial sample was predominantly female with an average age across treatment groups of 40–45 years; SF-36v2 age and sex norms most similar to the study sample were chosen. SF-36v2 baseline scores in the study sample were compared to 1998 US general population norms for (a) females, ages 35–44 years (n = 820); (b) males and females, ages 35–44 years (n = 1520); and (c) males and females, ages 18–96 years (n = 6742)[31]. The full study sample was used for these comparisons; analyses were not stratified by age or sex of SLE patients because of small sample size (n = 161) and few males (n = 7).

Relationships between changes in pain and fatigue and changes in health status and global assessments. Patients were classified as responders or nonresponders based on change in pain and fatigue scores. Responder status was defined using change from baseline to EOS, computed as change score = endpoint score–baseline score; a negative change score represents improvement. Responder groups were expected to demonstrate more change over time on outcome measures. FSS change score ≤ –1.0 from baseline to EOS was defined as an FSS responder and change > –1.0 as an FSS nonresponder. Similarly, a ≥ 20% increase in NRS pain score from baseline to endpoint was considered worsening and assigned as a nonresponder. Patients with < 20% increase in NRS pain score were considered pain responders, with improvement or no substantial increase in pain level.

Changes from baseline to EOS based on SF-36v2 and patient and physician global assessments were compared between pain and fatigue responder and nonresponder groups. ES were computed for responders and nonresponders as the PRO change score, divided by SD of baseline PRO score.

Relationship between responders based on changes in physician and patient global assessments. Concordance between responders defined based on patient assessments of global health and physician assessments of disease activity was examined to explore the relationship between physician and patient-defined assessments. Frequencies (n, %) of responders and nonresponders based on patient-reported global health assessment NRS and clinician-reported MDGA were compared for study completers with data for both measures at baseline and Day 196.

Responder status was defined as score change from baseline to EOS in patient global health assessment NRS and clinician-reported MDGA, where negative change scores represented improvement. Patient assessment responders were defined as < 20% increase in patient global health NRS score, and physician assessment responders as < 0.3-point increase in clinician-assessed MDGA VAS. Fisher's exact test was conducted to analyze the 2 × 2 contingency table.

RESULTS

Sample characteristics. Demographic and clinical characteristics for the 161 SLE trial patients are presented in Table 1. Patients were predominantly female (95.7%), white (72.0%), and not Hispanic or Latino (64.0%), with an average age of 43 ± 11 years (range: 18–71 yrs). The majority (71.4%) came from North America (US: n = 114, 70.8%; Canada: n = 1, 0.6%), with fewer patients from South America (Argentina: n = 28, 17.4%; Brazil: n = 13, 8.1%; Chile: n = 5, 3.1%). Baseline disease activity indicated moderate/severe SLE despite standard of care treatment.

Burden of SLE and health status. On average at baseline,

Table 1A. Sociodemographic characteristics of the SLE clinical trial participants.

Characteristics	SLE Trial Participants, n = 161
Age, yrs	
Mean (SD)	42.8 (11.2)
Median	44.0
Range	18–71
Age category, n (%)	
< 40 yrs	65 (40.4)
40– < 65 yrs	92 (57.1)
≥ 65 yrs	4 (2.5)
Sex, n (%)	
Male	7 (4.3)
Female	154 (95.7)
Ethnicity, n (%)	
Hispanic or Latino	58 (36.0)
Not Hispanic or Latino	103 (64.0)
Race, n (%)	
Asian	4 (2.5)
Black or African American	40 (24.8)
Native Hawaiian or other Pacific Islander	1 (0.6)
White	116 (72.0)
Weight, kg	
Mean (SD)	75.30 (19.41)
Median	72.30
Range	39.4–120.0
Region, n (%)	
North America	115 (71.4)
South America	46 (28.6)

SLE: systemic lupus erythematosus.

Table 1B. Disease characteristics of the SLE clinical trial participants.

Characteristics	SLE Trial Participants, n = 161
High type I IFN[a], n (%)	121 (75.2)
Baseline medication, n (%)	
Oral corticosteroids	115 (71.4)
Antimalarials	111 (68.9)
ANA-positive, n (%)	160 (99.4)
SELENA-SLEDAI[b], mean (SD)	11.0 (5.4)
BILAG ≥ 1A, n (%)	39 (24.2)
BILAG ≥ 2B no A, n (%)	76 (47.2)
BILAG A, n (%)	
General	2 (1.2)
Musculoskeletal	16 (9.9)
Mucocutaneous	15 (9.3)
Renal	7 (4.3)
Hematological	1 (0.62)
BILAG B, n (%)	
General	25 (15.5)
Musculoskeletal	99 (61.5)
Mucocutaneous	90 (55.9)
Renal	12 (7.5)
Hematological	20 (12.4)

[a] Measured using 4-gene panel of type I IFN-inducible genes. [b] Patients met at least 1 of 2 criteria for disease activity: SELENA-SLEDAI score ≥ 6 or at least 1 system with a score of A or 2 systems with a score of B on the BILAG index at screening. ANA: antinuclear antibody; BILAG: British Isles Lupus Assessment Group; IFN: interferon; SELENA: Safety of Estrogens in Lupus Erythematosus; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

patients reported compromised health status across all SF-36v2 subscales and summary scores (Table 2). Subscale means ranged from 34.5 ± 9.6 for GH to 42.1 ± 13.2 for MH. Summary scores also indicated problems with overall physical (PCS; mean ± SD = 35.2 ± 9.7) and mental (MCS; mean ± SD = 40.9 ± 12.9) components of health, relative to means of 50 in the normative US general population[31].

Comparison to US general population. Mean SF-36v2 subscale scores for the trial sample and the 3 US general population norms are presented in Figure 1. Compared with the US general population and age and sex norms, SLE trial patients had significantly worse health status across multiple subscales, with differences of moderate to large ES magnitudes ($p < 0.0001$ for all subscales, ES = –0.51 to –2.15).

Comparison of changes in pain and fatigue to changes in global assessments. Baseline, endpoint, and change scores for PRO (SF-36v2; patient global health assessment NRS) and clinician-reported MDGA are reported by pain responder status (Table 3). Pain responders, identified based on pain NRS scores, reported large improvements on SF-36v2 BP (mean change = 8.8, ES = 0.8). Generally, pain responders experienced larger amounts of change, representing improvement, in SF-36v2 subscales over time than pain nonresponders. Pain responders reported large improvements on SF (mean change = 8.7, ES = 0.7) and PF (mean change = 7.0, ES = 0.6) subscales, and PCS (mean change = 7.4, ES = 0.7).

Changes in patient global health assessment (mean change = –26.0, ES = –1.0) and clinician-reported MDGA (mean change = –0.7, ES = –1.5), suggested that pain response was associated with dramatic improvement in overall health status at EOS, as perceived by both patient and physician.

Fatigue responders. Baseline, endpoint, and change scores for PRO and clinician-reported MDGA are presented by fatigue responder status (Table 4).

Fatigue responders and nonresponders reported improvement in health status on the SF-36v2; however, larger changes were observed among responders, particularly in SF-36v2 BP (mean change = 6.1, ES = 0.6), PF (mean change = 6.8, ES = 0.6), and SF (mean change = 7.6, ES = 0.6) subscales, and PCS (mean change = 6.0, ES = 0.7). Patients experienced less improvement in domains related to mental and emotional aspects (e.g., MH and RE subscales and MCS).

Fatigue responders also experienced better overall health status than nonresponders. ES estimates suggested that

Table 2. Comparison of Medical Outcome Study Short Form-36 Survey, Version 2 (SF-36v2) subscale scores for SLE clinical trial participants and US general population norms.

SF-36v2 Subscale Scores (0–100)	SLE Trial Participants		US General Population Norms, Female, Ages 35–44 yrs, n = 820[a]		US General Population Norms, Male/Female, Ages 35–44 yrs, n = 1520[b]		US General Population Norms, Total Sample, Ages 18–96 yrs, n = 6742[c]	
	N	Mean (SD)	Mean[d] (SD)	Effect Size[e]	Mean[d] (SD)	Effect Size[e]	Mean[d] (SD)	Effect Size[e]
Bodily pain	160	37.5 (9.4)	49.95‡ (9.64)	–1.30	50.71‡ (9.32)	–1.42	50‡ (10)	–1.25
General health	160	34.5 (9.6)	50.15‡ (9.8)	–1.60	50.95‡ (9.54)	–1.72	50‡ (10)	–1.55
Mental health	160	42.1 (13.2)	47.74‡ (10.45)	–0.51	49.04‡ (10.15)	–0.66	50‡ (10)	–0.78
Physical functioning	161	35.0 (11.4)	51.4‡ (8.59)	–1.80	52.43‡ (7.67)	–2.15	50‡ (10)	–1.49
Role-emotional	160	36.4 (14.1)	49.91‡ (9.62)	–1.29	50.9‡ (8.97)	–1.52	50‡ (10)	–1.35
Role-physical	160	36.3 (10.9)	51.35‡ (8.75)	–1.65	52.1‡ (8.35)	–1.83	50‡ (10)	–1.37
Social functioning	160	36.2 (12.4)	49.3‡ (10.14)	–1.25	50.35‡ (9.55)	–1.44	50‡ (10)	–1.38
Vitality	160	40.1 (11.1)	48.36‡ (9.92)	–0.81	49.87‡ (9.83)	–0.98	50‡ (10)	–0.98

[a] Reference values are mean SF-36v2 subscale scores for 1998 US general population norms for females, ages 35–44 years (n = 820) reported in Ware, *et al* 2000[31]. [b] Reference values are mean SF-36v2 subscale scores for 1998 US general population norms for males and females, ages 35–44 years (n = 1520) reported in Ware, *et al* 2000[31]. [c] Reference values are mean SF-36v2 subscale scores for 1998 US general population norms (n = 6742, ages 18–96) reported in Ware, *et al* 2000[31]. [d] One-sample t tests to compare study sample means to known values: ‡ $p < 0.0001$. [e] Effect size was computed using the standardized mean difference, where (mean difference between study sample and reference group)/pooled SD. Pooled SD was computed as $^{s}pooled = sqrt [(s_1^2 (n_1 - 1) + s_2^2 (n_2 - 1))/n_1 + n_2 - 2]$. SLE systemic lupus erythematosus.

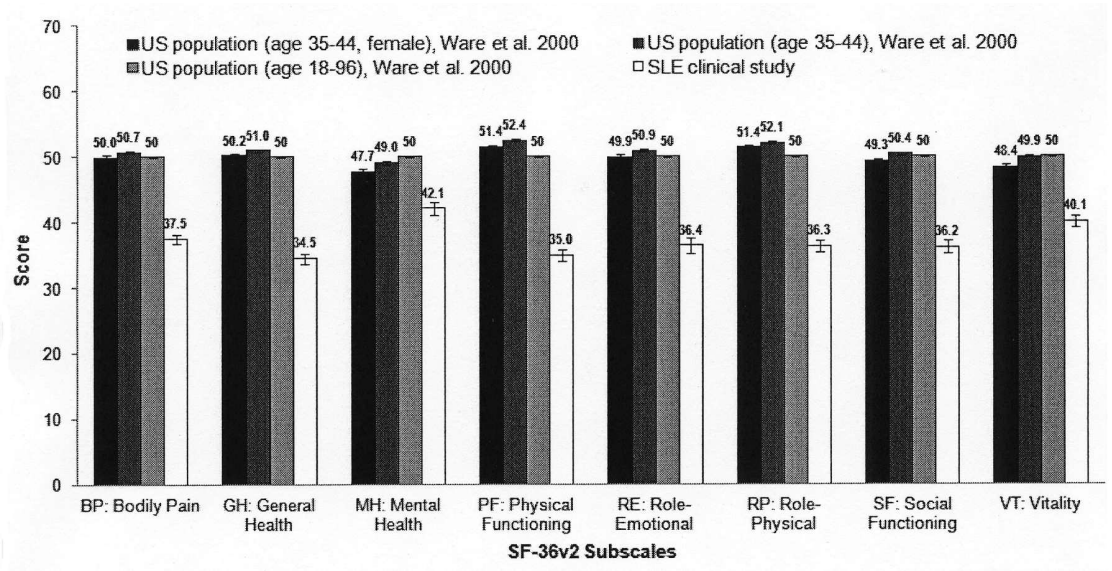

Figure 1. Comparison to US population norms of mean baseline Medical Outcome Study Short Form 36-item Survey, Version 2 (SF-36v2) subscale scores in a systemic lupus erythematosus (SLE) clinical trial.

fatigue responders experienced more improvement, particularly in patient global health (ES = –0.7) and clinician-reported MDGA (ES = –1.6).

Relationship between responders based on changes in patient and physician global assessments. Responder status was defined based on change scores on patient-assessed health status and physician-assessed disease activity. There was moderate agreement in responder status, with 68.1% of patients (n = 81) identified as responders based on patient global health assessment NRS and physician-assessed MDGA. Nearly one-third of patients (27.7%; n = 33) were identified as responders using clinician-assessed MDGA, but nonresponders based on the patient global health, indicating discrepancy between physician and patient evaluations. Five subjects (4.2%) were identified as nonresponders based on both patient and physician assessments. No patients were classified as responders by patient global health assessment, but as nonresponders based on clinician ratings. Fisher's test for the 2 × 2 contingency table was significant (p = 0.0027), indicating a relationship between responders defined based on patient self-evaluation and physician assessment.

Table 3. Change in health status by pain responder status[a] in the systemic lupus erythematosus clinical trial participants.

PRO Scores	Pain Responder (NRS change score ≥ 20% decrease; n = 49)				Pain Nonresponder (NRS change score < 20% decrease; n = 68)			
	Baseline Mean (SD)	Endpoint, Day 196 Mean (SD)	Change Score Mean (SD)	Effect Size[b]	Baseline Mean (SD)	Endpoint, Day 196 Mean (SD)	Change Score Mean (SD)	Effect Size[b]
SF-36v2 subscale scores (0–100)								
Bodily pain	38.1 (10.5)	46.8 (9.8)	8.8 (9.1)	0.8	36.4 (7.7)	36.0 (8.5)	–0.4 (7.7)	–0.1
General health	33.8 (10.0)	39.4 (11.9)	5.6 (7.5)	0.6	34.3 (9.5)	34.8 (9.5)	0.5 (6.3)	0.1
Mental health	42.8 (12.5)	46.9 (11.6)	4.1 (10.0)	0.3	42.1 (13.5)	42.8 (13.3)	0.7 (9.0)	0.1
Physical functioning	35.1 (10.9)	42.0 (11.6)	7.0 (9.7)	0.6	33.7 (10.9)	33.4 (10.6)	–0.3 (7.2)	0.0
Role-emotional	38.6 (13.3)	43.5 (11.8)	4.9 (13.1)	0.4	35.1 (14.7)	35.4 (15.3)	0.3 (12.9)	0.0
Role-physical	36.9 (10.8)	42.6 (10.5)	5.7 (9.8)	0.5	35.1 (10.4)	34.0 (10.2)	–1.1 (8.9)	–0.1
Social functioning	35.5 (12.3)	44.2 (10.6)	8.7 (10.6)	0.7	36.0 (12.6)	34.5 (12.9)	–1.5 (9.0)	–0.1
Vitality	41.3 (11.3)	46.7 (12.4)	5.4 (9.3)	0.5	39.5 (10.4)	39.6 (11.1)	0.2 (8.4)	0.0
SF-36v2 summary scores (0–100)								
Mental component summary	41.2 (12.2)	46.6 (11.5)	4.5 (10.6)	0.4	40.6 (13.5)	40.9 (14.6)	0.3 (9.5)	0.0
Physical component summary	34.9 (10.1)	42.3 (10.8)	7.4 (7.4)	0.7	34.1 (9.0)	33.3 (9.1)	–0.7 (6.2)	–0.1
Patient global health assessment NRS score (0–100)	51.7 (26.5)	25.7 (21.5)	–26.0 (21.6)	–1.0	46.3 (23.6)	54.6 (24.2)	8.2 (22.7)	0.3
Physician global assessment of disease activity score (0–3)	1.5 (0.5)	0.8 (0.5)	–0.7 (0.6)	–1.5	1.4 (0.5)	1.1 (0.6)	–0.3 (0.5)	–0.6

Higher SF-36v2 scores reflect better health status; higher scores indicate worse condition on other PRO measures (Patient global health assessment score and MDGA). Higher scores on the patient global health assessment score indicate worse overall status; higher MDGA scores indicate more severe disease. [a]Patient pain NRS was used to identify pain responder status, where improvement was defined as a 20% or more decrease in pain NRS score from baseline to endpoint. Change scores were computed as change score = endpoint score–baseline score, where a negative change score represented improvement. Pain NRS change score ≥ 20% decrease was defined as a pain responder and pain NRS change score < 20% decrease was defined as a pain nonresponder. [b] Effect size was computed as PRO change score/SD of PRO score at baseline. MDGA: physician global assessment; NRS: numeric rating scale; PRO: patient-reported outcome; SF-36v2: Medical Outcome Study Short Form-36 Health Survey Version 2; SLE: systemic lupus erythematosus; VAS: visual analog scale.

DISCUSSION

Our study investigated overall HRQOL burden of SLE and explored relationships between changes in certain PRO measures and overall health status using PRO in a clinical trial setting. Overall health status of study patients as measured by SF-36v2 was considerably worse at baseline compared to US general population and comparable age and sex norms. This highlights the multiple effects of SLE on health and functioning that contribute to disease burden. These findings are similar to previous cross-sectional studies[4,5,6], despite the more restrictive inclusion criteria for patients with moderately to severely active SLE despite standard of care used in this study. Baseline SF-36 decrements of up to 32 points have been reported for patients with SLE from 5 randomized controlled trials (RCT) with age-matched and sex-matched US norms[7]. The smaller differences (in the range of 10–15 points) observed in this SLE study sample relative to norms for females ages 35–44 years suggest that patients in our study may have had slightly better health than the RCT patients. However, possible differences in baseline patient characteristics and protocol-defined inclusion criteria used in the studies, as well as the relatively high proportion of patients in several of the RCT with a history of renal disease, may have contributed to the magnitude of decrements compared to norms. Nevertheless, the pattern of low SF-36 scores for patients with SLE across multiple domains relative to norms identified in both studies supports the broad damaging effect that SLE has on patient health status.

The relationships between changes in pain and fatigue, 2 common SLE symptoms, and changes in overall health demonstrated the potential effect of symptom improvement from the patient perspective. Comparisons of change scores between pain and fatigue responders and nonresponders showed that responders consistently had greater improvements than nonresponders. Pain responders and fatigue responders had larger improvements than nonresponders in health status on SF-36v2, particularly for BP, physical and social functioning domains, and overall physical health. Although smaller improvements were observed for the VT domain, fatigue as measured by FSS and VT based on SF-36 may measure different aspects of energy level. Also, pain response was associated with larger improvements in bodily pain domain than VT, but decreases in pain may relate to increases in energy level. The relationship between pain and fatigue was also evident; half (n = 25, 51%) of the 49 pain responders were also fatigue responders. However, this small sample size of "dual responders" did not permit further analysis of this subpopulation, and future research in larger samples will be needed to better understand the

Table 4. Change in health status by fatigue responder status[a] in the SLE clinical trial participants.

PRO Scores	Fatigue Responder (FSS change score ≤ –1.0; n = 40)				Fatigue Nonresponder (FSS change score > –1.0; n = 84)			
	Baseline Mean (SD)	Endpoint, Day 196 Mean (SD)	Change Score Mean (SD)	Effect Size[b]	Baseline Mean (SD)	Endpoint, Day 196 Mean (SD)	Change Score Mean (SD)	Effect Size[b]
SF-36v2 subscale scores (0–100)								
Bodily pain	40.8 (10.0)	46.9 (9.4)	6.1 (8.3)	0.6	36.3 (8.9)	38.3 (10.3)	2.0 (9.5)	0.2
General health	36.7 (10.6)	40.7 (10.4)	4.0 (7.8)	0.4	33.1 (9.0)	34.9 (10.4)	1.8 (6.6)	0.2
Mental health	42.3 (12.6)	45.4 (11.6)	3.0 (9.1)	0.2	42.4 (13.5)	44.3 (13.1)	1.9 (9.7)	0.1
Physical functioning	34.9 (10.9)	41.8 (11.0)	6.8 (9.5)	0.6	34.8 (11.6)	35.5 (12.0)	0.6 (7.9)	0.1
Role-emotional	38.2 (13.0)	41.1 (12.2)	2.9 (12.1)	0.2	36.0 (14.9)	37.9 (15.7)	1.9 (13.6)	0.1
Role-physical	39.8 (10.7)	43.7 (10.1)	3.9 (10.2)	0.4	34.8 (10.8)	35.3 (10.8)	0.4 (9.4)	0.0
Social functioning	36.8 (12.3)	44.4 (12.0)	7.6 (10.2)	0.6	35.8 (12.9)	36.0 (12.5)	0.2 (10.2)	0.0
Vitality	45.1 (11.2)	49.0 (10.5)	4.0 (9.4)	0.4	38.2 (10.3)	39.7 (11.7)	1.5 (9.0)	0.1
SF-36v2 summary scores (0–100)								
Mental component summary	42.3 (11.9)	45.3 (12.4)	3.0 (10.3)	0.3	40.6 (13.7)	42.3 (14.0)	1.7 (9.8)	0.1
Physical component summary	37.7 (9.2)	43.7 (9.3)	6.0 (8.7)	0.7	33.8 (9.9)	34.6 (10.2)	0.8 (6.7)	0.1
Patient global health assessment NRS score (0–100)	44.5 (29.2)	25.3 (21.1)	19.3 (25.8)	–0.7	48.4 (23.6)*	49.3 (26.5)	1.0 (26.9)*	0.0
Physician global assessment of disease activity (MDGA VAS) score (0–3)	1.5 (0.5)	0.7 (0.4)	–0.8 (0.6)	–1.6	1.5 (0.5)	1.1 (0.6)	–0.4 (0.5)	–0.7

Higher SF-36v2 scores reflect better health status; higher patient global health assessment scores indicate worse overall status; higher scores on the patient global health assessment score indicate worse overall status; higher MDGA scores indicate more severe disease. [a]FSS was used to identify fatigue responder status, where improvement was defined as a 1-point or more decrease in FSS score from baseline to endpoint. Change scores were computed as change score = endpoint score–baseline score, where a negative change score represented improvement. FSS change score ≤ –1.0 was defined as a fatigue responder and FSS change score > –1.0 was defined as a fatigue nonresponder. [b] Effect size was computed as PRO change score/SD of PRO score at baseline. * n = 83. FSS: Fatigue Severity Scale; PRO: patient-reported outcome; SF-36v2: Medical Outcome Study Short Form-36 Health Survey Version 2; SLE: systemic lupus erythematosus; VAS: visual analog scale.

relationship between these variables. In addition, the effects of comorbidities such as fibromyalgia and depression or particular tender points or "trigger spots," on changes in pain and fatigue were not evaluated in this analysis; these data were not systematically collected as part of the clinical trial study. Overall health and disease status based on patient and physician global health assessments also improved more for pain and fatigue responders than nonresponders, suggesting the potential benefits of improving pain and fatigue on other outcomes.

Although there was moderate agreement (68.1%) in patients who were identified as responders on both the patient and physician global assessments, 27.7% of subjects (n = 33) were identified as responders based on clinician-assessed MDGA but were nonresponders based on patient global health assessment. Identifying these discrepancies was an important finding and clearly indicates that these assessments are not redundant and not interchangeable, but rather provide different perspectives — that of a patient and a physician. Clinical improvements in disease activity, as perceived by clinicians, may not necessarily correspond to improvements in health status valued by patients. In turn, changes that affect patients in a meaningful way and improve their quality of life may not be based on the same indicators of improvement that physicians evaluate in clinical assessments.

Another study concluded from the literature that in the course of the disease, HRQOL for patients with SLE may not change dramatically over time, while disease activity can change more rapidly[15]. Moreover, health status and less- or non-observable symptoms such as pain and fatigue are better predicted by factors other than disease activity[13,14]. The heterogeneity of SLE manifestations has led to use of composite endpoints in evaluating disease activity, as witnessed in phase III belimumab[49,50] and phase II epratuzumab[51,52] studies. Interestingly, in the epratuzumab trial, where rapid improvement in disease activity was seen, close correlations were observed between physician and patient global ratings[53].

These findings on the burden of SLE, how changes in pain and fatigue affect overall health, and the unique perspectives offered by patient and clinician assessments, improve our understanding of the difficulties that patients experience daily. It provides insight into potential areas of unmet medical need that treatments must target. Physical function, fatigue, and pain were identified as primary needs in SLE that may require attention. Patients may also have other unmet needs; social functioning and mental health were identified as concepts affecting HRQOL and functioning from the patient perspective. Clinical trials have consistently included HRQOL measures[20]. Although a few trials have demonstrated differences between active and

control groups and dosage levels[36,54,55,56], changes in HRQOL may not often or always correlate with changes in disease activity. It is also relevant to focus on specific constructs, including pain, fatigue, and physical function, in developing strategies for PRO data collection in the context of evaluating medical treatments. While the SF-36v2, the health status tool used most frequently in clinical trials, includes a domain for "vitality" and aspects of physical function, it does not specifically measure physical components of fatigue.

Further explorations into relationships between disease and functioning can aid in identifying relevant endpoints. Information on patient concerns about sleep, body image, work ability, intimacy, and medication side effects need to be evaluated while also assessing treatment benefits. Understanding these relationships can also be useful in designing clinical trials, such as by developing endpoint models relevant to patients that inform the hierarchy of testing used for detecting changes and treatment benefit. This information can also spur development of treatments with the potential to improve clinical condition and HRQOL in patients with SLE. As suggested in recent guidance for developing SLE treatments[22,23], collecting PRO data early in exploratory clinical studies provides useful information and helps to gain experience with these outcomes.

Limitations to the study with a bearing on interpretation should be considered. The study had a relatively small sample size; results should be interpreted with caution. There was variable enrollment by country and site; these geographical differences may introduce possible bias. Comparisons of health status were made to available US norms for SF-36; these norms may not be universally representative of health status for each country included in the trial.

Further, although we compared trial SF-36 means with age-specific and sex-specific norms at the mean level, no adjustments to the normative scores were made to reflect the age and sex distribution of our trial sample, because of a lack of individual patient level data for the general population normative sample. While this limits the robustness of our estimates, our reported method of indirect comparisons has previously been used in the absence of individual patient level data.

In addition, the focus of analysis in the current study was change in terms of improvement shown by "responders." "Nonresponders" could have experienced no change or worsening; it must be acknowledged that clinically important improvements and deterioration may not be symmetrical and equivalent and "nonresponse" may not be the same as deterioration. Because of the nature of the inclusion and exclusion criteria used for entry into the phase Ib study, generalizability of these findings may be limited to clinical settings with similar patient populations.

Finally, heterogeneous baseline clinical and disease characteristics of this population can make between-group comparisons challenging. However, these differences are not uncommon in SLE clinical studies, where patients tend to have highly variable disease characteristics (e.g., number/type of organs affected, severity of organ damage, disease activity, frequency/severity of SLE flares).

SLE is associated with significant HRQOL burden on patients. The disease affects multiple domains of physical and psychological functioning. Pain and fatigue affect the daily lives of patients, and are important symptoms to consider in evaluating patient experience with the disease and treatment. While improvements in pain or fatigue appeared to improve overall patient health, the individual and dual roles of pain and fatigue as confounding or effect-modifying variables in evaluating efficacy requires further exploration. Patient global health and physician assessment of disease activity offer unique perspectives on treatment outcomes.

PRO measures add value in understanding treatment benefit in clinical trials from the patient point of view and provide an important perspective that is generally not observed by clinical assessments of disease activity. Early exploratory clinical studies should include validated PRO tools to collect data on PRO; early findings from experience with PRO measures can help to inform endpoint models for future trials and accurately evaluate benefits of treatments for SLE that affect patients in a meaningful way.

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REFERENCES

1. Aringer M, Stamm TA, Pisetsky DS, Yarboro CH, Cieza A, Smolen JS, et al. ICF core sets: how to specify impairment and function in systemic lupus erythematosus. Lupus 2006;15:248-53.
2. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008;58:15-25.
3. Sacks JJ, Helmick CG, Langmaid G, Sniezek JE. Trends in deaths from systemic lupus erythematosus—United States, 1979–1998. MMWR 2002;51:371-4.
4. Campbell R Jr., Cooper GS, Gilkeson GS. Two aspects of the clinical and humanistic burden of systemic lupus erythematosus: mortality risk and quality of life early in the course of disease. Arthritis Rheum 2008;59:458-64.
5. Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? J Rheumatol 2005;32:1706-8.
6. Wolfe F, Petri M, Alarcon GS, Goldman J, Chakravarty EF, Katz RS, et al. Fibromyalgia, systemic lupus erythematosus (SLE), and evaluation of SLE activity. J Rheumatol 2009;36:82-8.
7. Strand V, Petri M, Buyon J, Joh T, Freimuth W, Sigler L, et al. Systemic lupus erythematosus (SLE) impacts all domains of

health-related quality of life (HRQOL): baseline results from five randomized controlled trials (RCTs) [abstract]. Arthritis Rheum 2006;54 Suppl:S277.
8. Thumboo J, Strand V. Health-related quality of life in patients with systemic lupus erythematosus: an update. Ann Acad Med Singapore 2007;36:115-22.
9. McElhone K, Abbott J, Teh LS. A review of health related quality of life in systemic lupus erythematosus. Lupus 2006;15:633-43.
10. Cleanthous S, Tyagi M, Isenberg DA, Newman SP. What do we know about self-reported fatigue in systemic lupus erythematosus? Lupus 2012;21:465-76.
11. Tench CM, McCurdie I, White PD, D'Cruz DP. The prevalence and associations of fatigue in systemic lupus erythematosus. Rheumatology 2000;39:1249-54.
12. Krupp LB, LaRocca NG, Muir J, Steinberg AD. A study of fatigue in systemic lupus erythematosus. J Rheumatol 1990;17:1450-2.
13. Jump RL, Robinson ME, Armstrong AE, Barnes EV, Kilbourn KM, Richards HB. Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support. J Rheumatol 2005;32:1699-705.
14. Edworthy SM. Clinical manifestations of systemic lupus erythematosus. In: Harris ED, Budd RC, Firestein GS, et al, editors. Kelley's textbook of rheumatology. 7th ed. Philadelphia, PA: WB Saunders; 2005:1201-24.
15. Kiani AN, Petri M. Quality-of-life measurements versus disease activity in systemic lupus erythematosus. Curr Rheumatol Rep 2010;12:250-8.
16. Gallop K, Nixon A, Swinburn P, Sterling KL, Naegeli AN, Silk ME. Development of a conceptual model of health-related quality of life for systemic lupus erythematosus from the patient's perspective. Lupus 2012;21:934-43.
17. McKinley PS, Ouellette SC, Winkel GH. The contributions of disease activity, sleep patterns, and depression to fatigue in systemic lupus erythematosus. A proposed model. Arthritis Rheum 1995;38:826-34.
18. Wysenbeek AJ, Leibovici L, Weinberger A, Guedj D. Fatigue in systemic lupus erythematosus. Prevalence and relation to disease expression. Br J Rheumatol 1993;32:633-5.
19. Gladman DD, Urowitz MB, Ong A, Gough J, MacKinnon A. Lack of correlation among the 3 outcomes describing SLE: disease activity, damage and quality of life. Clin Exp Rheumatol 1996;14:305-8.
20. Strand V, Chu AD. Measuring outcomes in systemic lupus erythematosus clinical trials. Expert Rev Pharmacoecon Outcomes Res 2011;11:455-68.
21. Strand V, Gladman D, Isenberg D, Petri M, Smolen J, Tugwell P. Outcome measures to be used in clinical trials in systemic lupus erythematosus. J Rheumatol 1999;26:490-7.
22. Food and Drug Administration. Guidance for industry: systemic lupus erythematosus – developing medical products for treatment. Rockville, MD: Food and Drug Administration; 2010.
23. Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008;67:195-205.
24. Petri M, Wallace DJ, Spindler A, Chindalore V, Kalunian K, Mysler E, et al. Sifalimumab, a human anti-interferon-α monoclonal antibody, in systemic lupus erythematosus: a phase I randomized, controlled, dose-escalation study. Arthritis Rheum 2013;65:1011-21.
25. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Guidelines for referral and management of systemic lupus erythematosus in adults. Arthritis Rheum 1999;42:1785-96.
26. Petri M, Naqibuddin M, Carson KA, Wallace DJ, Weisman MH, Holliday SL, et al. Depression and cognitive impairment in newly diagnosed systemic lupus erythematosus. J Rheumatol 2010;37:2032-8.
27. Hay EM, Bacon PA, Gordon C, Isenberg DA, Maddison P, Snaith ML, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Q J Med 1993;86:447-58.
28. McHorney CA, Ware JE Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247-63.
29. McHorney CA, Ware JE Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32:40-66.
30. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36® Health survey manual and interpretation guide. Boston: New England Medical Center, The Health Institute; 1993.
31. Ware JE, Kosinski M, Dewey JE. How to score version two of the SF-36 Health Survey. Lincoln, RI: QualityMetric Inc.; 2000.
32. Rapp SR, Feldman SR. The promise and challenge of new biological treatments for psoriasis: how do they impact quality of life? Dermatol Ther 2004;17:376-82.
33. Turner-Bowker DM, Bartley PJ, Ware JE. SF-36® Health Survey & "SF" bibliography (1988-2000). 3rd ed. Lincoln, RI: QualityMetric Inc.; 2002.
34. Ware JE, Kosinski M, Bjorner JB. Determining important differences in scores (Chapter 10). User's manual for the SF-36v2 Health Survey. 2nd ed. Lincoln, RI: QualityMetric Inc.; 2007.
35. Strand V, Crawford B. Improvement in health-related quality of life in patients with SLE following sustained reductions in anti-dsDNA antibodies. Expert Rev Pharmacoecon Outcomes Res 2005;5:317-26.
36. Strand V, Aranow C, Cardiel MH, Alarcon-Segovia D, Furie R, Sherrer Y, et al. Improvement in health-related quality of life in systemic lupus erythematosus patients enrolled in a randomized clinical trial comparing LJP 394 treatment with placebo. Lupus 2003;12:677-86.
37. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-3.
38. Petri MA, Mease PJ, Merrill JT, Lahita RG, Iannini MJ, Yocum DE, et al. Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematosus. Arthritis Rheum 2004;50:2858-68.
39. Fava M, Thase ME, DeBattista C, Doghramji K, Arora S, Hughes RJ. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. Ann Clin Psychiatry 2007;19:153-9.
40. Goligher EC, Pouchot J, Brant R, Kherani RB, Avina-Zubieta JA, Lacaille D, et al. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. J Rheumatol 2008;35:635-42.
41. Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue. Measurement of fatigue in systemic lupus erythematosus: a systematic review. Arthritis Rheum 2007; 57:1348-57.
42. Farrar JT, Young JP Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58.
43. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain 2004;8:283-91.
44. Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, et al. Interpreting the clinical importance of group

differences in chronic pain clinical trials: IMMPACT recommendations. Pain 2009;146:238-44.
45. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105-21.
46. Lai JS, Beaumont JL, Ogale S, Brunetta P, Cella D. 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. J Rheumatol 2011;38:672-9.
47. Furie RA, Petri MA, Wallace DJ, Ginzler EM, Merrill JT, Stohl W, et al. Novel evidence-based systemic lupus erythematosus responder index. Arthritis Rheum 2009:15;61:1143-51.
48. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
49. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 2011;63:3918-30.
50. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:721-31.
51. Wallace DJ, Kalunian KC, Petri MA, Strand V, Kilgallen B, Kelley L, et al. Epratuzumab demonstrates clinically meaningful improvements in patients with moderate to severe systemic lupus erythematosus (SLE): Results from EMBLEM™ , a phase IIb study. [abstract]. Arthritis Rheum 2010;62:S605.
52. Wallace DJ, Strand V, Furie R, Petri M, Kalunian K, Pike M, et al. Evaluation of treatment success in systemic lupus erythematosus clinical trials: Development of the British Isles Lupus Assessment Group-based Composite Lupus Assessment endpoint [abstract]. Arthritis Rheum 2011;63 Suppl:S885.
53. Strand V, Gordon C, Kalunian K, Coteur G, Barry A, Keininger DL, et al. Meaningful improvements in health-related quality of life (HRQoL) with epratuzumab (anti-CD22 mAb targeting B-cells) in patients (pts) with SLE with high disease activity: results from 2 randomized controlled trials (RCTs) [abstract]. Arthritis Rheum 2008;58 Suppl:S570.
54. Strand V, Levy RA, Cervera R, Petri MA, Rudge H, Pineda L, et al. Belimumab, a BLyS-specific inhibitor, improved fatigue and SF-36 physical and mental component summary scores in patients with SLE: BLISS-76 and -52 studies [abstract]. Arthritis Rheum 2010;62 Suppl:S773.
55. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353:2550-8.
56. Nordmark G, Bengtsson C, Larsson A, Karlsson FA, Sturfelt G, Ronnblom L. Effects of dehydroepiandrosterone supplement on health-related quality of life in glucocorticoid treated female patients with systemic lupus erythematosus. Autoimmunity 2005;38:531-40.