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ORIGINAL ARTICLE

Changes in Quality of Life in the First 5 Years of Disease in a Multicenter Cohort of Patients With Systemic Lupus Erythematosus

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Objective. **The Medical Outcomes Study Short Form 36 (SF-36) is recommended to assess quality of life (QOL) in systemic lupus erythematosus (SLE). The aim of the current study was to assess QOL over time in the first 5 years of a multicenter inception cohort of patients with SLE.**

Methods. **An inception SLE cohort was assembled according to a standardized protocol between 2000 and 2012. In addition to clinical and laboratory assessments, patients completed the SF-36 at yearly intervals. Only patients who had ≥5 completed QOL questionnaires were included in these analyses. Generalized estimating equation models were run separately for each of the 8 subscales and for the physical and mental component summary scores, adjusting for repeated measures by patients.**

Results. **A total of 495 patients were included. The mean ± SD disease duration at the first visit was 5.3 ± 4.1 months. The mean ± SD age at enrollment was 35.8 ± 13.2 years. All 8 subscales and the 2 summary scores showed improvement in the first 2 years from enrollment. Between years 2 and 5, none of the subscales or summary scores showed any change. Minimum clinically important improvement was achieved by 35–56% of the patients and was influenced by demographic and disease factors.**

Conclusion. **Unlike late-stage lupus, where QOL is stable over time, in patients with early disease, all subscales improve in early followup up to 2 years. Therefore, the SF-36 may be a sensitive outcome measure in early disease in patients with SLE.**

INTRODUCTION

Morbidity in systemic lupus erythematosus (SLE) is high, with the potential to greatly impact daily life; therefore, a comprehensive evaluation of SLE should include an assessment of quality of life (QOL). The Systemic Lupus International Collaborating Clinics (SLICC) group has recommended that 3 domains be included in the description of patients with SLE: disease activity, accumulated damage, and QOL (1). It was further recommended that the Medical Outcomes Study Short Form 36 (SF-36) be used as the measure of QOL in patients with SLE. The SF-36 is a

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Significance & Innovations

- We used an inception cohort to investigate quality of life change in early disease.
- Quality of life changed in the first 2 years of disease and then was stable for the next 3 years.
- The Medical Outcomes Study Short Form 36 can be used as an outcome measure in newly diagnosed patients with systemic lupus erythematosus.

valid and reliable tool that captures the physical, psychological, and social impact of chronic diseases such as SLE (2–4). Health-related QOL of patients with SLE was significantly worse and affected all health domains at an earlier age in comparison to patients with some other common chronic diseases (5,6).

The objective of this study was to determine whether QOL changes over time in early disease by studying a multinational multicenter inception cohort of patients with SLE within the first 5 years of their disease.

PATIENTS AND METHODS

SLICC inception cohort. SLICC comprises 33 centers from 11 countries in North America, Europe, and Asia. An inception cohort of 1,845 SLE patients was assembled according to a standardized protocol between 2000 and 2012 to study risk factors for atherosclerosis. The data retrieval protocol included clinical and laboratory features of lupus, including the SF-36 at yearly intervals.

Patient selection. Patients who were followed for the first 5 years were included. In the 5-year period, a maximum of 6 SF-36 questionnaires could have been completed in the SLICC inception cohort. Patients who had ≥5 SF-36 annual questionnaires completed were identified.

Clinical assessments. Patients with SLE meeting ≥4 1997 American College of Rheumatology (ACR) criteria for SLE (7) were entered into the cohort within 15 months of diagnosis, and were reviewed annually. Clinical and laboratory measures were recorded on a standard data retrieval form and entered onto an Oracle Database. Disease activity was assessed with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (8) and accumulated damage was recorded according to the SLICC/ACR Damage Index (SDI) (9).

Outcome measures. The standard version (version 1, 4-week recall) of the SF-36 was used in the language of the country in which the participating patients resided. This self-administered questionnaire measures QOL in 8 domains or subscales of perceived health: physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health. Scores range from 0–100, with higher scores reflecting better QOL. The SF-36 subscales can be summarized into the physical component summary (PCS) and mental component summary (MCS) scores. The summary scores are standardized to the Canadian population (mean ± SD score 50 ± 10). Several advantages of the summary scores over the 8 subscales have been reported (2,10–12). In the SLICC inception cohort, patients completed the SF-36 once a year.

Minimum clinically important differences (MCIDs) in SF-36. Based on published results, the magnitude for MCID has been identified as between 5 and 10 for individual subscales of the SF-36 for rheumatoid arthritis, psoriatic arthritis, psoriasis, and SLE (13–15). The observed change was classified as "no improvement" if the subscale change was <5, as "marginal change" if the change was ≥5 but <10, and as "clear improvement" if the change was ≥10. Published results also indicate that the magnitude for MCID for the summary scores (PCS and MCS) is between 2.5 and 5 (16). These were also classified as no improvement, marginal change, and clear improvement when the change was <2.5, between 2.5 and 5, and ≥5, respectively.

Predictive and associated factors. Predictive factors (at the time of the first clinic visit following SLE diagnosis) included age, sex, ethnicity, damage (SDI), and disease activity (SLEDAI-2K).

Statistical analyses. Descriptive statistics were used to compare the study population to the remaining patients included in the SLICC Registry. In order to test for change in SF-36 domains over the 5-year period, generalized estimating equation (GEE) models were run separately for each of the 8 domains and the 2 composite summary scores. Each model was adjusted for repeated measures within each patient. Based on initial plotting of the results of the SF-36 over time, there appeared to be a different pattern in years 0, 1, and 2 compared to years 2–5. The time period was therefore evaluated separately for 1) models including only the results from years 0, 1, and 2 and 2) models including only the results from years 2, 3, 4, and 5. These models only looked at the overall effect of years since entry into the study. Next, in order to look at the effect of potential risk factors contributing to the change in SF-36, GEE models were run using the observed scores from the SF-36 at years 0, 1, and 2 exclusively. In these analyses, the risk factors included were sex, race/ethnicity, SLEDAI-2K score ≥6 at enrollment, and age at enrollment.

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Table 1. Characteristics of the patient population at enrollment*

	Study population (n = 495)	Patients who did not have 5 SF-36 assessments in their first 5 years (n = 357)	*P* vs. study population
Women, no. (%)	446 (90.1)	310 (86.8)	0.14
Ethnicity, no. (%)			< 0.0001
White	285 (57.6)	137 (38.4)	
African American	73 (14.8)	57 (16.0)	
Asian	79 (16.0)	56 (15.7)	
Hispanic	37 (7.5)	102 (28.6)	
Other	21 (4.2)	5 (1.4)	
Age, mean ± SD years	35.8 ± 13.2	33.8 ± 13.5	0.03
Disease duration, mean ± SD months	5.3 ± 4.1	5.5 ± 4.2	0.47
SLEDAI-2K score, mean ± SD	5.6 ± 5.6	5.5 ± 5.7	0.73
SDI score, mean ± SD	0.09 ± 0.43	0.14 ± 0.45	0.19
SDI score >0, no. (%)	28 (5.7)	33 (9.2)	0.05
PCS score, mean ± SD	39.4 ± 11.3	37.9 ± 10.6	0.12
MCS score, mean ± SD	44.9 ± 11.8	44.7 ± 11.7	0.86

* SF-36 = Medical Outcomes Study Short Form 36; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; PCS = physical component summary; MCS = mental component summary.

The percentages of patients who showed no improvement, marginal change, or clear improvement within the first 2 years from enrollment were evaluated. Logistic regressions were used to determine predictors of the presence of MCID (clear improvement) in the summary scores (PCS and MCS) only. The risk factors included in the logistic regression models were sex, presence of SDI damage at enrollment, white ethnicity, age at enrollment, SLEDAI-2K score ≥6 at enrollment, and PCS and MCS score values at enrollment. The stepwise approach was used to retain the significant risk factors.

RESULTS

Of the SLICC inception cohort of 1,845 patients, a total of 852 were seen for >5 years. Of this group of patients, 495 patients completed ≥5 yearly SF-36 questionnaires. A total of 195 patients had 5 completed SF-36 questionnaires, whereas 300 had 6 completed SF-36 questionnaires.

Of the 495 patients, 446 (90.1%) were women and 285 (57.6%) were white. They were enrolled at a mean ± SD age of 35.8 ± 13.2 years within a mean ± SD of 5.3 ± 4.1 months of SLE diagnosis (Table 1). The mean ± SD SLEDAI-2K score at enrollment was 5.6 ± 5.6. The mean ± SD SDI score was 0.09 ± 0.43 (only 28 patients had an SDI score >0). Their mean ± SD PCS score was 39.4 ± 11.3 and their mean ± SD MCS score was 44.9 ± 11.8, indicating significant physical limitations and some mental limitations in their QOL, respectively. Comparison of the patients included in the study to patients from the SLICC cohort who were seen for 5 years is shown in Table 1. Only in the ethnic distribution were there statistically significant differences, with the study group having fewer Hispanics than the patients excluded from this analysis.

SF-36 scores in the first 5 years. The mean ± SD yearly scores for the individual domains as well as the summary scores of the SF-36 are shown in Table 2. There was a general trend toward improvement in all domains, most notably in the physical domains. Table 2 shows the im-

Table 2. Mean ± SD yearly scores for the subscales and PCS and MCS*

	Years since entry into the study					
	0	1	2	3	4	5
Physical function	64.7 ± 26.5	70.7 ± 25.3	72.5 ± 25.8	71.5 ± 26.8	72.4 ± 26.3	72.8 ± 26.2
Role physical	44.2 ± 43.0	55.8 ± 42.4	60.2 ± 42.5	59.2 ± 43.1	59.9 ± 43.5	61.2 ± 43.3
Bodily pain	58.2 ± 27.5	62.5 ± 25.6	64.6 ± 25.1	62.9 ± 26.6	64.8 ± 26.5	64.9 ± 26.2
General health	48.2 ± 22.1	50.9 ± 22.4	52.6 ± 23.4	52.7 ± 23.8	52.8 ± 23.8	53.2 ± 24.3
Vitality	46.2 ± 23.2	49.5 ± 23.2	52.4 ± 23.2	50.8 ± 23.9	51.5 ± 23.7	52.0 ± 24.4
Social function	62.8 ± 27.4	69.7 ± 26.2	72.9 ± 27.0	70.8 ± 27.4	72.9 ± 27.5	72.7 ± 26.9
Role emotional	62.1 ± 42.7	70.5 ± 40.1	71.6 ± 29.8	68.6 ± 42.0	69.6 ± 42.2	72.1 ± 40.6
Mental health	65.0 ± 20.0	68.8 ± 18.6	69.8 ± 19.0	68.2 ± 20.9	69.0 ± 20.4	70.2 ± 19.6
PCS	39.4 ± 11.3	41.7 ± 10.9	42.8 ± 11.1	42.6 ± 11.2	43.0 ± 11.6	43.0 ± 12.0
MCS	44.9 ± 11.8	47.0 ± 11.0	47.7 ± 11.1	46.6 ± 11.8	47.1 ± 12.0	47.7 ± 11.8

* PCS = physical component summary; MCS = mental component summary.

Table 3. Parameter estimates for the individual subscales and summary scores of the Medical Outcomes Study Short Form 36*

	Using visits in years 0, 1, and 2 only			Using visits in years 2, 3, 4, and 5 only		
	Parameter estimate†	95% CI	*P*	Parameter estimate†	95% CI	*P*
Physical function	3.86	2.69, 5.04	< 0.0001	0.20	−0.40, 0.80	0.51
Role physical	7.98	5.64, 10.32	< 0.0001	0.35	−0.92, 1.63	0.59
Bodily pain	3.15	1.87, 4.43	< 0.0001	0.28	−0.46, 1.02	0.46
General health	2.21	1.24, 3.19	< 0.0001	0.18	−0.38, 0.75	0.53
Vitality	3.09	2.03, 4.15	< 0.0001	−0.04	−0.64, 0.57	0.90
Social function	5.02	3.67, 6.37	< 0.0001	0.15	−0.60, 0.90	0.70
Role emotional	4.71	2.50, 6.92	< 0.0001	0.28	−1.04, 1.60	0.68
Mental health	2.41	1.48, 3.33	< 0.0001	0.19	−0.32, 0.70	0.46
PCS	1.70	1.18, 2.22	< 0.0001	0.09	−0.19, 0.38	0.53
MCS	1.39	0.83, 1.95	< 0.0001	0.06	−0.26, 0.38	0.73

* 95% CI = 95% confidence interval; PCS = physical component summary; MCS = mental component summary.
† The parameter estimate represents the average change (slope) for each consecutive year since entry into the study. If positive, it indicates the score increased; if negative, the score decreased.

provement from time 0 (study enrollment), with the majority of the improvement occurring within the first 2 years. The regression models evaluating the SF-36 domains and summary scores over the entire 5-year period showed significant improvement in all domains (data not shown). Table 3 depicts the results of the regression models separately for the earlier (0–2) and later (2–5) years of followup. For all of the domains, there is a statistically significant increase in the score over the years 0, 1, and 2, but no significant change is seen over the years 2–5.

Factors associated with change in SF-36 scores. Finally, the models including only years 0, 1, and 2 were run to test for differences between sex, race/ethnicity, SLEDAI-2K score ≥6 at enrollment, and age at enrollment. As shown in Table 4, men had greater improvement in vitality and social function, as well as in PCS score. Older age was associated with a slower improvement in physical function, role physical, bodily pain, and PCS score. Active disease lowered the improvement in bodily pain and did not alter the degree of improvement in any other subscales or summary scores, but did show a trend toward also lowering improvement in role physical, social function, and role emotional. In regard to ethnicity, all were compared to whites in the analysis. Only in Asians was the difference statistically significant, with Asian patients showing more improvement than whites.

Factors associated with achieving MCID. Between 35% and 56% of the patients demonstrated clear improvement at 2 years (Table 5). Overall, only 10% of the patients fell into the marginal change category. On the whole, patients

Table 4. Regression models for years 0, 1, and 2 of the subscales and summary scores (PCS and MCS) of the Medical Outcomes Study Short Form 36*

	Sex (0 = female, 1 = male)		Age (for each year)		Active disease (0 = SLEDAI-2K <6, 1 = SLEDAI-2K ≥6)		Asian vs. white		African American vs. white		Hispanic vs. white	
	PE ± SE†	*P*	PE ± SE†	*P*	PE ± SE†	*P*	PE ± SE†	*P*	PE ± SE†	*P*	PE ± SE†	*P*
Physical function	5.5 ± 3.1	0.08	−0.5 ± 0.1	< 0.0001	−3.0 ± 2.0	0.12	5.2 ± 2.2	0.02	−2.7 ± 3.0	0.38	1.4 ± 4.0	0.73
Role physical	8.8 ± 4.9	0.07	−0.5 ± 0.1	< 0.0001	−5.8 ± 3.0	0.06	8.3 ± 3.7	0.03	0.4 ± 4.1	0.92	7.5 ± 5.8	0.20
Bodily pain	5.0 ± 3.0	0.10	−0.2 ± 0.1	0.007	−4.4 ± 2.0	0.03	7.7 ± 2.6	0.004	−2.4 ± 2.9	0.42	7.5 ± 4.1	0.07
General health	4.1 ± 3.1	0.19	−0.1 ± 0.1	0.27	0.7 ± 1.8	0.71	5.4 ± 2.4	0.03	0.8 ± 2.6	0.77	0.9 ± 3.9	0.82
Vitality	7.2 ± 2.9	0.01	−0.1 ± 0.1	0.11	−0.4 ± 1.8	0.83	9.1 ± 2.4	0.0002	1.7 ± 2.6	0.50	12.3 ± 2.9	< 0.0001
Social function	8.0 ± 3.2	0.01	−0.1 ± 0.1	0.17	−4.0 ± 2.1	0.06	7.1 ± 2.7	0.008	−1.3 ± 3.0	0.66	4.6 ± 3.5	0.20
Role emotional	4.8 ± 4.5	0.29	−0.2 ± 0.1	0.12	−5.5 ± 2.9	0.06	3.5 ± 3.6	0.33	−6.3 ± 4.2	0.13	−8.3 ± 5.9	0.16
Mental health	4.1 ± 2.3	0.08	0.0 ± 0.1	0.85	0.0 ± 1.5	1.00	0.7 ± 1.9	0.74	0.4 ± 2.3	0.86	−1.3 ± 2.8	0.63
PCS	2.4 ± 1.2	0.04	−0.2 ± 0.03	< 0.0001	−1.3 ± 0.9	0.11	3.3 ± 1.0	0.0009	−0.3 ± 1.2	0.79	3.0 ± 1.8	0.10
MCS	2.4 ± 1.3	0.07	0.0 ± 0.03	0.41	−0.6 ± 0.9	0.52	1.3 ± 1.1	0.22	−0.3 ± 1.3	0.78	−0.3 ± 1.6	0.87

* PCS = physical component summary; MCS = mental component summary; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.
† The parameter estimate (PE) represents the average change (slope) for each risk factor. If positive, it indicates the score increased when the risk factor has a value of 1; if negative, the score decreased.

Table 5. Change in minimum clinically important difference in the first 2 years for each of the 8 subscales and the 2 summary composite scales of the Medical Outcomes Study Short Form 36*

	No improvement	Marginal change	Clear improvement
Subscales†			
Physical function	196 (40)	57 (12)	242 (49)
Role physical	268 (54)	0 (0)	227 (46)
Bodily pain	227 (46)	8 (2)	260 (53)
General health	191 (39)	76 (15)	228 (46)
Vitality	174 (35)	67 (14)	254 (51)
Social function	220 (44)	0 (0)	275 (56)
Role emotional	322 (65)	0 (0)	173 (35)
Mental health	249 (50)	50 (10)	196 (40)
Summary scales‡			
PCS	208 (42)	47 (10)	240 (49)
MCS	217 (44)	61 (12)	217 (44)

* Values are the number (percentage). PCS = physical component summary; MCS = mental component summary.
† No improvement = change <5, marginal change = change between 5 and 10, and clear improvement = change ≥10.
‡ No improvement = change <2.5, marginal change = change between 2.5 and 5, and clear improvement = change ≥5.

either improved significantly or did not improve at all. There was no relationship between improvement in PCS and MCS score ($P = 0.14$ by McNemar's test for difference between paired proportions). In multivariate analysis, patients with damage at enrollment, older age, and higher PCS scores were less likely to improve their PCS score in 2 years, whereas patients with active SLEDAI-2K (score ≥6) at enrollment and higher MCS scores were more likely to improve in their PCS score over the 2 years from enrollment. Men and patients with a high PCS score or a low MCS score at enrollment were more likely to improve their MCS score within 2 years (Table 6).

DISCUSSION

Patient-reported health-related QOL is an important outcome both in observational studies and in therapeutic trials. The most commonly used health-related QOL outcome is the SF-36. Whether SF-36 is responsive to change is still in question. It has been shown previously that in SLE patients with established disease, the SF-36 changes little over an 8-year period (17). Changes in the SF-36 are not affected by cumulative disease activity, steroid use, or damage accumulation during the interval, but are affected by the presence of fibromyalgia. Strand et al (18) reported a significant difference in health-related QOL measured by the SF-36 between drug-treated and placebo-treated patients in a drug trial comparing LJP 394 treatment with placebo. This also was recently demonstrated in a belimumab trial (19). Similarly, in observational studies, sensitivity to change was demonstrated in the SF-36 (20,21). Hanly et al studied patients with lupus presenting with a neuropsychiatric event at one assessment and a physician-defined outcome at a subsequent assessment and had SF-36 at both assessments. In these studies, changes in the SF-36 summary and subscale scores, in particular those related to mental health, were associated with the clinical outcome of the neuropsychiatric event (22). Previous studies have not examined changes in QOL over time from disease inception.

This is the first investigation of change in SF-36 over the first 5 years in an inception SLE cohort. The study showed improvement in all 8 domains and in the 2 summary scores, which occurred in the first 2 years of followup, and then remained stable through years 2–5. By order of magnitude, the domain of greatest change was role physical, followed by social function and role emotional. The domains with the smallest change were mental health and general health. Men improved more than women in the vitality and social function subscales and in the PCS summary score. Older age was associated with a lesser improvement in physical function, role physical, and bodily pain, as well as in PCS score. Active disease lowered the improvement in bodily pain and showed a trend toward also lowering improvement in role physical, social function, and role emotional. Only Asians were different from whites in their change in SF-36. They showed more improvement in almost all subscales except role emotional and mental health and in the MCS score, where they were not different from whites. The reason for this improvement is not immediately apparent.

Almost 50% of the patients achieved at least an MCID response with regard to SF-36 domains and composite scores within 2 years of inception. Patients who were older

Table 6. Predictors for minimum clinically important difference (clear improvement) in PCS and MCS scores over the first 2 years from enrollment*

	PCS			MCS		
	OR	95% CI	*P*	OR	95% CI	*P*
Male sex				2.10	1.06, 4.19	0.03
SDI score >0	0.33	0.13, 0.85	0.02			
White						
Age	0.98	0.96, 0.99	0.006			
SLEDAI-2K score ≥6	1.61	1.05, 2.47	0.03			
PCS score at enrollment	0.90	0.88, 0.92	< 0.0001	1.02	1.00, 1.05	0.02
MCS score at enrollment	1.03	1.01, 1.05	0.007	0.88	0.86, 0.90	< 0.0001

* PCS = physical component summary; MCS = mental component summary; OR = odds ratio; 95% CI = 95% confidence interval; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

at presentation and were already physically impaired with evidence of damage were less likely to achieve PCS score improvement, whereas those with more active disease and a better MCS score were more likely to improve. Conversely, male patients and those with better physical function at presentation, or those with a lower MCS score at presentation, were more likely to improve their MCS score within 2 years.

This study demonstrated that in early disease, the SF-36 is sensitive to change and is related to disease activity at baseline. This is likely due to the fact that patients started with active disease and received appropriate therapy. Once the disease was stabilized at years 2–5, the SF-36 remained unchanged. Although we did not test this within this study, this hypothesis is supported by the studies that showed improvement in the SF-36 in clinical trials (18,19,21), but no change in studies with prevalent patients late in the course of disease (17). We also did not include fibromyalgia in the current models, since this item is not collected in the SLICC database. However, a relationship between fibromyalgia and the SF-36 has been demonstrated previously (14). Therefore, the SF-36 can be used as an outcome measure in patients with active disease undergoing therapy early in the disease course.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Urowitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Urowitz, Gladman, Ibañez, Gordon, Bernatsky, Hanly, Wallace, Alarcón, Khamashta, Bruce, Manzi, Sturfelt, Nived, Aranow, Stoll.

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