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Patient-Reported Outcomes in Systemic Lupus Erythematosus

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Abstract

Successful management of complex conditions such as systemic lupus erythematosus, SLE, and comorbid conditions benefit significantly from patient-reported outcomes (PRO) instruments that validly and precisely measure relevant aspects of health status (e.g., symptoms) and health related quality of life. Measuring health related quality of life and other aspects of health status (e.g., symptoms, functioning) with PROs provides SLE patients with an opportunity to participate in their treatment and to facilitate better communication with the multi-disciplinary team of health professionals involved in their care. Health outcomes research has produced a number of well-validated instruments that can be used across diseases whereas some have been specifically developed for SLE. The use of either a generic and SLE-specific PRO depends on the particular needs of a variety of clinical applications including population monitoring, treatment decision-making in clinical practice, clinical trials research, and for evaluating and comparing the effect of therapies across conditions, therapies, trials and patients in clinical research studies.

Keywords

systemic lupus erythematosus (SLE, lupus); quality of life (QoL); patient-reported outcomes (PROs)

Introduction

SLE is a chronic inflammatory autoimmune disorder with variable multi-system involvement. The survival of patients with SLE has significantly improved but like many chronic diseases, there is currently no cure, and morbidity and mortality remain high [1] Treatment of more severe cases of SLE often involves a balance between managing the

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manifestations of the disease and minimizing the treatment-related side effects. The disease has a significant impact on many aspects of patients' lives and their overall well-being, or health-related quality of life (HRQOL) because SLE affects a relatively younger age group and improved survival has translated into longer disease duration [1-3]. Therefore, patients with SLE must cope with a significant disease burden imposed by the numerous symptoms of the disease itself and its treatment, including fatigue, pain, sleep disturbance, renal and skin problems, and neurological/psychiatric conditions (e.g., anxiety, depression, headaches, motor/sensory deficits, seizures, cognitive impairment, neuropathy) [4-10]. Increasing attention to comorbidities of patients with SLE, which themselves add to the burden of the disease, has a substantial impact on patient outcomes and HRQOL [4, 11].

Successful management of complex conditions such as SLE and comorbid conditions can benefit significantly from patient-reported outcomes (PRO) instruments that validly and precisely measure the relevant aspects of health status (e.g., symptoms) and HRQOL. Physicians focus on disease activity and damage as their primary therapeutic goal [12], however, there is a mixed literature with regard to the relationship between disease activity or organ damage and changes in HRQOL in patients with SLE [13-20]. Discordant perspectives between patient and provider when assessing disease burden and activity can result in treatment non-adherence, treatment interruptions and misunderstandings in communication between patients and providers [21-23]. PROs can have a critical role in clinical trials and clinical care assessments because PROs provide relevant yet complementary information to disease activity and damage indices when it comes to prioritizing treatment decisions, managing symptoms, formulating interventions, providing a complete approach to the management of the disease, and possibly justifying the considerable costs of new therapies. HRQOL measures have been recommended for inclusion in core data sets for observational studies and clinical trials by OMERACT [24, 25]. Further, measuring HRQOL and other aspects of health status (e.g., symptoms, functioning) with PROs provides patients with an opportunity to participate more fully in their treatment and ultimately facilitate better communication with the multi-disciplinary team of health professionals involved in their care [13]. We review both generic and SLE-specific PRO instruments and their use in patients with SLE below.

Generic PRO instruments

Generic PRO tools have been employed to assess health-related quality of life (HRQOL) in SLE patients, including the Medical Outcomes Study Short Form 36 (SF-36) [26, 27] and EuroQoL-5 Dimensions (EQ-5D) [28, 29]. While these tools allow HRQOL comparisons between SLE patients and other patients with rheumatic and non-rheumatic diseases, some limitations in assessing SLE-specific outcomes exist.

The SF-36 is among the most widely employed generic PRO tool in SLE studies. The 36-item questionnaire evaluates eight separate HRQOL domains (physical functioning, general health, mental health, vitality, role physical, role emotional, bodily pain, and social functioning) and includes two summary scores (physical component score [PCS] and mental component score [MCS] [26]. Two versions of the SF-36 are available to evaluate health status in 1- or 4-week intervals. The questionnaire is scored from 0 (worse health) to 100

(better health). The SF-36 was originally validated in an SLE sample from the United Kingdom (U.K.) and found to have favorable psychometric properties including good internal consistency, criterion validity compared to the Medical Outcomes Study Short Form 20+ (SF20+), good discriminant validity compared to a British control population, and construct validity in comparisons with the British Isles Lupus Activity Group (BILAG) score [27], but an inverse association with disease damage (using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology- Damage Index [SDI]) was found only for the physical function domain. Responsiveness of SF-36 has since been shown in Canadian and French SLE samples [30, 31]. Minimally important clinical differences (MICDs) have been established in other rheumatic diseases, and range from 5-10 for individual domain scores and from 2.5-5 for PCS and MCS summary scores [32].

The SF-36 has been utilized in both SLE clinical research studies (for example, [33-35]) and in clinical trials [36-38]. Further, the SF-36 is frequently employed as a legacy HRQOL instrument to validate other tools, including SLE-specific PRO-instruments [39-42]. One criticism of the SF-36 is that it does not assess all dimensions of health status that are important to SLE patients, such as body image and appearance, self-confidence, and social support [43]. Also, there have been concerns about the sensitivity of the SF-36 to capture the frequent changes in health status seen in SLE patients, especially over long periods of time. For example, little change in HRQOL was found in SLE patients who completed the SF-36 instrument over an eight-year period in one study [44], while in another study change in SF-36 was seen only during the first two years following SLE diagnosis then remained stable for the subsequent three years of follow-up [35]. In contrast, certain components of the SF-36 have been sensitive to change over shorter periods of time in clinical drug trials [36-38]. These studies highlight the importance of critically evaluating the use of the SF-36 in certain clinical situations and suggest that use of the SF-36 to evaluate HRQOL may be most appropriate for SLE studies with short-term follow-up or SLE patients early in the disease course.

The EQ-5D has also been employed in SLE studies, offering the advantage of allowing for economic evaluation in addition to measuring HRQOL [28, 29]. The 6-item questionnaire assesses health on the day of completion, and assesses 5 dimensions of disability, such as mobility and self-care, and a single visual analog scale (VAS) score for patient-reported overall health. The disability dimensions have a 3-item response scale and results are reported as a summary score from 0 (death or health worse than death) to 1.0 (best imaginable health). EQ-5D VAS scores range from 0 (worst imaginable health) to 100 (best imaginable health) and can be used to calculate quality adjusted life years (QALY's) for economic analysis. When psychometric properties of the EQ-5D in patients with SLE have been assessed in a U.S. multiethnic population [45], no floor or ceiling effects were found. Discriminant validity was detected among patients with high versus low SLE disease activity, but the EQ-5D did not differ among patients with a range of disease damage. Content validity and reliability of the EQ-5D were not assessed. The EQ-5D summary score was sensitive to change over time when compared to EQ-5D VAS and self-reported improvements, but the overall effect size was small. More recently, construct validity was established in a Chinese sample of SLE-patients when compared to the Lupus Quality of Life Questionnaire (LupusQoL), and discriminant validity was seen with both SLE disease

activity and damage scores [46]. Additionally, significant ceiling effects were detected in the EQ-5D, with almost half of participants reporting no problems in some disability domains including self-care. The EQ-5D has been primarily used in clinical SLE research studies [47-51]. For example, Strand and colleagues found that SLE patients taking corticosteroids had lower HRQOL, measured by the EQ-5D, than those who were not taking corticosteroids, and concluded that medication side effects contribute to poorer HRQOL in these patients [50]. EQ-5D was also included in the belimumab clinical trials, with changes in patient-reported pain/discomfort domain noted [38].

The National Institutes of Health initiative Patient-Reported Outcomes Measurement Information System (PROMIS) was established to develop self-report measures of adult and pediatric health status across a range of areas, or domains (e.g., fatigue, pain) that are applicable to a broad array of health conditions.[52] PROMIS is domain-specific but is not disease-specific. More information about specific PROMIS domains, item banks, and survey administration tools can be found in Chapter 12.

Computerized adaptive testing or CAT enables precise and efficient estimation of a person's trait levels with only a subset of items from the item pool or "bank," and not all participants answer the same items. This efficiency and precision have been demonstrated with PROMIS CATs in Dutch patients with rheumatoid arthritis and in U.S. patients with rheumatoid arthritis, osteoarthritis and normal ageing cohorts comparing PROMIS Physical Function short forms and CATs relative to existing "legacy" measures (e.g., HAQ-DI, SF-36) [53, 54].

The content relevance of PROMIS to SLE has been evaluated in a qualitative study of multiethnic Asian individuals with SLE, which confirmed that PROMIS domains (e.g., physical function, pain, fatigue, sleep disturbance, sleep-related impairment, anger, anxiety, and depression) address the priority domains identified by these patients and could reasonably serve as a core set of HRQOL, although some content gaps remain to be filled [55].

The body of literature demonstrating the validity of PROMIS measures in specific clinical populations is still very much in a nascent stage but has included several studies in patients with SLE including one with juvenile-onset SLE [56] and several studies of adults with SLE described below. A cross-sectional study of SLE patients recruited through an internet panel company used measures from PROMIS and another NIH-funded initiative, Quality of Life in Neurological Disorders (Neuro-QoL), to assess the PRO measures' associations with patient-reported SLE disease severity [57]. The PROMIS measures included the PROMIS-29 health profile, a measure composed of 4-items from each of seven domains (depression, anxiety, physical function, pain Interference, fatigue, sleep disturbance, and ability to participate in social roles and activities) and a 0-10 pain intensity item, and the psychosocial illness impact-negative short form. Compared with the general population norms, nearly all scores were at least ½ of a standard deviation (SD) worse (i.e., 5 T-score units) with fatigue, pain interference, physical function, and psychosocial illness impact being the worst (i.e., 1 SD worse than the norms). Acceptable test-retest reliability (>0.7) was found on all instruments (range 0.78 – 0.94).

The Activity in Lupus to Energize and Renew (ALTER) study was a cross-sectional study designed to test the relationship between subjective fatigue and objectively-measured physical activity in patients with SLE [58-60]. The study included PROMIS measures (PROMIS Version 1.0 8-item short forms for fatigue, pain interference, anxiety, depression, sleep disturbance, sleep-related impairment, and physical function), and accelerometer-based physical activity in patients with SLE. All PROMIS short forms demonstrated excellent internal consistency reliability (Cronbach's alpha all >0.90). Results demonstrated significant negative correlations between minutes of bout moderate-to-vigorous physical activity and physical function, fatigue and pain interference. Bout moderate/vigorous physical activity minutes correlated with lower PROMIS-measured fatigue ($r=-0.20$, $p=0.03$). Both light physical activity and moderate/vigorous physical activity minutes correlated with better physical function ($r=0.19$, $p=0.04$ and $r=0.25$, $p=0.006$, respectively). Mean PROMIS T-scores for fatigue, pain interference, anxiety, sleep disturbance, sleep-related impairment, and physical function were each $\frac{1}{2}$ of a standard deviation worse than the general U.S. population mean.

PROMIS allows for standardized comparison of health status across chronic disease populations in addition to comparing with population-normed data since PROMIS measures are disease agnostic. For example, comparisons of the PROMIS scores reported by SLE patients in this study to a large sample of individuals with arthritis (either rheumatoid arthritis or osteoarthritis) who completed the same PROMIS measures demonstrated that anxiety, depression, fatigue, and pain Interference scores were worse in this SLE sample, while physical function and satisfaction with social role scores were similar [61]. Studies of rheumatic disease patients incorporating PROMIS measures have also shown that, compared to patients with systemic sclerosis [62], patients with SLE reported similar fatigue, more sleep disturbance, and better physical function. Compared to patients with osteoarthritis [63], SLE patients had more fatigue but better physical function [58-60].

PROMIS measures offer several advantages, including: brevity and reduced burden; improved measurement with increased precision, allowing for increased power and reduced sample sizes; and flexible administration (established short forms of various lengths, custom short forms, CATs). They are domain rather than disease-specific and have a standardized scoring/metric, with a mean of 50 and standard deviation of 10, with most domains centered around the U.S. general population, allowing for comparability across short forms and CATs and across studies and clinical conditions. Users of PROMIS measures have the ability to transform scores from other measures to the PROMIS score metric through PROsetta Stone linking methodology; and the measures are psychometrically sound, developed using state-of-the-science methods.

Although studies using PROMIS measures in people with SLE are only just emerging, these measurement tools appear to be appropriate for use in this population. The evidence to date suggests that PROMIS represents a system of valid and psychometric robust measurement tools that can provide brief-yet-precise scores for monitoring patients' HRQOL across relevant domains with minimal respondent burden. Additional research is needed to contribute to the evidence supporting the validity of the PROMIS measures in SLE. There is a need for studies to focus on the development of interpretive aids for PROMIS measures so

researchers, clinicians and patients can better understand what the scores and score changes mean in an informative, clinical context.

SLE-Specific PRO Tools

More recently, there has been an emphasis on developing SLE-specific PRO tools for use in clinical studies and clinical trials. Generic PRO tools may inadequately assess certain domains of the lupus experience, such as self-image or family planning, and SLE-specific PRO tools address these gaps. Further, generic instruments may not be sensitive enough to capture the frequent fluctuations in health status that is seen with SLE. Examples of SLE-specific PRO measures include Lupus Quality of Life (LupusQoL) [39], Lupus Patient-Reported Outcome (LupusPRO) [40], SLE-specific Quality of Life Questionnaire (SLEQOL) [41], and SLE Quality of Life Questionnaire (L-QoL) [42].

The most widely studied SLE-specific PRO is the LupusQoL tool. Originally developed in the U.K. [39], the instrument has since been validated in a United States (U.S.) sample of SLE patients [64]. Validity and other psychometric properties of non-English translations of LupusQoL have been published for Spanish [65], Turkish [66, 67], Persian [68], Italian [69], French [70], and Chinese [71] language cohorts. LupusQoL evaluates eight domains including physical health, pain, planning, intimate relationships, burden to others, emotional health, body image, and fatigue. Questions pertain to the patient experience in the preceding four weeks and responses are given on a five-item scale. A LupusQoL summary score is reported on 0 to 100 scale, with higher values indicating better health-related QOL (HRQOL). LupusQoL has been shown to have favorable psychometric properties in the original U.K. version and in other language iterations of the tool. In the original U.K. sample, LupusQoL demonstrated good acceptability, reliability, and test-retest reliability. Concurrent validity was established by comparing to domains of SF-36 with good correlations. Patients with higher SLE disease activity, assessed with the BILAG score, had poorer HRQOL in all domains except fatigue, establishing construct validity [39]. Responsiveness of Lupus QoL was assessed by comparison to the SF-36, with one study of Canadian SLE patients reporting responsiveness equivalent to the SF-36 [30] and another in a French sample finding that LupusQoL may be better than the SF-36 at capturing changes in respondents with improving health status [31]. In the French SLE sample, MCIDs ranged from 1.1 to 9.2 for respondents with global improvement in health status and from -0.5 to -6.4 for respondents with worsening health status [31]. Additional studies are needed to more firmly establish MCIDs. Finally, LupusQoL has been employed in clinical research studies [72-75] but not yet in clinical trials.

LupusPRO tool was developed in a U.S. SLE sample to allow improved generalizability to U.S. patients [40]. The developers also sought to include issues pertinent to male SLE patients and assess non-HRQOL domains. Cross-cultural validations of the English version of LupusPRO has been established in Canada [76] and the Philippines [77], and the validity of translations into French-Canadian [78], Spanish [79], Turkish [80], and Chinese [81] have also been reported. The 43-item questionnaire includes eight HRQOL domains such as lupus symptoms, physical health, and body image, as well as four non-HRQOL domains including desires/goals and satisfaction with care. Respondents indicate their experience in the

preceding four weeks on a five-item response scale, and scores range from 0 (worst QOL) to 100 (best QOL). The initial validation cohort [40] demonstrated good internal consistency for all domains except lupus medication, good test-retest reliability was noted for all HRQOL domains, but test-retest reliability was lower for some of the non-HRQOL domains. Strong correlations with domains of the SF-36 were found, establishing concurrent validity. Criterion validity was suggested by strong correlations of LupusPRO domains with measures of disease activity, such as BILAG, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI), and Lupus Foundation of America (LFA) definition of disease flare, but correlations with disease damage were moderate. LupusPRO domains were compared to change in self-reported health status, physician global assessment, and LFA flare status to evaluate responsiveness, but only weak to moderate correlations were found. MCIDs have also not been established for the Lupus PRO. Finally, beyond validation studies, LupusPRO has been utilized in one clinical research study [82] and no clinical trials to date.

Additional SLE-specific PRO tools include SLEQOL and L-QoL. SLEQOL were originally developed and validated in an English-speaking SLE sample in Singapore [41] but have not been assessed in a U.S. cohort. While SLEQOL had acceptable internal consistency, test-retest reliability, construct validity, and responsiveness, it also demonstrated significant floor effects, such that respondents reported good QOL beyond what can be measured by the instrument, and concurrent validity of the tool was low when the summary score was compared to the SF-36 [41]. Thus, co-administration of SLEQOL with a second validated HRQOL measure, such as the SF-36, may be required to address these limitations.

L-QoL is the only SLE-specific PRO developed using a needs-based QOL model, and validation has only been assessed in a U.K. SLE sample thus far [42]. L-QoL had excellent internal consistency, test-retest reliability and concurrent validity. Construct validity was assessed only against patient-reported disease activity and severity, and no validated physician assessments were employed. L-QoL has not been employed in any clinical research studies or clinical trials to date, and further assessment of L-QoL construct validity and responsiveness will strengthen its use in future studies.

Summary/Discussion

Health outcomes research has produced a number of well validated instruments that can be used across disease and some have been specifically developed for SLE. Some of the most precise and comprehensive questionnaires are lengthy and complex, leading to a level of respondent burden that can hinder recruitment, limit the representativeness of the patient population being studied, and lead to problems of missing data [24]. Another approach has been to develop shorter questionnaires which represent a compromise in measurement precision, range, but offer other desirable attributes in favor of practicality and the ability to compare to other chronic diseases as well as the general population. The use of either a generic and SLE-specific PRO is likely to depend on the variety of clinical applications including population monitoring, treatment decision-making in clinical practice, clinical trials research, and for evaluation and comparison of the effect of therapies across conditions, therapies, trials and patients in clinical research studies [24].

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Key Points

- Successful management of complex conditions such as systemic lupus erythematosus, SLE, and comorbid conditions benefit significantly from patient-reported outcomes (PRO) instruments that validly and precisely measure relevant aspects of health status (e.g., symptoms) and health related quality of life.
- Measuring health related quality of life and other aspects of health status (e.g., symptoms, functioning) with PROs provides SLE patients with an opportunity to participate in their treatment and to facilitate better communication with the multi-disciplinary team of health professionals involved in their care
- Health outcomes research has produced a number of well validated instruments that can be used across diseases and some have been specifically developed for SLE.
- The use of either a generic or SLE-specific PRO depends on the specific needs for a variety of clinical applications including population monitoring, treatment decision-making in clinical practice, clinical trials research, and for evaluating and comparing the effect of therapies across conditions, therapies, trials and patients in clinical research studies.