Review Article

Health-related Quality of Life in Patients with Systemic Lupus Erythematosus: An Update

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Abstract

With improvements in mortality in systemic lupus erythematosus (SLE), the functional status of these patients, assessed using health-related quality of life (HRQoL) instruments, is increasingly being recognised as an important outcome measure in clinical research. Domains of HRQoL of particular importance to SLE patients include fatigue, ability to work, good health, independence, social and family life, learned helplessness (reflecting the unpredictability of lupus), pain and the home environment. The SF-36 currently appears to be the best available generic instrument for the assessment of HRQoL in SLE, and is likely to be complemented by several newly-developed disease-specific HRQoL instruments. It has been shown that SLE patients have poorer functional status than the general population, and that specific manifestations of SLE (disease activity, previous renal involvement and fibromyalgia) may influence HRQoL. HRQoL in SLE patients has been improved by (1) psycho-educational interventions including telephone counselling, a self-help course, group psychotherapy; (2) therapies including Riquent, belimumab, mycophenolate mofetil, dehydroepiandrosterone, oestrogen therapy and a cholesterol- lowering diet. Additional research is needed to identify strategies which can improve HRQoL in SLE patients.

Ann Acad Med Singapore 2007;36:115-22

Key words: Clinical Trials, Intervention studies, Outcome assessment (health care), Review

Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease associated with significant morbidity and mortality. With improvements in survival in SLE, attention has also been focused on the reductions in health-related quality of life (HRQoL) associated with this condition. HRQoL has variously been defined as a multi-domain concept that represents the patient's overall perception of the impact of an illness and its treatment,[1] and the degree to which persons perceive themselves able to function physically, emotionally and socially.[2] Patient-reported HRQoL instruments attempt to perform this measurement in an accurate and reproducible manner.

It is well known that HRQoL is significantly impacted by SLE, particularly when the disease is active. Compared with age and gender matched norms, there are significant decrements reported not only in physical function and physical domains, but across all 8 domains assessed by the SF-36, including social and emotional functioning. It is therefore important to measure HRQoL in order to improve it. It is also clear from several studies[3,4] that physician and patient perceptions of SLE activity and global health differ, suggesting that HRQoL needs to be measured in addition to measures of disease activity and damage. Further, these measures may not vary in tandem. For example, SLE patients with fibromyalgia may have no active disease or damage, and yet may have poorer HRQoL than SLE patients without fibromyalgia,[5] or SLE patients with kidney manifestations may be asymptomatic until significant renal impairment is evident. Additionally, different interventions may improve disease activity to a similar degree but may have different effects on HRQoL. For example, although mycophenolate mofetil and cyclophosphamide are both

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effective treatments for lupus nephritis,[6] 75% of patients in a pilot study had better HRQoL with the former and expressed a preference for this medication because of an improved adverse event profile.[7] Increasing awareness of the need to measure HRQoL in SLE is reflected in the international consensus effort in rheumatology: "Outcome Measures in Rheumatology Clinical Trials"(OMERACT), which recommended that 5 domains be assessed in clinical trials in SLE, namely disease activity, damage, HRQoL, adverse events and economic impact.[4,8]

Recent reviews of HRQoL in SLE have shown that (1) HRQoL is reduced in SLE patients and the extent of this reduction is comparable to severe medical illnesses, including AIDS, Sjogren's syndrome and rheumatoid arthritis, psoriatic arthritis, congestive heart failure, post-myocardial infarction while fibromyalgia patients have poorer HRQoL than SLE patients;[3,9-11] (2) HRQoL is not well-correlated to disease activity or damage cross-sectionally [but does correlate with these in prospective, randomised controlled clinical trials (see below)]. Thus, the 3 outcome measures (disease activity, damage and quality of life) are relatively independent of one another, reflecting different domains impacted by SLE, and all 3 should be assessed in a patient with SLE to capture the complete clinical picture, and add discriminative power when assessing promising new therapies; (3) Other factors such as age, disease duration, fatigue and psychosocial factors impact on HRQoL in a complex manner; (4) HRQoL measures which are sensitive to change should be an essential outcome measure in clinical trials on SLE patients, as illustrated by data from recent clinical trials which showed that the SF-36 is sensitive to changes in HRQoL in SLE.[9,12,13] Use of a generic instrument such as SF-36 facilitates comparisons to other chronic disease states as well as economic analyses (e.g., SF-6D) but a disease-specific measure is also crucial. Both should be utilised in randomised controlled trials (RCTs) and validation of the systemic lupus erythematosus-quality of life (SLE-QOL) or other disease-specific HRQoL measures in SLE are eagerly awaited.

These reviews extend the findings of previous reviews and that of a comprehensive review of psychosocial research in SLE.[14-16] This update aims to complement these reviews by summarising what is known of methods to improve HRQoL in SLE. To facilitate this, the domains of HRQoL which are known to be important in SLE are first reviewed, and interventions which have been shown to improve HRQoL in these domains are then summarised.

Review of the Literature on HRQoL in SLE

To identify relevant publications, we performed a literature review using 2 methods. First, a literature search in Medline using the search strategy "quality of life and lupus" was performed. Abstracts of the 212 identified articles were reviewed, and relevant English language publications were obtained for full-text review. Second, lists of references from reviewed full-text publications were scanned to identify relevant references, whose abstracts and (if appropriate) full texts were reviewed. We limited this review to publications in the English language and to adult patients with SLE.

Domains of HRQoL of Importance in SLE

The domains of HRQoL affected vary among different illnesses, because each disease has differing impacts on subjects. This is demonstrated by a study of patients with rheumatic diseases, where patients with rheumatoid arthritis had more difficulty with activities of daily living than patients with SLE, while patients with fibromyalgia had the poorest global assessment of functional status.[17] In order to capture the impact of SLE on HRQoL, it is thus necessary to identify the domains (or areas) of HRQoL affected by SLE, and to use a HRQoL instrument which measures these domains.

Domains of HRQoL affected by SLE have been identified using in-depth interviews with patients[18-22] and are listed in Table 1. Most of these studies used structured interviews with patients, at times as part of the development process for a HRQoL instrument. One study of 20 patients used techniques to understand a subject's underlying representation of disease, and identified important domains of HRQoL as well as other aspects of a subject's internal perception of his or her illness.[20] Not surprisingly, domains of importance to patients reflect their concerns related to the nature of SLE as a chronic condition which may wax and wane, may affect multiple organ systems and which is associated with significant morbidity and mortality.

It is germane that the domains of HRQoL affected by SLE may vary in different socio-cultural contexts, because HRQoL is affected by culture. Table 1 shows that the majority of the studies assessing important domains of HRQoL in SLE patients have been performed in Western socio-cultural contexts. This highlights the need for such studies in a wide variety of socio-cultural contexts. As part of the developmental process for the SLE quality of life (SLEQoL) instrument by Leong et al,[23] 100 patients with SLE in Singapore were asked to provide feedback on 51 items suggested as important by rheumatologists. No additional items were suggested by patients, and the 40 items remaining after item reduction (using Rasch and factor analysis and expert review) were grouped into 8 domains: social and occupational activities, mood and self-image, physical functioning, physical symptoms, self-esteem and the unpredictability of the illness and its response

Table 1. Health-related Quality of Life: Domains of Concern to SLE Patients

Domain	Population/s studied	Interventions which have improved HRQoL in these domains
Ability to work	Western	
Fatigue	Western	
Good health/Wellness	Western	
Independence/Personal self-management	Western	
Social and family life/friends	Western	Telephone counselling
Fear, including fear of death	Western	
Learned helplessness (also expressed as dependence/feelings of inadequacy/loss of self)	Western	SLE self-help course
Pain/symptoms	Western	
House/home/living environment	Western	
Uncertainty/ unpredictability of lupus	Western	
Misunderstood by others	Western	
Medical treatment	Western	
Emotional stress	Western	
Limitations/restricted activities	Western	
Hobbies/cultural activities	Western	

Some of these domains may partially overlap, reflecting the different rubrics used in various studies.

to treatment. To some extent, these domains reflect the views of patients, though, as has been noted, patients gave input on these items but were not the source for item generation.[3] Interestingly, these 40 items could generally be categorised into the domains identified from patient-based studies in Western populations, supporting the validity of this instrument and suggesting that there may be at least several domains of HRQoL which are common to at least some Eastern and Western socio-cultural contexts. Two other disease-specific HRQoL instruments, the LupusQoL and the SLE Symptom Checklist, did include patient input in the development process.[3,22,24]

In selecting a HRQoL measure for use in SLE, several issues, some of which are informed by the HRQoL domains of importance to SLE patients, need to be considered.[15] First, does the measure assess domains of importance to SLE patients (i.e. content validity)? Second, is the measure acceptable to SLE patients? The number of questions and the nature of each question in a measure influence its acceptability and thus the willingness of patients to complete it, especially if administered serially. Third, are psychometric properties of the measure adequate for use in SLE patients? These properties include internal consistency, assumptions for Likert scale scoring (if used by the measure), test-retest reliability, construct validity and sensitivity to change.[25] Fourth, does the measure actually assess the domain/s of HRQoL that it purports to measure (i.e. construct validity)?[25] Fifth, is the measure available in a variety of languages? Sixth, has the measure been validated for use in each of these languages and are these language versions equivalent? Prior to the development of SLE-specific HRQoL instruments, the SF-36 was recommended as the instrument of choice for measuring HRQoL in SLE,[8] with cross-sectional validation studies in SLE patients having been performed using English and Chinese SF-36 versions.[26-29] The SF-36 has been used successfully to assess HRQoL in SLE patients in Canada, Norway, Singapore, Spain and the United States. Several prospective studies have shown (in contrast to cross-sectional studies) that HRQoL in SLE improves with reductions in disease activity.[30,31] The SF-36 has several features that make it a suitable instrument for measuring HRQoL in SLE. The 8 domains of health assessed include fatigue, social functioning and general health, which are of particular concern to SLE patients. Its brevity (36 questions) and ease of administration have resulted in good patient acceptance, cross-cultural translation and validation and wide use across many chronic disease indications. Cross-sectional and prospective studies of SLE patients in a variety of socio-cultural contexts have shown that the SF-36 has good psychometric properties and construct validity.[26-30,32,33] Additionally, the SF-36 is available in many languages worldwide. There is also some evidence that various versions of the SF-36 , including the English (UK) and Chinese (Hong Kong) versions, are equivalent.[34-36] However, concerns have been raised regarding the sensitivity to change of the SF-36.[37] In this regard, it is interesting that the SLEQoL, as a disease-specific HRQoL instrument which measures important domains of HRQoL for SLE patients, has been shown to have a greater sensitivity to change than the SF-36.[23] This further highlights the need to include both a generic and disease-specific HRQoL measure in the assessment of HRQoL in SLE in clinical trials and cohort studies. In addition to the SLEQoL, other recently-developed disease-specific HRQoL instruments for SLE include the LupusQoL,[24] SLE Symptom Checklist[22] and the SLEQoL from Leeds.[38]

Measures to Improve HRQoL in SLE

Not unexpectedly, HRQoL in SLE patients is reduced when compared with the general population. In Singapore, for example, SLE patients had lower scores for all SF-36 domains when compared with the general population.[28,39]

Table 2. Interventions to Improve HRQoL in Patients with SLE

Ref	Intervention	Study Design	Outcome	Comments
Positive results				
44	Telephone counselling	RCT (n = 58) comparing treatment counselling versus symptom monitoring strategies over 6-month period.	Improved AIMS2 physical function and social support scale scores in treatment counselling group compared to symptom monitoring group (P <0.05); AIMS2 affect and pain scores and FSS improved (P <0.05) for both groups.	
45	SLE self-help course: 7 weekly classes (2.5 hours each)	Cohort study (n = 313), measurements at baseline, after the last class (7 weeks after baseline) and 2 months after the last class.	Statistically significant decreases in depression (measured using 6 items from the 36 item Self-control Schedule) and increases in enabling skill (measured using 4 items developed for this study).	
46	Brief supportive-expressive group psychotherapy	RCT, subjects randomly assigned to receive either usual care (n = 66) or a 12-week brief supportive-expressive group psychotherapy followed by 3 monthly booster sessions (n = 58).	Women who received brief supportive-expressive group psychotherapy experienced significant reductions in illness intrusiveness for 2 of 3 domains: (1) relationships and personal development (F = 2.34; P = 0.065) and (2) intimacy (F = 5.057; P = 0.013). Benefits were evident at 6- and 12-month follow-up.	
47	A psychoeducational intervention	RCT where patients and their partners (n = 64) received an intervention designed to enhance self-efficacy, couples communication about lupus, social support, and problem-solving: a 1-hour session with a nurse educator with subsequent monthly telephone counselling for 6 months, versus the control group (n = 58) who received an attention placebo: a 45-minute video presentation about lupus and monthly telephone calls.	Adjusting for baseline covariates, in the intervention group, scores for self-efficacy (P = 0.004), global mental health status (P = 0.03) were significantly higher at 12 months; the mean score for global physical function was 7 points higher, which was a clinically meaningful change (P = 0.2) and mean score for fatigue was lower (P = 0.05).	
48	UVA-1 cold light treatment	Double blind, placebo controlled, crossover study (n = 11), with UVA-1 cold light treatment and a placebo light treatment for the first 3 weeks of 2 consecutive 12-week periods.	The SF-36 vitality scale improved more after UVA-1 (15.91 points CI 29.58 to 2.24) than after placebo treatment (2.27 points, 95% CI 8.60 to 13.14, P = 0.03)	
49	Prasterone 200 mg/day (i.e. dehydroepiandro-sterone)	Randomised, double-blind placebo controlled trial in patients with active SLE (SLEDAI >2): prasterone 200 mg/day plus standard SLE treatments (n = 147) versus placebo (n = 146) plus standard SLE treatments for up to 12 months.	Worsening in the patient's global assessment of HRQoL occurred in 10.9% of the prasterone group versus 22.6% of the placebo group (P = 0.007). However, there was no difference in non-responders measured using the Krupp Fatigue Severity Score (14.4% vs 10.9%, P = 0.367).	

Table 2. contd.

Ref	Intervention	Study Design	Outcome	Comments
Positive results				
50	Dehydroepiandrosterone 20 or 30 mg om	Randomised, double-blind placebo controlled trial in patients (n = 41) with SLE	Improvements in SF-36 role emotional scores, Hopkins symptom checklist, and McCoy Sex Scale Questionnaire (P <0.05)	Patients in the placebo group also showed statistically significant improvement in RE scores.
51	Culturally-sensitive cholesterol-lowering diet	RCT of 6 weekly group counselling sessions followed by 2 weekly telephone counselling sessions for 6 weeks versus no intervention.	Improvement in HRQoL measured using VAS for several domains (general energy level, performing certain tasks, quality of sleep, etc.) Subjects in the diet group reported an increase of 15% to 17% in QoL (mean ± SD, baseline: 59.4 ± 7.8; 6 weeks: 69.5 ± 5.1; 12 weeks: 68.4 ± 7.8), whereas the control group reported a decrease of 4% to 6% in this measure (treatment by time interaction) (P = 0.05).	The authors note that counselling per se may have contributed to the observed difference
7	Mycophenolate mofetil (MMF) versus oral cyclophosphamide	Retrospective assessment of HRQoL in patients treated with both medications.	MMF treatment was associated with higher numerical scores for all domains across the SF-36 (statistically significant for PF, VT and SF) and World Health Organization Quality of Life (WHOQOL) (statistically significant for the psychological domain).	
52	Riquent (abetimus sodium)	Multi-centre randomised double blind controlled trial of Riquent (n = 114) versus placebo (n = 116) in patients with previous lupus nephritis.	SF-36 role emotional scores improved with Riquent (7.3 versus 8.2), P = 0.01, SF (4.3 versus 0.7), and RP (11.3 versus 6.0). In 37 patients with renal flares with prospective data available, those receiving Riquent reported stabilisation or improvement in all but one domain compared to deterioration in all domains with placebo.	
9	Riquent (abetimus sodium)	Responders (defined as having persistent 10% or 20% reductions in dsDNA levels) in 2 randomised controlled trials of Riquent vs placebo (n = 487).	Responders showed improvements in SF-36 scores which were clinically important for bodily pain (8.2 points), VT (8.0 points) and general health (6.6 points) scales in one trial, and for RF, general health and SF in the other.	
12,13	Belimumab	Multi-centre RCT (n = 449) in patients with active SLE comparing 3 doses of belimumab with placebo over 1 year.	Seropositive subjects receiving belimumab showed improvements in SF-36 PCS scale (P <0.05), PF (P = 0.0019) and RF (P = 0.0298) scales. Responders (with decreased disease activity using pre-defined criteria) reported greater improvements in PCS (increase = 5.1 points) at week 52, than non-responders (increase = 1.7 points) with belimumab; not with placebo (1.7 vs 1.3 points, respectively).	

Table 2. contd.

Ref	Intervention	Study Design	Outcome	Comments
Positive results				
53	OCP or HRT	SELENA Trials: OCP use in 178 premenopausal and HRT in 350 post-menopausal SLE patients in 2 RCTs	OCP use resulted in improvements in SF-36 RP and RE scores (8-9 points); SF and VT scores (2-3 points), vs no change/worsening with placebo. HRT use in an older population resulted in small improvements in PF, RE and SF. Excluding severe flares showed increased improvement in HRQoL with hormone therapy in both trials.	
Negative results				
54	Brief supportive-expressive group psychotherapy	Multi-centre RCT of psychotherapy and standard medical care (n = 64) versus standard medical care (n = 69), 12 weekly sessions.	No difference in psychological distress, quality of life, disease activity, health service utilisation,and diminished productivity on intention-to-treat analysis.	Exceptionally rigorous study design and analysis.

AIMS2: Arthritis Impact Measurement Scales; FSS: Fatigue Severity Scale; HRQoL: health-related quality of life; HRT: hormone replacement therapy; OCP: oral contraceptive; PCS: physical component summary; PF: physical functioning; RCT: randomised controlled trial; RE: role emotional; RP: role physical; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SF: social functioning; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; VAS: visual analogue scale; VT: vitality

An important reason for measuring HRQoL in SLE patients is therefore to improve it. To do so, factors affecting HRQoL need to be identified, and interventions to modify these factors need to be devised and tested. Cross-sectional studies have identified age, disease duration, educational status, disease activity, self-efficacy, social support, knowledge of lupus and fibromyalgia as factors associated with QoL in SLE patients.[3,26,40] Prospective studies, which allow for the identification of potential cause and effect relationships, have shown that potentially modifiable factors, including disease activity and damage, psychosocial factors and the use of corticosteroids or cytotoxic agents may influence HRQoL.[31,41] Additionally, specific manifestations of SLE may influence HRQoL. For example, SLE patients with end-stage renal failure or fibromyalgia had poorer HRQoL than subjects without these conditions.[5,42] In 5 recent randomised controlled trials of different interventions in SLE conducted primarily in North America, HRQoL scores were low compared to age and gender matched norms, with baseline SF-36 levels similar to those reported by patients with inflammatory arthritis, chronic congestive cardiac failure and post-myocardial infarction.[11] Decrements in SF-36 domain and summary scores were best predicted by a history of renal disease, the presence of anti-dsDNA antibodies, higher Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) and/or Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores, age, hypocomplementemia and African-American descent. Reassuringly, HRQoL in SLE patients as a group appears to remain relatively constant when measured at baseline and after 2 years.[43]

Interventions which have been shown to improve HRQoL in SLE are summarised in Table 2.[7,12,13,44-54] These interventions have been assessed using study designs of varying rigour, and include psychotherapy, a SLE self-help course and various pharmacologic and biologic therapies. Several aspects of these studies deserve comment. First, the fact that several pharmacologic therapies have improved HRQoL is consistent with clinical experience that reducing disease activity and/or levels of anti-dsDNA antibodies can improve HRQoL for SLE patients.[9] Second, the observation that several non-pharmacological approaches can improve HRQoL suggests that the combinations of pharmacologic and non-pharmacologic therapies may have an additive (or perhaps synergistic) effect on improving HRQoL, though this remains to be tested. Third, the large number of HRQoL instruments used in these studies limits comparison among studies, and suggests the need for standardisation of instruments to measure HRQoL in such research. The increasing use of the SF-36 is encouraging in this regard, especially as it is a generic measure well-validated across multiple disease states. Fourth, it is interesting that spontaneous improvement in affect, pain and fatigue was noted in a "control" group where symptoms were monitored without specific intervention.[46] This suggests that providing

attention to these aspects of patients lives per se may improve HRQoL. Fifth, it was somewhat disappointing and surprising that a randomised controlled trial of brief supportive-expressive group psychotherapy by Dobkin et al[54] failed to show the efficacy of this approach, despite an exceptionally rigorous methodology. Sixth, these studies were conducted in Western socio-cultural contexts. As HRQoL is affected by culture, the results of these studies need to be extrapolated with caution to other socio-cultural contexts, and such studies should ideally be performed in these contexts to confirm the efficacy of these interventions to improve HRQoL in SLE patients.

An interesting observation is that the presence of skin lesions or alopecia reduces HRQoL in SLE patients.[56] Several uncontrolled studies suggest that HRQoL in these patients can be improved with interventions. For example, patients with disfiguring skin lesions from discoid lupus erythematosus (DLE) may benefit from the use of cosmetics to camouflage these lesions or the treatment of these lesions. This was suggested by a study of 20 such female patients (2 of whom had chronic discoid lupus erythematosus), in whom mean Dermatology Quality of Life questionnaire scores improved from 9.2 to 5.5 points ($P = 0.0009$) over a 2-week period.[55] An unblinded study of topical pimecrolimus cream in 10 patients with discoid lupus (specifically excluding patients with SLE) found a 20% improvement in scores using the Skindex-29, a disease specific HRQoL measure.[56]

Future Directions in Outcomes Research in SLE

The demonstration that specific interventions can improve HRQoL in SLE is an encouraging development, as is the development of several disease-specific HRQoL instruments. The use of these disease-specific instruments (with their greater sensitivity to change) in future clinical trials in SLE is likely to improve the identification of interventions which may improve HRQoL in these patients.

Acknowledgements

We acknowledge with thanks the assistance of Dr Wee Hwee Lin in performing a literature search for articles forming part of this manuscript, and Ms Connie Tse with preparation of this manuscript.

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