Systemic lupus erythematosus: a behavioural medicine perspective

Daleboudt, G.M.N.

CHAPTER 4

HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND PROLIFERATIVE LUPUS NEPHRITIS

Gabriëlle M.N. Daleboudt

Stefan P. Berger

Ad A. Kaptein

Psychology, Health, & Medicine 2011; 16(4): 393-404

ABSTRACT

Background The present study investigated the influence of two different treatments for a kidney inflammation (i.e., proliferative lupus nephritis) on health-related quality of life (HRQoL) in patients with the chronic, autoimmune disease systemic lupus erythematosus (SLE). One treatment protocol, the National Institutes of Health (NIH) protocol, was characterized by a high dose of cyclophosphamide (CYC; an immunosuppressive drug), and the second treatment, the Euro-Lupus protocol, involved a low dose CYC. *Methods* Thirty-two SLE patients were included based on a received treatment for an episode of proliferative lupus nephritis according to either the Euro-Lupus or NIH protocol. The two groups were compared on HRQoL as measured by the Medical Outcomes Study Short Form 36 (SF-36) and the SLE Symptom Checklist (SSC). *Results* The Euro-Lupus group (N = 16) tended to show a higher HRQoL than the NIH group (N = 16) on four of seven scales of the SF-36. In addition, the Euro-Lupus group experienced less burden of the symptom nausea/vomiting than the NIH group as assessed by the SSC. Fatigue was the most disturbing symptom in both groups. The most burdensome aspects of treatment were related to chemotherapy (55.2%) and prednisone use (34.5%). Patients with a low HRQoL and high levels of fatigue were more likely to have low levels of serum complement C4 (i.e., elevated immune activity). *Conclusion* Patients who are treated according to the Euro-Lupus protocol may experience a higher HRQoL than patients who receive the NIH treatment. However, chemotherapy remains burdensome in the low dose treatment regimen. Potential interventions to further enhance HRQoL in SLE patients with proliferative lupus nephritis are discussed.

INTRODUCTION

Few studies have investigated the effect of treatment on health-related quality of life (HRQoL) in patients with the chronic, autoimmune disease systemic lupus erythematosus (SLE). This could be due to a lack of valid and reliable disease-specific HRQoL measurements for SLE patients. However, over the last few years several attempts to develop such measurements have shown good results.[1,2,3] The present study used one of those newly validated instruments to assess HRQoL in SLE patients with proliferative lupus nephritis.

In SLE, the immune system attacks the body's own cells, which can result in inflammation of multiple organ systems at the same time. SLE is most prevalent among women in their reproductive years with usual disease onset between ages 15 and 40.[4] The worldwide prevalence is estimated to be about one per 1000 and the female to male ratio is 10:1.[5] Most patients present with vague and varying symptoms including marked malaise, extreme fatigue and fever. Also sun over-sensitivity, painful joints, oral ulcers, and on the psychosocial level mild depression, are frequently reported. The course of disease of SLE is characterized by alternating periods of either relatively stable disease or high disease activity. In the face of active disease, patients may need to take high doses of strong immunosuppressive agents. But also when the disease is relatively stable, maintenance doses are often required to preserve low activity and patients are closely monitored for signs of flare-ups.

Lupus nephritis is the most prevalent organ involvement in SLE that affects up to 60% of patients[6] and results in a substantial increase in morbidity and mortality.[7] A renal biopsy is required to confirm a diagnosis of lupus nephritis. Six different classes of lupus nephritis can be distinguished.[8] Most importantly, a subdivision between proliferative and non-proliferative lesions can be made which guides the choice of treatment regimen.[9] This study will only relate to the treatment of patients with proliferative lesions in their biopsy.

Up to 2004, the National Institutes of Health (NIH) regimen was the standard treatment for proliferative lupus nephritis at Leiden University Medical Centre (LUMC) and involved high doses of cyclophosphamide (CYC) and corticosteroids for two years. Although this therapy regimen results in a complete or partial remission in more than 80% of patients[10], it also has many severe side effects. Immediate side effects include nausea, vomiting, fatigue, and hair loss. In the long term cytopenias (i.e., a reduction in the number of blood cells), infections, infertility, and malignancy can occur.[11] Since 2004, a modified version of the Euro-Lupus protocol has been introduced as an alternative treatment because it involves lower doses of CYC and corticosteroids and a large portion of the CYC is substituted by mycophenolate mofetil (MMF). An important advantage of MMF is that it can be taken orally, whereas CYC had to be given intravenously. The efficacy of MMF has been shown to be at least equivalent or even superior to CYC, while MMF has fewer side effects.[11]

There are many factors that influence the impact of illness on quality of life, such as demographics, the condition itself, treatment, and psychosocial factors. It would be expected that less toxic treatments with fewer side effects will enhance patients' HRQoL significantly. Two previous studies have investigated the effect of treatment for lupus nephritis on HRQoL. The first study showed that a MMF-based induction treatment for proliferative lupus nephritis was associated with better HRQoL than CYC.[13] The second study found a higher self-reported treatment burden and worse mental HRQoL in a for proliferative lupus nephritis CYC treated patient group compared with a group treated with corticosteroids and azathioprine.[14]

The present study aimed to assess HRQoL in two different treatment groups for proliferative lupus nephritis and to examine the associations of HRQoL with socio-demographic and clinical characteristics. In addition, HRQoL of SLE patients was compared with HRQoL of patients with other chronic illnesses and with HRQoL of a reference population of healthy respondents. It was expected that HRQoL would be higher in patients who received the less toxic Euro-Lupus treatment and that HRQoL of SLE patients

would be lower than HRQoL of patients with other chronic illnesses and of a reference population of healthy respondents.

METHODS

Participants

Patients were selected from the electronic patient registration at Leiden University Medical Centre (LUMC). Inclusion criteria were a diagnosis of proliferative lupus nephritis and a received treatment according to either the NIH or the Euro-Lupus protocol. Thirty-seven patients who fulfilled the inclusion criteria were approached to participate in the study. One patient refused to join the study without knowing its aim, two patients could not be contacted and two patients decided not to participate on personal grounds. Hence, the final participant group consisted of 32 patients (86.5% participation rate), with 16 patients in each treatment group.

Participants completed two self-administered paper-and-pencil questionnaires in a private room at LUMC. Participants filled out the questionnaires on the basis of recall about the first half year of treatment. Prior to the assessment, participants provided informed consent. The study was approved by the Committee on Medical Ethics LUMC.

Materials

Research in the area of quality of life has shown that combining generic and disease-specific HRQoL assessments in SLE patients results in the optimal measurements.[15] Therefore, the Medical Outcomes Study Short Form 36 (SF-36) was used as a generic measurement of HRQoL.[16] The questions about mood were excluded because memory for emotions has been shown to be especially subjective to bias from subsequent experiences.[17] As a result, two of the nine scales (i.e. vitality and mental health) of the SF-36 were not included in this study.

The SLE Symptom Checklist (SSC) was included to assess disease-specific HRQoL.[1] The questions about mood were again excluded and because of this, one of the five components of the SSC was not assessed. The remaining four components of the SSC

include: (1) socio-demographic characteristics; (2) presence and burden of 38 symptoms; (3) influence on daily life and (4) treatment burden.

Besides assessing HRQoL, disease activity was recorded according to the following parameters: proteinuria (i.e., the amount of protein in the urine), serum albumin (i.e., an important plasma protein), serum creatinine (i.e., a measure of kidney function), serum complement C3 and C4 (i.e., a measure of immune activity) and haematuria (i.e., the amount of blood in the urine). These parameters were registered at the start of the treatment, at every monthly follow-up up to six months, and at the time of assessment.

Design and Procedure

Data were analysed using SPSS Version 16.0 software. Means on measures of HRQoL were compared between the two patient groups with an independent t-test. One sample t-tests were performed to investigate differences in HRQoL between the two treatment groups and a reference population of healthy respondents and patients with other chronic illnesses (copied from Aaronson et al., 1998).[18] Associations among the HRQoL measures, socio-demographic characteristics, and disease parameters were examined with Spearman's rho correlations. Effect sizes were classified using Cohen's d. G-Power 3.1.2 was used to compute post-hoc power analyses.

RESULTS

Participants

Table 1 gives an overview of the socio-demographic characteristics. The mean age of the total participant group was 35.3 (*SD* = 10.4). Patients had been diagnosed with SLE on average 11.1 (*SD* = 5.0) years ago. The majority of patients were of Dutch origin (65.6%). The time since the start of treatment for patients in the NIH group was longer than for patients in the Euro-Lupus group ($t = 4.30$, df = 16.5, $p = .001$).

Table 1. Socio-demographic characteristics for the NIH, Euro-Lupus and total patient group

	NIH[a] (N = 16)	Euro-Lupus[b] (N = 16)	Total (N = 32)
Female to male ratio	10:6	14:2	24:8
Age mean (SD)	36.8 (10.3)	33.8 (10.7)	35.3 (10.4)
Age at diagnosis of SLE mean (SD)	25.2 (7.0)	25.3 (10.3)	25.3 (8.7)
Disease duration mean (SD)	12.4 (4.9)	9.8 (4.8)	11.1 (5.0)
Years since start of treatment mean (SD)	8.5 (3.7)	4.5 (.82)**	6.5 (3.4)
Origin			
Dutch	11 (34.4%)	10 (31.3%)	21 (65.6%)
Surinam	3 (9.4%)	4 (12.5%)	7 (21.9%)
Other	2 (6.3%)	2 (6.3%)	4 (12.5%)
Marital status			
Living alone	7 (21.9%)	4 (12.5%)	11 (34.4%)
Married/cohabitating	9 (25.0%)	12 (34.4%)	21 (59.4%)
Higher education:			
Vocational	9 (28.1%)	10 (31.3%)	19 (59.4%)
University	3 (9.4%)	1 (3.1%)	4 (12.5%)
Work status:			
Student	1 (3.1%)	4 (12.5%)	5 (15.6%)
Employed	8 (25.0%)	7 (21.9%)	15 (46.8%)
Unemployed	7 (21.9%)	5 (15.6%)	11 (34.4%)

[a]Treatment for proliferative lupus nephritis consisted of high dose cyclophosphamide.

[b]Treatment for proliferative lupus nephritis consisted of low dose cyclophosphamide and mycophenolate mofetil.

**$p < .01$.

Disease activity parameters at the start of treatment show that the two treatment groups only differed in proteinuria values and level of hypoalbuminemia (see Table 2). Both groups showed good improvements at six months follow-up and were comparable on all disease parameters. Patients in general showed stable disease at the time of assessment.

Table 2. Disease activity parameters at the start of treatment, after six months and at time of assessment between the NIH and Euro-Lupus group

	NIH	Euro-Lupus	Reference
Serum creatinin (µmol/L)			max. 106
Start of treatment (N = 32)	143.8 (97.5)	139.3 (133.0)	
After six months (N = 32)	117.1 (26.6)	97.9 (59.3)	
Assessment (N = 32)	108.4 (57.4)	85.6 (44.7)	
Proteinuria (g/24hrs)			0 – 0.15
Start of treatment (N = 28)	4.7 (3.0)	2.6 (1.5)*	
After six months (N = 21)	1.1 (1.2)	1.0 (.91)	
Assessment (N = 17)	.38 (.50)	.75 (1.4)	
Serum albumin (g/L)			40 – 50
Start of treatment (N = 28)	24.4 (6.3)	30.2 (6.5)*	
After six months (N = 24)	40.9 (6.1)	41.3 (3.8)	
Assessment (N = 16)	42.4 (7.1)	42.7 (3.7)	
Hematuria[a]			0
Start of treatment (N = 30)	4.0 (1.3)	3.6 (1.3)	
After six months (N = 22)	2.4 (2.0)	1.8 (1.4)	
Assessment (N = 27)	1.1 (1.6)	.79 (1.3)	
Serum C3[b] (N= 21)	31.6 (13.4)	28.3 (15.3)	47 – 80
Serum C4[b] (N = 22)	11.5 (6.2)	9.3 (11.5)	13 – 39
Serum C1Q[b] (N = 20)	10.9 (4.3)	12.11 (7.9)	9 – 14

[a]Hematuria was scored as follows: 1 = trace, 2 = few, 3 = several, 4 = many, 5 = full. [b]Values only for the start of treatment.

*$p < .05$.

Medical Outcomes Study Short Form-36 (SF-36)

The NIH and Euro-Lupus did not show significant differences on the seven HRQoL scales, but effect sizes were moderate for the scales physical functioning, social functioning, change in health and role limitations emotional (see Table 3). Post-hoc power analysis suggests moderate to high power to detect differences for these four scales and low power for the scales pain, general health, and role limitations physical. Hence, it is likely that the two treatment groups differ on several HRQoL scales but that the sample size was too small to detect differences.

Table 3. Mean scores (SD) on the SF-36 for the Euro-Lupus, NIH, and total patient group in comparison with a reference population of healthy respondents (asterisks indicate significant differences with the reference population, no significant differences between the Euro-Lupus and NIH group were found)

Scale	Reference population	SLE	Euro-Lupus	NIH	Cohen's d[a]	Power[a]
Physical Functioning	81.9 (23.2)	55.3 (25.6)***	61.0 (20.8)**	50.0 (29.1)**	0.44	76.5%
Social Functioning	86.9 (20.5)	44.9 (27.7)***	50.8 (27.2)***	39.1 (27.7)***	0.43	74.1%
Role Limitations	79.4 (35.5)	55.5 (42.0)**	57.8 (42.5)	53.1 (42.7)*	0.11	9.3%
Role Limitations	84.1 (32.3)	51.0 (44.8)***	58.3 (47.9)*	43.8 (41.7)**	0.32	45.6%
Pain	79.5 (25.6)	67.2 (23.8)**	67.9 (25.8)	66.6 (22.4)*	0.05	5.9%
General Health	72.7 (22.7)	41.4 (22.0)***	41.3 (23.1)***	41.6 (21.7)***	0.01	5.0%
Change in Health	52.7 (19.4)	81.2 (26.9)***	87.5 (20.4)**	75.0 (31.6)*	0.47	83.0%

*p < .05. **p < .01. ***p < .001.

[a]Cohen's d and power were calculated for scores between the Euro-Lupus and NIH group.

The NIH group showed a lower HRQoL than a reference population of healthy respondents on six scales, whereas the Euro-Lupus group had a lower functioning than this population on four scales. In addition, the NIH group differed at a more conservative significance level from the reference population than the Euro-Lupus group on the scale role limitations emotional. Hence, HRQoL of the NIH group could have been more affected by treatment as it was less comparable with that of a reference population than HRQoL of the Euro-Lupus Group. When HRQoL of the two treatment groups together were compared with HRQoL of the reference population, SLE patients showed a lower HRQoL on all scales, except for the scale change in health.

To investigate whether HRQoL of SLE patients differed from that of patients with other chronic illnesses, the scores of the two treatment groups together were compared with scores for patients with migraine and cancer (derived from Aaronson et al., 1998)[18]. Table 4 shows the scores for all three groups. In general, SLE patients had a lower HRQoL than patients with migraine and cancer. The three patient groups did report a comparable level of pain and cancer patients showed a lower HRQoL on the scale role limitations physical than SLE patients.

Table 4. Mean scores (SD) on the SF-36 for SLE patients compared with migraine and cancer patients

	SLE (N = 32)	Migraine[a] (N =)	Cancer[a] (N =)
Physical Functioning	55.3 (25.6)	82.4 (21.3)***	63.6 (25.1)
Social Functioning	44.9 (27.7)	76.2 (20.9)***	73.9 (24.1)***
Role Limitations Physical	55.5 (42.0)	62.2 (40.8)	35.0 (40.3)*
Role Limitations Emotional	51.0 (44.8)	74.5 (37.8)**	58.4 (43.6)
Pain	67.2 (23.8)	64.9 (22.4)	69.3 (26.6)
General Health	41.4 (22.0)	67.5 (20.5)***	52.5 (21.4)**

[a]Values copied from Table 4 from Aaronson et al. (1998).[18]

*p < .05. **p < .01. ***p < .001.

SLE Symptom Checklist (SSC)

Of the 38 symptoms on the SSC, nausea/vomiting was the only symptom for which patients in the NIH group reported a higher burden than patients in the Euro-Lupus group (t = 3.39, df = 30, p = .002). Almost all patients (96.6%) mentioned the symptoms "fatigue" and "rounding of face". Fatigue caused the highest burden in both treatment groups.

Patients in the NIH and Euro-Lupus group reported a comparable level of influence of treatment on their daily lives. Physical activities were most influenced and especially riding the bike. As for the non-physical activities, the influence on work and study was the greatest.

Level of treatment burden did not differ between the two treatment groups. Sixteen patients (55.2%) reported chemotherapy and/or adverse effects of chemotherapy as the most burdensome aspect(s) of treatment. Frequently mentioned adverse effects of chemotherapy were fatigue (17.3%), nausea (13.8%), hospital stay (13.8%) and hair loss (6.9%). Ten patients (34.5%) experienced prednisone and/or adverse effects of prednisone as the most disturbing effect(s) of treatment. Weight gain and joint involvement were stated as adverse effects of prednisone by three (10.3%) and two (6.9%) patients, respectively. All mentioned aspects did not show a relationship with type of treatment.

Correlations

Table 5 gives an overview of the correlations between HRQoL measures, disease activity parameters and socio-demographic characteristics. Patients with a low HRQoL on the scales physical functioning, pain, and role limitations emotional of the SF-36 tended to report high levels of fatigue. A high HRQoL on social functioning was associated with high serum levels of C4 (i.e., low immune activity).

Patients who experienced a high influence of treatment on daily life, as measured by the SSC, tended to be younger, to have lower serum levels of C4 (i.e., elevated immune activity), to have a higher proteinuria (i.e., a large amount of protein in the urine) and to report a higher level of fatigue. High levels of fatigue were also associated with a high self-reported treatment burden.

Because fatigue was experienced as the most burdensome symptom by both groups, its association with disease activity was investigated. Patients who had low levels of serum C4 (i.e., elevated immune activity) were more likely to report high levels of fatigue. The severity of fatigue was not related to the extent to which treatment influenced sleeping habit.

Table 5. Correlations between health-related quality of life measures and age, proteinuria, serum C4, albumin and fatigue

	Age	Fatigue	Proteinuria[a]	Albumin[b]	Serum C4[c]	Physical Functioning	Social Functioning	Role Limitations	Role Limitations	Pain	General Health	Change Health	Total Complaints	Total Distress	Treatment Burden	Mean influence Daily	Physical	Emotional
Age	1.000																	
Fatigue	-.195	1.000																
Proteinuria[a]	-.287	.148	1.000															
Albumin[b]	.107	-.225	**-.421***	1.000														
Serum C4[c]	**.610****	**-.430***	.020	.177	1.000													
Physical Functioning	.201	**-.411***	**-.405***	.123	.097	1.000												
Social Functioning	.257	-.284	-.325	.139	**.469***	**.606****	1.000											
Role Limitations Physical	-.147	-.005	.064	.222	-.099	-.156	-.145	1.000										
Role Limitations Emotional	.206	**-.458****	-.047	**.410***	.347	.178	.047	**.495****	1.000									
Pain	.085	**-.498****	-.276	.208	.253	**.465****	.343	**-.432***	-.015	1.000								
General Health	.110	-.037	-.327	-.255	.177	.218	.345	-.067	-.246	.200	1.000							
Change in Health	-.182	**.434***	-.037	-.152	-.054	-.291	-.177	.011	-.142	-.273	.272	1.000						
Total Complaints	.166	.133	.050	.158	.205	**-.389***	-.069	.149	.137	**-.437***	**-.378***	.099	1.000					
Total Distress Level	.124	.294	.090	.068	-.009	**-.509****	-.193	.213	.043	**-.610****	-.320	.305	**.867****	1.000				
Treatment Burden	-.157	.299	.236	-.244	-.291	**-.424***	**-.388***	-.010	-.089	**-.551****	-.268	.278	.224	**.445***	1.000			
Mean Influence Daily Life	**-.439***	**.422***	**.451***	-.090	**-.544****	**-.687****	**-.660****	.184	-.121	**-.354***	**-.531****	.164	.340	**.417***	**.378***	1.000		
Physical	-.331	**.409***	.198	-.089	-.367	**-.589****	-.347	.069	-.179	-.337	**-.394***	.254	.332	**.497****	**.376***	**.774****	1.000	
Emotional	.169	.174	.087	.241	.012	-.299	**-.552****	-.118	-.014	-.112	-.229	.143	.175	.111	.123	**.368***	.116	1.000

[a]The amount of protein in the urine. [b]An important plasma protein. [c]An index of immune activity.

*$p < .05$. **$p < .01$.

DISCUSSION

The present study aimed to assess HRQoL in SLE patients who were treated for proliferative lupus nephritis according to one of two treatment protocols, and to examine associations of HRQoL with socio-demographic and disease characteristics. The results seem to support the prediction that patients who were treated according to the Euro-Lupus protocol showed a better physical and psychological functioning than patients from the NIH group. However, a manifest better HRQoL was not demonstrated. Chemotherapy remained burdensome in low dose and also prednisone use contributed to a worse HRQoL in both groups. All patients rated fatigue as the most disturbing symptom, which was frequently perceived as an adverse effect of chemotherapy. Worse HRQoL and high levels of fatigue were associated with low levels of serum C4 (i.e., elevated immune activity).

Few studies have investigated the effect of different treatments on HRQoL in patients with proliferative lupus nephritis.[13,14] One retrospective between-subjects study assessed HRQoL in 12 patients who had experienced two episodes of lupus nephritis for which they were treated with either CYC and prednisone or MMF and prednisone.[13] Although scores on the SF-36 did not show many significant differences, they did tend to be higher overall in the MMF group.

In contrast, a randomized controlled trial (RCT) found no substantial differences in HRQoL as measured by the SF-36.[14] Patients who were treated for proliferative lupus nephritis with either CYC pulses or with azathioprine (AZA) and methylprednisolone tablets were compared on HRQoL measures at the start of treatment and at a follow-up of 12 and 24 months. The AZA group did show a significantly lower treatment burden as measured by the SSC. Such an effect was not found in the present study, which could be explained by the low dose CYC in the Euro-Lupus group while the AZA group in the RCT was completely deprived of CYC. Surprisingly, the AZA group did not report less burden of nausea/vomiting, whereas in the present study the Euro-Lupus group reported a significantly lower burden. However, it appears that the questionnaire in the RCT study referred to a period in which no CYC pulses were given[14], which can explain the different findings. It seems that a low dose CYC does reduce the disturbance of a symptom like

nausea/vomiting, but that treatment burden as a whole may decrease only if CYC is totally abandoned.

The finding that fatigue was the most disturbing symptom is in line with results from previous studies.[14,19] The few studies that have investigated the relationship between fatigue and HRQoL, also support the finding that high levels of fatigue are associated with worse HRQoL.[21,21]

The association between fatigue and disease activity has been examined more extensively, but results are inconsistent. Although SLE Disease Activity Index (SLEDAI) scores have not shown a relationship with fatigue[20,21], physician's ratings of disease activity have been associated with fatigue levels.[22] In addition, comparable to the association between fatigue and serum C4 levels in the present study, low serum C3 levels and high lymphocyte counts have been related to high levels of fatigue.[19]

Many studies have investigated the relation between HRQoL and disease activity, and although results from these studies are inconsistent, in general, HRQoL is not well correlated with disease activity.[23] The present study did find moderate correlations for serum C4, proteinuria and serum albumin with some measures of HRQoL. The association of serum C4 with both HRQoL and fatigue suggests an important role of serum C4 level in physical and psychological functioning. A focus on improvements in serum level of C4 may contribute to an enhancement in HRQoL and a reduction in fatigue.

In line with a previous study, the results showed that SLE patients have a significantly lower HRQoL than patients with other common chronic illnesses.[24] Interventions other than reductions in CYC and prednisone dose seem desirable to enhance HRQoL. A range of psychological interventions, such as self-management interventions, cognitive behavioral therapy, and coping skills training, have been successful in enhancing HRQoL and fatigue in patients with diabetes, COPD, cancer and cardiovascular disease.[25] Only one known study has addressed the effect of a psychological intervention in SLE patients.[26] This study investigated the application of

cognitive behaviour therapy to alter illness perceptions and also looked at the effects of therapy on psychological well-being. The beneficial effects on psychological functioning were limited, but levels of psychological distress did show significant reductions.[26] Psychological interventions aimed at enhancing HRQoL are expected to be beneficial for SLE patients and future research should address the implementation of the available range of interventions.

One important limitation of the present study is the retrospective reporting of quality of life. Patents' reports may have been influenced by recall bias and subsequent experiences. In addition, the time interval between treatment and time of assessment varied between the two treatment groups, as patients in the NIH group were mostly treated before 2004 and those in the Euro-Lupus group only from or after 2004. However, measuring HRQoL on the basis of recall with varying time intervals between patients is common, as reflected in the number of studies that apply such a method.[13,27,28] Moreover, a response shift, the re-evaluation of HRQoL in response to changing health, occurs as soon as six days after an event[29] and time period is one of many factors that may influence recall bias.[30] Other limitations of the present study include the small sample size and the non-random allocation of patients to treatment groups, which limits its power and generalizability. Finally, the patient group consisted mainly of patients of Dutch (Caucasian) origin.

In conclusion, the Euro-Lupus protocol tends to result in better HRQoL outcomes than the NIH protocol. However, SLE patients with lupus nephritis remain having a lower HRQoL compared to patients with other common chronic illnesses. Chemotherapy remains burdensome in low dose and also prednisone use may contribute to a low HRQoL in both groups. Psychological interventions could be beneficial to further enhance HRQoL, but research is needed to find out which interventions will be the most effective.

REFERENCES

1. Grootscholten, C., Ligtenberg, G., Derksen, R. H., Schreurs, K. M., de Glas-Vos, J. W., Hagen, E. C. et al. (2003). Health-related quality of life in patients with systemic lupus erythematosus: development and validation of a lupus specific symptom checklist. Quality of Life Research, 12, 635-644.
2. Leong, K. P., Kong, K. O., Thong, B. Y., Koh, E. T., Lian, T. Y., Teh, C. L. et al. (2005). Development and preliminary validation of a systemic lupus erythematosus-specific quality-of-life instrument (SLEQOL). Rheumatology, 44, 1267-1276.
3. McElhone, K., Abbott, J., Shelmerdine, J., Bruce, I. N., Ahmad, Y., Gordon, C. et al. (2007). Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus. Arthritis & Rheumatism, 57, 972-979.
4. Simard, J. F. & Costenbader, K. H. (2007). What can epidemiology tell us about systemic lupus erythematosus? International Journal of Clinical Practice, 61, 1170-1180.
5. Manson, J. J. & Rahman, A. (2006). Systemic lupus erythematosus. Orphanet Journal of Rare Diseases, 1, 6.
6. Bihl, G. R., Petri, M., & Fine, D. M. (2006). Kidney biopsy in lupus nephritis: look before you leap. Nephrology Dialysis Transplantation, 21, 1749-1752.
7. Bernatsky, S., Boivin, J. F., Joseph, L., Manzi, S., Ginzler, E., Gladman, D. D. et al. (2006). Mortality in systemic lupus erythematosus. Arthritis & Rheumatism, 54, 2550-2557.
8. Weening, J. J., D'Agati, V. D., Schwartz, M. M., Seshan, S. V., Alpers, C. E., Appel, G. B. et al. (2004). The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney International, 65, 521-530.
9. Contreras, G., Roth, D., Pardo, V., Striker, L. G., & Schultz, D. R. (2002). Lupus nephritis: a clinical review for practicing nephrologists. Clinical Nephrology, 57, 95-107.
10. Buhaescu, I., Covic, A., & Deray, G. (2007). Treatment of proliferative lupus nephritis--a critical approach. Seminars in Arthritis & Rheumatism., 36, 224-237.
11. Houssiau, F. (2007). Thirty years of cyclophosphamide: assessing the evidence. Lupus, 16, 212-216.
12. Petri, M. (2004). Cyclophosphamide: new approaches for systemic lupus erythematosus. Lupus, 13, 366-371.
13. Tse, K. C., Tang, C. S., Lio, W. I., Lam, M. F., & Chan, T. M. (2006). Quality of life comparison between corticosteroid- and-mycofenolate mofetil and corticosteroid- and-oral cyclophosphamide in the treatment of severe lupus nephritis. Lupus, 15, 371-379.
14. Grootscholten, C., Snoek, F. J., Bijl, M., van Houwelingen, H. C., Derksen, R. H., & Berden, J. H. (2007). Health-related quality of life and treatment burden in patients with proliferative lupus nephritis treated with cyclophosphamide or azathioprine/ methylprednisolone in a randomized controlled trial. Journal of Rheumatology, 34, 1699-1707.

15. Thumboo, J. & Strand, V. (2007). Health-related quality of life in patients with systemic lupus erythematosus: an update. Annals of Academic Meicine Singapore, 36, 115-122.
16. Van der Zee, K. I. & Sanderman, R. (1993). Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding/Measuring the general state of health with the RAND-36. A manual. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken.
17. Levine, L.J. & Safer, M.A. (2002). Sources of bias in memories of emotions. Current Directions in Psychological Science, 11, 169-173.
18. Aaronson, N. K., Muller, M., Cohen, P. D., Essink-Bot, M. L., Fekkes, M., Sanderman, R. et al. (1998). Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. Journal of Clinical Epidemiology, 51, 1055-1068.
19. Wysenbeek, A. J., Leibovici, L., Weinberger, A., & Guedj, D. (1993). Fatigue in systemic lupus erythematosus. Prevalence and relation to disease expression. British Journal of Rheumatology, 32, 633-635.
20. Bruce, I. N., Mak, V. C., Hallett, D. C., Gladman, D. D., & Urowitz, M. B. (1999). Factors associated with fatigue in patients with systemic lupus erythematosus. Annals of Rheumatic Diseases, 58, 379-381.
21. Wang, B., Gladman, D. D., & Urowitz, M. B. (1998). Fatigue in lupus is not correlated with disease activity. Journal of Rheumatology, 25, 892-895.
22. Krupp, L. B., LaRocca, N. G., Muir, J., & Steinberg, A. D. (1990). A study of fatigue in systemic lupus erythematosus. Journal of Rheumatology, 17, 1450-1452.
23. McElhone, K., Abbott, J., & Teh, L. S. (2006). A review of health related quality of life in systemic lupus erythematosus. Lupus, 15, 633-643.
24. Jolly, M. (2005). How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? Journal of Rheumatology, 32, 1706-1708.
25. Llewelyn, S. & Kennedy, P. (2003). Handbook of Clinical Health Psychology. West Sussex: John Wiley & Sons Ltd.
26. Goodman, D., Morrissey, S., Graham, D., & Bossingham, D. (2005). The application of cognitive behaviour therapy in altering illness representations of systemic lupus erythematosus. Behaviour Change, 22, 156-171.
27. Ito, H., Matsuno, T., Hirayama, T., Tanino, H., & Minami, A. (2007). Health-related quality of life in patients with systemic lupus erythematosus after medium to long-term follow-up of hip arthroplasty. Lupus, 16, 318-323.
28. West, E. & Jonsson, S. W. (2005). Health-related quality of life in rheumatoid arthritis in Northern Sweden: a comparison between patients with early RA, patients with medium-term disease and controls, using SF-36. Clinical Rheumatology, 24, 117-122.
29. Nieuwkerk, P. T., Tollenaar, M. S., Oort, F. J., & Sprangers, M. A. (2007). Are retrospective measures of change in quality of life more valid than prospective measures? Medical Care, 45, 199-205.
30. Coughlin, S.S. (1990). Recall bias in epidemiologic studies. Journal of Clinical Epidemiology, 43(1), 87-91.