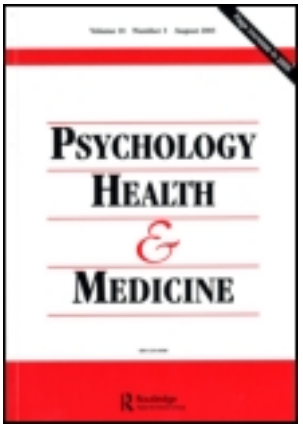

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Health-related quality of life in patients with systemic lupus erythematosus and proliferative lupus nephritis

Gabriëlle M.N. Daleboudt [a b], Stefan P. Berger [b], Elizabeth Broadbent [c] & Ad A. Kaptein [a]

[a] Department of Medical Psychology, Leiden University Medical Center, Leiden, The Netherlands

[b] Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands

[c] Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

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Health-related quality of life in patients with systemic lupus erythematosus and proliferative lupus nephritis

Gabriëlle M.N. Daleboudt[a,b]*, Stefan P. Berger[b], Elizabeth Broadbent[c] and Ad A. Kaptein[a]

[a]*Department of Medical Psychology, Leiden University Medical Center, Leiden, The Netherlands;* [b]*Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands;* [c]*Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand*

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This 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 auto-immune 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. Thirty-two SLE patients were included based on the received treatment for an episode of proliferative lupus nephritis, according to either the Euro-Lupus or the NIH protocol. The two groups were compared on HRQoL as measured by the SF-36 and the SLE Symptom Checklist (SSC). 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 from nausea or 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 use of prednisone (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). In 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 the HRQoL in SLE patients with proliferative lupus nephritis are discussed.

Keywords: cyclophosphamide; disease activity; health-related quality of life; proliferative lupus nephritis; SLE

Introduction

Only few studies have investigated the effect of different treatments on health-related quality of life (HRQoL) in patients with the chronic auto-immune 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

*Corresponding author. Email: g.m.n.daleboudt@lumc.nl

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(Grootscholten et al., 2003; Leong et al., 2005; McElhone et al., 2007). This study used one of these 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 (Simard & Costenbader, 2007). The worldwide prevalence is estimated to be about one per 1000, and the female-to-male ratio is 10:1 (Manson & Rahman, 2006). Most patients present with vague and varying symptoms, including marked malaise, extreme fatigue, and fever. Sun over-sensitivity, painful joints, oral ulcers, and, on the psychosocial level, mild depression are also frequently reported. The course 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. 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, an inflammation of the kidneys, is the most prevalent manifestation in SLE that affects up to 60% of patients (Bihl, Petri, & Fine, 2006) and results in a substantial increase in morbidity and mortality (Bernatsky et al., 2006). A renal biopsy is required to confirm a diagnosis of lupus nephritis. Six different classes of lupus nephritis can be distinguished (Weening et al., 2004). Most importantly, a subdivision between proliferative and non-proliferative lesions can be made, which guides the choice of treatment regimen (Contreras et al., 2002). 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 Center (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 (Buhaescu, Covic, & Deray, 2007), 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 (Petri, 2004). 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 the MMF is that it can be taken orally, whereas the 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 (Buhaescu et al., 2007).

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 would enhance patients' HRQoL significantly. Two previous studies have investigated the effect of treatment for lupus nephritis on HRQoL. The first study showed that an MMF-based induction treatment for proliferative lupus nephritis was associated with better HRQoL than CYC (Tse, Tang, Lio, Lam, & Chan, 2006). The second study found a higher self-reported treatment burden and worse mental HRQoL in a proliferative lupus nephritis CYC-treated patient group compared with a group treated with corticosteroids and azathioprine (AZA) (Grootscholten et al., 2007).

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 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 (Thumboo & Strand, 2007). The Medical Outcomes Study Short Form 36 (SF-36) was used as a generic measurement of HRQoL (Van der Zee & Sanderman, 1993). The questions about mood were excluded because memory for emotions has been shown to be especially subjective to bias from subsequent experiences (Levine & Safer, 2002). 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 (Grootscholten et al., 2003). 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 included: (1) socio-demographic characteristics; (2) the presence and burden of 38 symptoms; (3) influence on daily life, and (4) treatment burden.

Disease activity was measured with 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 complements C3 and C4 (i.e. a measure of immune activity), and hematuria (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 analyzed using the 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 (Aaronson et al., 1998). 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 software was used to compute post hoc power analyses.

Results

Participants

Table 1 shows an overview of the socio-demographic characteristics. The mean age of the total participant group was 35.3 (standard deviation, SD = 10.4). Patients had been diagnosed with SLE on average 11.1 (SD = 5.0) years ago. The majority of patients was 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, $p = 0.001$).

Disease activity parameters at the start of treatment show that the two treatment groups only differed in proteinuria values and level of hypoalbuminemia (Table 2). Both groups showed good improvements at six months follow-up and were

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

	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%)
Others	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%)

Notes: **$p < 0.01$. [a]Treatment for proliferative lupus nephritis consisted of high-dose CYC. [b]Treatment for proliferative lupus nephritis consisted of low-dose CYC and MMF.

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

	NIH	Euro-Lupus	Reference
Serum creatinine (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/24 h)			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 (0.91)	
Assessment ($N = 17$)	0.38 (0.50)	0.75 (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)	0.79 (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

Notes: *$p < 0.05$. [a]Hematuria was scored as follows: 1 = trace, 2 = few, 3 = several, 4 = many, and 5 = full. [b]Values only for the start of treatment.

comparable on all disease parameters. Patients in general showed stable disease at the time of assessment.

Medical Outcomes Study Short Form-36

The NIH and Euro-Lupus groups 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 (Table 3). Post hoc power analysis suggests moderate 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.

The NIH group showed 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 of healthy respondents than the Euro-Lupus group on the scale role limitations emotional. Hence, HRQoL of the NIH group could have been more affected by the treatment as it was less comparable with that of a reference population of healthy respondents than HRQoL of the Euro-Lupus group. When HRQoL of the two treatment groups together were compared with HRQoL of the reference population of healthy respondents, 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 the scores of patients with migraine and cancer (Aaronson et al.,

Table 3. Mean scores (SD) on the SF-36 for the Euro-Lupus, NIH, and total patient groups in comparison with a reference population of healthy respondents.

Scale	Reference population	SLE	Euro-Lupus	NIH	Effect size[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 physical	79.4 (35.5)	55.5 (42.0)**	57.8 (42.5)	53.1 (42.7)*	0.11	9.3
Role limitations emotional	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

Notes: Asterisks indicate that significant differences with the reference population and no significant differences between the Euro-Lupus and NIH groups were found. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. [a]Effect sizes and power were calculated for scores between the Euro-Lupus and NIH groups.

1998). 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.

SLE symptom checklist

Of the 38 symptoms on the SSC, ''nausea or 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 groups reported a comparable level of influence of treatment on their daily lives. Physical activities were most influenced, e.g. riding a bike. As for the non-physical activities, the influence on work and study was the greatest.

The level of treatment burden did not differ between the two treatment groups (the NIH and Euro-Lupus group). Sixteen patients (55.2%) reported chemotherapy, adverse effects of chemotherapy, or both 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, adverse effects of prednisone, or both 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 the 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 reported that treatment had a strong influence on their daily lives, 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

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

	SLE ($N = 32$)	Migraine[a] ($N = 423$)	Cancer[a] ($N = 485$)
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)**

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. [a]Values are obtained from Table 4 of Aaronson et al. (1998).

Table 5. Correlations between HRQoL measures and age, proteinuria, serum C4, albumin, and fatigue.

	Age influence																	
Physical	Emotional	Fatigue	Proteinuria[a]	Albumin[b]	Serum C4[c]	Physical functioning	Social functioning	Role limitations physical	Role limitations emotional	Pain	General health	Change in health	Total complaints	Total distress	Treatment burden level	Mean influence	Mean influence daily life	Mean
Age	1.000																	
Fatigue	−0.195	1.000																
Proteinuria[a]	−0.287	0.148	1.000															
Albumin[b]	0.107	−0.225	−0.421*	1.000														
Serum C4[c]	0.610**	−0.430*	0.020	0.177	1.000													
Physical functioning	0.201	−0.411*	−0.405*	0.123	0.097	1.000												
Social functioning	0.257	−0.284	−0.325	0.139	0.469*	0.606**	1.000											
Role limitations physical	−0.147	−0.005	0.064	0.222	−0.099	−0.156	−0.145	1.000										
Role limitations emotional	0.206	−0.458**	−0.047	0.410*	0.347	0.178	0.047	0.495**	1.000									
Pain	0.085	−0.498**	−0.276	0.208	0.253	0.465**	0.343	−0.432*	−0.015	1.000								
General health	0.110	−0.037	−0.327	−0.255	0.177	0.218	0.345	−0.067	−0.246	0.200	1.000							
Change in health	−0.182	0.434*	−0.037	−0.152	−0.054	−0.291	−0.177	0.011	−0.142	−0.273	0.272	1.000						
Total complaints	0.166	0.133	0.050	0.158	0.205	−0.389*	−0.069	0.149	0.137	−0.437*	−0.378*	0.099	1.000					
Total distress level	0.124	0.294	0.090	0.068	−0.009	−0.509**	−0.193	0.213	0.043	−0.610**	−0.320	0.305	0.867**	1.000				
Treatment burden	−0.157	0.299	0.236	−0.244	−0.291	−0.424*	−0.388*	−0.010	−0.089	−0.551**	−0.268	0.278	0.224	0.445*	1.000			
Mean influence daily life	−0.439*	0.422*	0.451*	−0.090	−0.544**	−0.687**	−0.660**	0.184	−0.121	−0.354*	−0.531**	0.164	0.340	0.417*	0.378*	1.000		
Physical	−0.331	0.409*	0.198	−0.089	−0.367	−0.589**	−0.347	0.069	−0.179	−0.337	−0.394*	0.254	0.332	0.497**	0.376*	0.774**	1.000	
Emotional	0.169	0.174	0.087	0.241	0.012	−0.299	−0.552**	−0.118	−0.014	−0.112	−0.229	0.143	0.175	0.111	0.123	0.368*	0.116	1.000

Notes: *$p < 0.05$, **$p < 0.01$. [a]The amount of protein in the urine. [b]An important plasma protein. [c]An index of immune activity.

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.

Discussion

This study aimed to assess HRQoL in SLE patients who were treated for an episode of proliferative lupus nephritis according to one of two treatment protocols, and to examine associations of HRQoL with socio-demographic and disease characteristics. The results support the prediction that patients treated according to the Euro-Lupus protocol showed better physical and psychological functioning than patients treated according to the NIH protocol. However, a manifest higher HRQoL was not demonstrated. Chemotherapy remained burdensome in low dose, and also the use of prednisone contributed to a low HRQoL in both groups. All patients rated fatigue as the most disturbing symptom, which was frequently perceived as an adverse effect of chemotherapy. Low 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 (Grootscholten et al., 2007; Tse et al., 2006). 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 (Tse et al., 2006). 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 using the SF-36 (Grootscholten et al., 2007). Patients who were treated for proliferative lupus nephritis with either CYC pulses or with azathioprine (AZA) and methylprednisolone were compared on HRQoL measures at the start of treatment and at a follow-up of 12 and 24 months. The AZA group showed a significantly lower treatment burden as measured by the SSC. The reason that a similar effect was not found in the present study may be because the Euro-Lupus group still had a low-dose CYC, while the AZA group in the RCT was completely deprived of CYC. Surprisingly, the AZA group did not report a lower burden of nausea or 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 (Grootscholten et al., 2007), which may explain the different findings. It seems that a low-dose CYC does reduce the experience of nausea or vomiting, but 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 (e.g. Grootscholten et al., 2007; Krupp, LaRocca, Muir, & Steinberg, 1990; Wysenbeek, Leibovici, Weinberger, & Guedj, 1993). 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 (Bruce, Mak, Hallett, Gladman, & Urowitz, 1999; Wang, Gladman, & Urowitz, 1998).

The association between fatigue and disease activity has been examined more extensively, but results are inconsistent. Although SLE Disease Activity Index scores have not shown a relationship with fatigue (Bruce et al., 1999; Wang et al., 1998), physician's ratings of disease activity have been associated with fatigue levels (Krupp et al., 1990). 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 associated with high levels of fatigue (Wysenbeek et al., 1993).

Many studies have investigated the relationship between HRQoL and disease activity, and although results from these studies are inconsistent, in general, HRQoL is not well correlated with disease activity (McElhone, Abbott, & Teh, 2006). 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 previous work, the results showed that SLE patients have significantly lower HRQoL than patients with other common chronic illnesses (Jolly, 2005). 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, chronic obstructive pulmonary disease, cancer, and cardiovascular disease (Llewelyn & Kennedy, 2003). Only one known study has addressed the effect of a psychological intervention in SLE patients (Goodman, Morrissey, Graham, & Bossingham, 2005). This study investigated the application of cognitive behavior 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 (Goodman et al., 2005). 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. Patients' 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 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 (e.g. Ito, Matsuno, Hirayama, Tanino, & Minami, 2007; Tse et al., 2006; West & Jonsson, 2005). Moreover, a response shift, the re-evaluation of HRQoL in response to changing health, occurs as soon as six days after an event (Bernhard, Hurny, Maibach, Herrmann, & Laffer, 1999), and time period is one of many factors that may influence recall bias (Coughlin, 1990). Other limitations of the present study include the small sample size and the non-random allocation of patients to treatment groups, which limit 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 outcomes of HRQoL than the NIH protocol. However, SLE patients with lupus nephritis remain with lower HRQoL compared with patients with other common chronic illnesses.

Chemotherapy remains burdensome in low dose, and use of prednisone may also contribute to 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.

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