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

CECILE GROOTSCHOLTEN, FRANK J. SNOEK, MARC BIJL, HANS C. van HOUWELINGEN, RONALD H.W.M. DERKSEN, and JO H.M. BERDEN, for the Dutch Working Party on SLE

ABSTRACT. ***Objective.*** To study prospectively the effect of treatment with cyclophosphamide pulses (CYC) or azathioprine with methylprednisolone (AZA), both for 24-month periods, on health-related quality of life (HRQOL) in patients with proliferative lupus nephritis (LN) in a randomized controlled trial. We expected better HRQOL during AZA treatment.

Methods. HRQOL and disease activity were measured at start and after 12 and 24 months. Generic questionnaires [patient's visual analog scale (VAS), Medical Outcomes Study Short Form-36 Health Survey (SF-36), Profile of Mood States] and a disease-specific measure [Systemic Lupus Erythematosus (SLE) Symptom Checklist] were used. Treatment burden was assessed at 24 months. Disease activity was measured with the SLE Disease Activity Index (SLEDAI) and physician's VAS.

Results. Complete questionnaire data were available from 47 of the 87 patients included in the trial. These patients were representative of the whole group, except that completers were more often Caucasian. HRQOL scores improved significantly during treatment, particularly during the first year, on both generic and disease-specific outcomes. No statistically significant differences were found in HRQOL between the CYC and AZA groups, except for the SF-36 mental component summary scale, which showed more favorable scores in the AZA group. The mean reported treatment burden at 24 months was significantly higher in the CYC group. HRQOL scores did not correlate with the SLEDAI and physician's VAS. The disease activity measures correlated positively with each other.

Conclusion. Treatment of patients with proliferative LN with immunosuppressive drugs and corticosteroids improves HRQOL, particularly in the first year. Due to the small groups studied, the absence of differences between AZA and CYC for most HRQOL scales should be interpreted cautiously: our data suggest that there may be no significant differences. Differences were a higher perceived treatment burden and worse mental HRQOL in the CYC group. (First Release July 15 2007; J Rheumatol 2007;34:1699–707)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS LUPUS NEPHRITIS QUALITY OF LIFE
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From the Division of Nephrology, Radboud University Nijmegen Medical Center, Nijmegen; Department of Medical Psychology, VU University Medical Center, Amsterdam; Division of Clinical Immunology, University Medical Center Groningen, Groningen; Department of Medical Statistics, Leiden University Medical Center, Leiden; and Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands.

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C. Grootscholten, MD, PhD; J.H.M. Berden, MD, PhD, Division of Nephrology, Radboud University Nijmegen Medical Center; F.J. Snoek, PhD, Department of Medical Psychology, VU University Medical Center; M. Bijl, MD, PhD, Division of Clinical Immunology, University Medical Center Groningen; H.C. van Houwelingen, PhD, Department of Medical Statistics, Leiden University Medical Center; R.H.W.M. Derksen, MD, PhD, Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, for the Dutch Working Party on SLE.

Address reprint requests to Dr. J.H.M. Berden, Division of Nephrology (464), Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: j.berden@nier.umcn.nl

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Quality of life (QOL) is a critical issue in the care of patients with systemic lupus erythematosus (SLE)[1,2], since both the disease itself and the treatment have a significant effect on the well-being of the patient. Fatigue in particular is known to have a disabling effect on the daily functioning of patients with SLE[3], not necessarily correlated with objective measures of disease activity[4-7]. One of the most serious manifestations of SLE is proliferative lupus nephritis (LN)[8,9]. The treatment of patients with proliferative LN consists of both cytotoxic drugs and corticosteroids. Cyclophosphamide (CYC) pulse therapy has been regarded as the standard treatment for a long period, and is known to cause serious negative side effects, such as infertility and malignancies[10]. In a search for an alternative, less toxic therapy, azathioprine (AZA) could be considered[11]. In a randomized controlled trial we compared the efficacy of CYC pulse treatment with AZA combined with methylprednisolone. The rationale of the original study was

that with AZA/methylprednisolone an acceptably higher number of renal relapses would occur, but that side effects would be less than with treatment with CYC intravenously. The primary endpoint was the occurrence of doubling of serum creatinine. Secondary endpoints included infections, side effects, and QOL. The treatment was different in the first 2 years only. Although more relapses occurred in the AZA-treated patients, no significant differences regarding the occurrence of doubling of serum creatinine or renal function at last visit were found after a median followup of 5.7 years[12]. The purpose of the current study was to evaluate, on an exploratory basis, the QOL outcomes from this trial. We expected fewer side effects with AZA/methylprednisolone compared to CYC, positively affecting perceived life quality and reducing treatment burden. Moreover, the change in QOL during both treatment schedules was studied.

MATERIALS AND METHODS

Design and patients. Details of the first Dutch Lupus Nephritis Study have been described[12]. In short, this study is an open-label, randomized controlled trial with repeated measurements, including clinical measures and patient-reported outcomes. All 87 study patients met the following criteria: presence of ≥ 4 American College of Rheumatology criteria for SLE[13], age 18 to 60 years, creatinine clearance (Cockcroft-Gault[14]) > 25 ml/min, and biopsy-proven proliferative LN[15]. Patients with World Health Organization (WHO) class IV LN were eligible when they had signs of active nephritis or a deterioration of renal function. Patients with WHO class III LN had to meet both criteria. Patients were assigned by a computer at a central office. The following minimization criteria were used: center, serum creatinine (< 150 or > 150 µmol/l), WHO class (III or IV), and previous treatment with immunosuppressive medication for LN (yes or no). Data were collected at a central office and data were anonymized before the analyses were carried out. For the detailed study protocol see our prior publication[12]. The study was approved by the ethics committees of all participating hospitals and written informed consent was obtained from all patients.

Treatments. Patients in the CYC arm were given 6 pulses of CYC (750 mg/m^2 body surface area) every 4 weeks, followed by 7 pulses every 12 weeks, combined with oral prednisone, initially 1 mg/kg/day, tapered to a final dose of 10 mg daily after 6 months. Patients in AZA arm started with AZA 2 mg/kg/day at Day 1, combined with methylprednisolone intravenously (ivMP; 1000 mg) on 3 consecutive days.

This cycle of 3 pulses was repeated after 2 and 6 weeks. In addition, oral prednisone (20 mg/day) was given for 5 months and then tapered to 10 mg/day. In an uncontrolled study this regimen was found to be effective and associated with minimal toxicity[16]. The combination treatment of ivMP and AZA was chosen since treatment with 6 monthly doses of ivMP alone was associated with an increased risk of doubling of serum creatinine as compared to CYC-containing regimens[17]. We argued that AZA would halt the progression of chronic lesions[18], while ivMP would more rapidly affect acute inflammation[19,20]. The cumulative corticosteroid doses during the first 2 years in the 2 groups were 11 g for a person weighing 70 kg treated with intravenous CYC, and for the patients treated with AZA/ivMP/prednisone the dose was 20 g (11 g for ivMP and 9 g for oral prednisone).

After 2 years of treatment, both groups continued taking AZA (2 mg/kg/day) and prednisone (10 mg/day) for 2 more years, after which both drugs were successively tapered over a year (to 1 mg/kg/day and 10 mg every other day, respectively), and continued for another 2 years.

Disease activity measures. The overall disease activity was measured at each visit using the SLE Disease Activity Index (SLEDAI), ranging from 0 to 105[21]. Physicians were also asked to rate the disease activity on a visual analog scale (VAS) score (physician's VAS) ranging from 0 to 10. For both activity measures a lower score denotes less disease activity.

Quality of life. Patients were invited to complete a booklet of questionnaires at study entry and at 12 and 24 months. The questionnaires were filled out at home and returned to a central office, using a prepaid and preaddressed envelope. Biographical and sociodemographic data were gathered using 16 questions on the duration of lupus, marital status, ethnicity, employment, etc. Health-related quality of life (HRQOL) was used as a multidimensional concept, including generic measures of perceived health status, mood, effect on daily life, and disease-specific symptom distress.

Generic QOL measures. Perceived general health status was measured by a VAS with the following question: "Everything considered, how do you feel at this moment?" The scale ranges from 1 to 10, a higher number representing a higher degree of general well-being (patient's VAS).

The widely-used Medical Outcomes Study Short Form-36 Health Survey (SF-36) was used as a generic measure of QOL[22-25]. The SF-36 has been tested and recommended to be used in patients with SLE[26,27]. It contains 8 domains, including fatigue, and one question relating to change in health. After recoding, all 8 scales can reach a maximum of 100, with a higher number representing better functioning and/or fewer limitations. Summary health scores [physical component summary (PCS) and mental component summary (MCS)] are calculated[28]. These standardized scores [with a mean of 50 and a standard deviation (SD) of 10 in the general population] make international comparisons possible.

The Dutch shortened version of the Profile of Mood States (POMS) was used to measure emotional well-being[29-31]. It consists of 32 items with a 5-point response format, ranging from "not at all" to "extremely," covering 4 negative mood states (depression, anger, fatigue, and tension) and one positive affect (vigor), referring to "the past few days, including today."

Treatment burden. The experienced treatment burden was measured at 24 months using 2 questions: "The treatment so far was..." on a 5-point Likert scale ranging from "not burdensome" (1) to "extremely burdensome" (5) and "What aspect of the treatment did you experience as most burdensome?" as an open-ended question.

Effect on activities of daily life. The effect of SLE on activities of daily life was assessed by using an adapted version of the IRGL (Influence of Rheumatic diseases on General health and Lifestyle) questionnaire[32], based on the AIMS (Arthritis Impact Measurement Scales)[33]. The IRGL has been validated in The Netherlands for patients with rheumatoid arthritis[32].

For our study only the IRGL subscales "mobility" and "impact of disease" were applied. The mobility part consists of 6 items measuring activities such as walking stairs. The influence of disease on daily life is evaluated by 10 items. For all questions, the answers range from "almost never" to "almost always" on a 4-point Likert scale. Scores range from 6 to 24 for mobility, and from 10 to 40 for effect of disease, a higher score denoting better mobility and more effect of disease, respectively.

Disease-specific QOL. To study the presence and perceived burden of both disease-related and treatment-related symptoms, we used the SLE Symptom Checklist (SSC)[34]. The SSC refers to the month preceding the day of completing the questionnaire. It consists of 38 symptoms. Each item is scored on a frequency scale, and if a symptom is present, also on a discomfort scale. The total distress score is calculated by summation of the perceived burden of each symptom as given on a 4-point Likert scale ["not present" (0), "present, but not burdensome" (1), "a little burdensome" (2), "quite burdensome" (3), or "extremely burdensome" (4)]. In a different cohort of 87 patients with stable SLE (median disease duration of 8 yrs) a mean number of symptoms of 12.9 with a total distress level of 30.1 was found[34]. The SSC was shown to have a satisfactory reliability (Cronbach's alpha 0.89 for both number of symptoms and total distress level) and reproducibility. Further, it was proven to be sensitive to change[34].

Statistical analyses. SPSS 12.0.1 was used for the analyses. Descriptive statistics included frequency tables of the patients' characteristics. Values are expressed as means and SD for normally distributed data, or as median with interquartile range (IQR) for skewed data. Comparisons between the different

instruments and the 2 treatment groups were studied with chi-square or nonparametric tests. Pearson correlation coefficients were calculated for comparisons between the diverse HRQOL scales. Changes of the diverse scales and activity measurements during the first 2 years of treatment were studied with mixed-model analyses.

The mixed-model module in SPSS is an extension of the well known analysis of variance technique for repeated measures that allows testing for treatment and time effects and the interaction of treatment and time, in the presence of missing data. For all analyses a p value < 0.05 was regarded as statistically significant, except for correlation coefficients, where the effect of multiple comparisons was adjusted according to Bonferroni.

RESULTS

Baseline characteristics. At study entry, 70 out of the 87 included patients (80%) had completed the questionnaire booklet. The first and second questionnaire were completed by 56 patients, and questionnaire data on all 3 timepoints were available from 47 patients, due to loss of followup or death, or loss of interest during followup. Of these 47 patients, 27 were randomized to CYC and 20 to AZA. Baseline characteristics are summarized in Table 1. As can be seen, completers more often were Caucasian and they had a lower complement C3 at study entry, but no differences for the other measures of disease activity were present. There were no differences between the patients randomized to CYC and those randomized to AZA, except for age, which was higher in the AZA group (Table 2). Sociodemographic data of the 47 patients are shown in Table 3. Comparing the completers with noncompleters with regard to the HRQOL scales showed that at study entry completers scored lower on the POMS anger scale, and slightly higher on the POMS vigor and IRGL mobility score than noncompleters.

Clinical outcomes. Whereas more renal relapses were present in the AZA group, so far no statistically significant differences in the primary study endpoint (doubling of serum creatinine) or measures at last visit (creatinine and proteinuria) have been found[12]. Partial remission was reached by most patients within the first year of treatment, and after 2 years about 60% of the patients had reached complete remission. Remission criteria did not include subjective variables.

The time course of disease activity as measured by the SLEDAI and physician's VAS is shown in Figures 1A and 1B. There were no differences between the 2 treatment groups or for the total group of patients as compared with the completers. With regard to complete remission, therapy failure or renal relapse, or reaching primary study endpoint (doubling of serum creatinine), no statistically significant differences existed between the completers and noncompleters (Table 1).

Table 1. Baseline characteristics and outcome after 2 years of treatment of all patients and those for whom 3 questionnaires were available. Data are given as medians and interquartile ranges, or as percentages.

Characteristic	All Patients, n = 87	3 Questionnaires, n = 47	p*
CYC/AZA	50/37	27/20	NS
Female	86	89	NS
Caucasian	76	87	0.007
Nephritis in the past	23	21	NS
LN first symptom of disease	41	47	NS
Age, yrs	33 (25–33)	31 (25–40)	NS
Disease duration, mo	16 (1–79)	8 (1–66)	NS
SLEDAI	20 (14–24)	21 (17–26)	NS
Biopsy measures			
WHO class IV, %	91	91	NS
Activity index	9.3 (6.7–11.7)	10.3 (6.7–12.3)	NS
Chronicity index	2.7 (2.0–3.7)	2.3 (1.7–3.3)	NS
Laboratory measures			
Serum creatinine, µmol/l**	111 (85–156)	105 (83–140)	NS
Serum C3, g/l	0.50 (0.37–0.64)	0.45 (0.32–0.55)	0.035
Serum C4, g/l	0.10 (0.08–0.15)	0.10 (0.07–0.12)	NS
Anti-dsDNA, IU/ml	158 (26–545)	142 (28–516)	NS
Proteinuria, g/24 h	3.9 (2.1–6.5)	4.2 (2.8–7.1)	NS
Disease course***	n = 78	n = 47	
Complete remission during first 2 yrs, %	59	60	NS
Time to reach complete remission, wks	44 (20–80)	44 (20–86)	NS
Serum creatinine × 2†	4	1	NS
Therapy failure or renal relapse during first 2 yrs	5	2	NS

* Comparison of patients who completed 3 questionnaires and those who did not. ** To convert values of creatinine to mg/dl, divide by 88.4. *** Only for patients still available at 2 years (n = 78). † Doubling of serum creatinine, the primary study endpoint. CYC: cyclophosphamide/prednisone; AZA: azathioprine/methylprednisolone/prednisone; LN: proliferative lupus nephritis; SLEDAI: SLE Disease Activity Index; anti-dsDNA: anti-double stranded DNA antibodies; NS: not significant.

Table 2. Comparison of baseline characteristics between the 2 treatment groups for the 47 patients who completed 3 questionnaires.

Characteristic	CYC, n = 27	AZA, n = 20	p
Caucasian, %	85	90	NS
Nephritis in the past	26	15	NS
LN first symptom of disease	52	40	NS
Age, yrs	28 (23–35)	33 (29–43)	0.048
SLEDAI	22 (17–27)	20 (16–22)	NS
Biopsy measures			
WHO class IV, %	93	90	NS
Activity index	9.0 (7.3–12.7)	10.7 (6.4–12.2)	NS
Chronicity index	2.3 (1.7–3.3)	2.3 (1.7–3.3)	NS
Laboratory measures			
Serum creatinine, µmol/l*	105 (84–146)	104 (80–138)	NS
Serum C3, g/l	0.41 (0.28–0.52)	0.49 (0.39–0.56)	NS
Serum C4, gl/l	0.10 (0.06–0.11)	0.10 (0.09–0.16)	NS
Anti-dsDNA, IU/ml	136 (24–632)	142 (41–429)	NS
Proteinuria, g/24 h	5.4 (3.2–7.1)	3.9 (2.6–7.1)	NS

* To convert values of creatinine to mg/dl divide by 88.4. NS: not significant.

Table 3. Sociodemographic characteristics at study entry of 47 patients who completed 3 questionnaires.

Characteristic	n (%)
Currently employed	21 (45)
Marital status	
Married/living together	30 (64)
Divorced	1 (2)
Never married	16 (34)
One or more children	22 (47)
Education > 9 yrs	40 (85)
Member of lupus association	21 (45)

Health-related quality of life

Generic. General well-being, measured with the patient's VAS, improved over time, but was not different between the 2 treatment groups. After 2 years of treatment the median patient's VAS had increased from 6 to 7 (Figure 1C).

As would be expected, there were relatively low scores (compared to norm data) of most subscales of the SF-36 at study entry. A significantly lower score for perceived general health was found in the AZA group compared with the CYC group. In Figure 2 the SF-36 scores are compared with those in Dutch lupus patients with stable disease[34] and in the general Dutch population[35]. The scores were comparable with results from most other studies in lupus patients, except for role-emotional, which was scored higher in our population (80.1) than in other SLE populations (ranging from 52 to 65)[2,36-39]. Mixed-model analyses revealed a significant effect of time on all subscales, but no differences between the 2 treatment groups, except for the MCS scores. The latter showed a significantly larger improvement in the AZA group, suggesting better mental functioning. However, due to the ceiling effect of this scale, these differences might not be clinically relevant.

Overall, all scores improved during treatment, with the largest changes during the first year of treatment (see Table 4 for data of all 47 patients). Figure 3 shows a comparison between the 2 treatment groups for the MCS and PCS scores. There were no correlations between the presence of alopecia and the PCS and MCS, but there was an inverse correlation with the patient VAS ($R = –0.329$, $p < 0.001$). Also, there were no correlations with the PCS and MCS for symptoms related to corticosteroid use. Only the presence of weight gain was negatively correlated with the PCS ($R = –0.302$, $p < 0.001$).

Results for the different POMS mood scales are also summarized in Table 4. During treatment, the subscales vigor, fatigue, and tension improved significantly, without differences between AZA and CYC. If patients for whom LN was the first symptom of SLE were compared with those who had been diagnosed with SLE before, no differences in the POMS subscales were found (data not shown).

Treatment burden. After 2 years of therapy the patients reported they experienced their treatment as rather troublesome (mean 2.9, SD 1.4). The reported treatment burden was higher in the CYC group than in the AZA group [3.6 (SD 1.1) vs 2.2 (SD 1.2); $p < 0.001$].

Patients in the CYC group mentioned the (day care) admissions for the CYC pulses as most burdensome, while in the AZA group, having to take medication and experiencing side effects of the corticosteroids was rated most burdensome. The latter group also more often mentioned admission for renal biopsy and collecting urine during 24 h as burdensome.

Effects on activities of daily life. Mobility improved during treatment, while the effect on daily life did not change. There were no differences between the CYC and AZA groups on IRGL scores. The IRGL scores at all timepoints were compa-

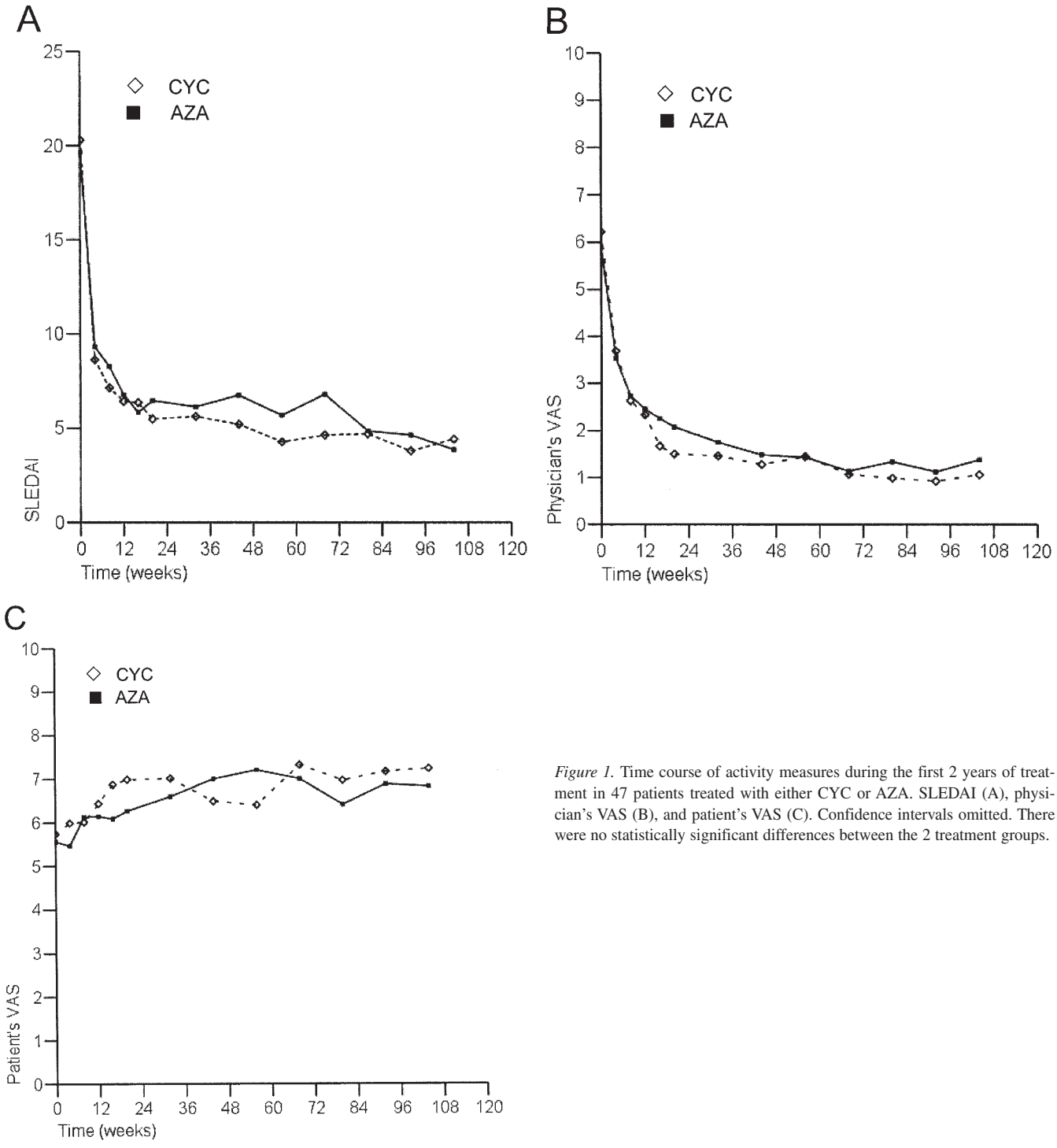

Figure 1. Time course of activity measures during the first 2 years of treatment in 47 patients treated with either CYC or AZA. SLEDAI (A), physician's VAS (B), and patient's VAS (C). Confidence intervals omitted. There were no statistically significant differences between the 2 treatment groups.

rable with means found in age- and sex-matched Dutch patients with rheumatoid arthritis[32].

Disease-specific effects. The mean number of complaints (SSC) did not change significantly during treatment, while the mean reported symptom distress decreased significantly ($p = 0.009$) from 34.6 (SD 15.9) to 28.4 (SD 14.5) after 1 year of therapy, to stabilize at 2 years (29.3, SD 17.7; see Table 4 and Figure 3). There were no statistically significant differences between the 2 treatment groups.

Fatigue was reported most frequently, and rated as the most distressing symptom. At study entry 94% of the patients mentioned they were fatigued, with a mean distress level of 3.2 (SD 0.8). After 2 years of therapy, fatigue was still present in most patients (87%), while the distress had decreased to 2.7 (SD 0.8).

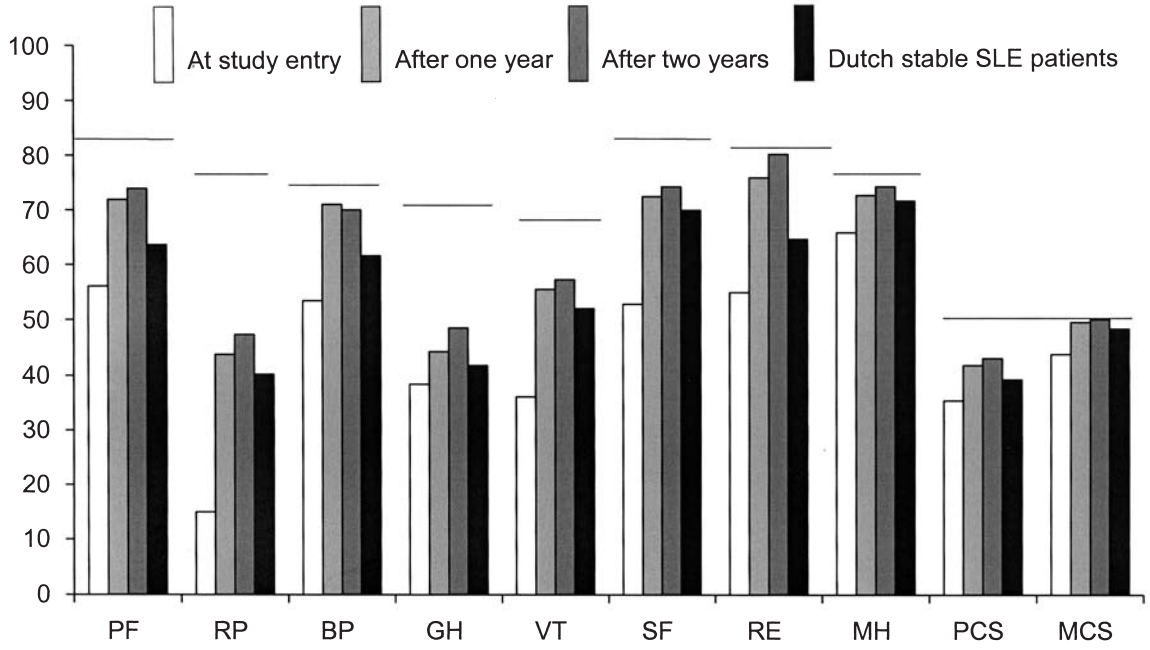

Figure 2. Comparison of SF-36 scores between study patients, Dutch patients with stable lupus (n = 33)[34], and the general Dutch population (n = 1742; shown as horizontal bars)[35]. Because there were no differences between CYC and AZA patients (except for MCS scores), data of all patients in the study were used. PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health; PCS: physical component summary; MCS: mental component summary.

With regard to nausea and vomiting, symptoms that are more often thought to be caused by CYC than by AZA, there were no differences between the 2 treatment arms at all 3 timepoints. Nausea and vomiting were present in 15% of the CYC patients and in 20% of the AZA patients at 1 year. After 2 years of treatment 33% of the CYC and 35% of the AZA patients reported this side effect. The presence of nausea and vomiting was negatively correlated with the PCS score ($R = -0.367$, $p < 0.001$).

External validity. By analyzing all patients who completed the questionnaire at study entry and at one of the other timepoints (n = 63), using mixed-model analysis, we found comparable results, suggesting that our data are valid for Dutch patients with proliferative LN.

DISCUSSION

In this randomized controlled trial in patients with proliferative lupus nephritis, we showed that treatment with immunosuppressive drugs improved QOL across different domains during the first year. In contrast to our expectations, no substantial differences were observed between patients treated with CYC and those treated with AZA. The latter group did report more favorable MCS scores and less treatment burden.

The absence of HRQOL differences between the AZA and CYC groups might be explained by the fact that our study was underpowered. Another explanation can be the process of coping. Patients tend to adapt cognitively to changes in their physical health[40]. This phenomenon is seen in other patient groups as well (e.g., diabetes and rheumatoid arthritis). In Table 4 and Figure 2, one can see that after the initial improvement on almost all scales any further improvement was small and patients remained lower on most scales compared to the Dutch population. Another factor might be the timing of the questionnaires: they were sent every 12 months and related to the past month or days (depending on the questionnaire). We may have missed differences, especially those that may have been present at 6 months, since the CYC was administered monthly until that point. Finally, due to a higher cumulative dose of corticosteroids the HRQOL in the AZA group might have been affected.

We had expected to find a difference with respect to the symptom "nausea/vomiting." The absence of a difference between the AZA and CYC groups might be explained by the fact that the nausea/vomiting due to CYC did not occur within the period referred to in the SSC (1 month), since after 6 months the CYC pulses were given quarterly. Another explanation is that nausea and vomiting can also be caused by drugs other than CYC, or that nausea increases with the number of pills that are prescribed. Alternatively, the drugs prescribed to prevent nausea and vomiting during CYC treatment proved to be effective, or the patients did not remember having been nauseated (recall bias).

While other symptoms either disappeared or emerged, fatigue remained present in most patients and was regarded as the most burdensome symptom. This is in agreement with previous studies[4,6,34].

Our study focused on HRQOL in patients with proliferative LN, who were included in a prospective study, using a

Table 4. Time course of diverse QOL scales and activity measures during the first 2 years of treatment in 47 patients with proliferative lupus nephritis, treated in the first Dutch Lupus Nephritis Study. Means (SD) or medians (IQR) are given.

Item	Range	At Study Entry	After 1 Year	After 2 Years	p
SF-36					
Physical functioning	0–100	56.1 (23.5)	71.9 (18.9)	73.9 (21.4)	0.000
Role-physical	0–100	15.0 (27.3)	43.8 (40.8)	47.3 (43.1)	0.000
Bodily pain	0–100	53.4 (26.6)	71.0 (21.5)	70.0 (21.3)	0.000
General health*	0–100	38.4 (17.5)	44.3 (21.2)	48.5 (20.8)	0.003
Vitality	0–100	36.1 (20.6)	55.5 (18.6)	57.3 (18.4)	0.000
Social functioning	0–100	52.8 (30.0)	72.4 (23.6)	74.2 (22.6)	0.000
Role-emotional	0–100	54.9 (44.1)	75.8 (35.5)	80.1 (34.5)	0.002
Mental health	0–100	65.8 (15.0)	72.6 (17.0)	74.2 (16.7)	0.016
Physical summary score	3–78	35.4 (8.1)	41.8 (9.2)	43.1 (10.7)	0.000
Mental summary score	6–72	43.8 (10.0)	49.5 (9.6)	50.0 (8.4)	0.000**
POMS					
Depression	0–32	4 (1–8)	2 (0–4)	2 (0–6)	NS
Vigor	0–20	7.5 (5–11)	8 (5–12)	9 (6–13)	0.036
Fatigue	0–24	8 (3–12)	5 (2–9)	6.5 (2–11)	0.007
Anger	0–28	2 (1–6)	4 (1–6.3)	3.5 (1–7)	NS
Tension	0–24	5 (3–8)	3 (1–6)	2 (0–6)	0.001
IRGL					
Mobility	6–24	16.0 (5.7)	18.1 (5.4)	18.8 (5.3)	0.000
Impact on daily life	10–40	21.6 (7.3)	20.5 (6.9)	20.2 (7.9)	NS
SSC					
Total distress level	0–152	34.6 (15.9)	28.4 (14.5)	29.3 (17.7)	0.009
No. of complaints	0–38	13.6 (4.9)	12.0 (5.5)	12.5 (6.4)	NS
Patient VAS	0–10	6 (5–7)	7 (6–8)	7 (6.5–8)	0.000
Physician VAS	0–10	6 (4–8)	1 (0–2)	1 (0–2)	0.000
SLEDAI	0–105	21 (17–26)	4 (2–6.5)	2.5 (2–6)	0.000

p value refers to the differences between the values at the 3 timepoints (time effect). * Value at Time 0 in AZA group was significantly lower than in CYC group (29.4 vs 45.6). ** The increase of the mental summary score in time was different between the 2 treatment arms (larger in the AZA group). SF-36: Medical Outcomes Study Short Form-36 Health Survey; POMS: Profile of Mood States; IRGL: Influence of rheumatic diseases on general health and lifestyle; SSC: SLE Symptom Checklist; VAS: visual analog scale.

randomized controlled design. In contrast to most HRQOL studies in patients with SLE[2,37,39,41-44], our population consisted of patients with active proliferative LN only, and patients had comparable characteristics at study entry. Although there was a significant loss to followup, the studied patients were representative of the total group of patients included in the trial. Moreover, if all patients who completed the questionnaires at study entry and after either 1 or 2 years (n = 16) were added to the analyses, the results did not change. We therefore have little reason to question the external validity of our findings.

There are several limitations of our study that need to be mentioned. First, the study was limited by a rather low response rate, and due to this, a small study population. The questionnaires were sent to patients through a central office, and patients were not contacted or urged if they had not responded. Further, not all patients could read or write the Dutch language, which caused a selection bias. This is supported by the difference in ethnicity between the total study population and the patients who were described in this report. By using an interval of 1 year between each questionnaire, we may have missed differences between AZA and CYC treatment at other, earlier, timepoints.

It is unfortunate that no followup data on the QOL after 2 years of treatment are available, as it would have been interesting to know whether the QOL improvements that we noted at 12 and 24 months were sustained over time. Future studies with longer followup should be able to clarify this issue. Nevertheless, after 4 years, the patient's VAS as measured during the outpatient visits was available for 67% of the patients. This VAS was comparable with the observed score at 2 years and showed a median of 7.5 (IQR 6.5–8.0). There were no differences between the CYC and AZA groups.

We conclude that in our 47 patients with proliferative LN successful treatment significantly improved HRQOL within a period of 12 months, and this effect was sustained in the second year of treatment. We did not have sufficient power to suggest use of one therapeutic strategy over the other based on this study. It also remains to be determined whether current alternative treatments like mycophenolate mofetil (MMF) have a more favorable effect on HRQOL. In a limited number of patients with LN, treatment with MMF resulted in better scores on several QOL domains compared to treatment with oral CYC[45].

These findings and our prior data[12,46] do not support the use of azathioprine/methylprednisolone as a first-line thera-

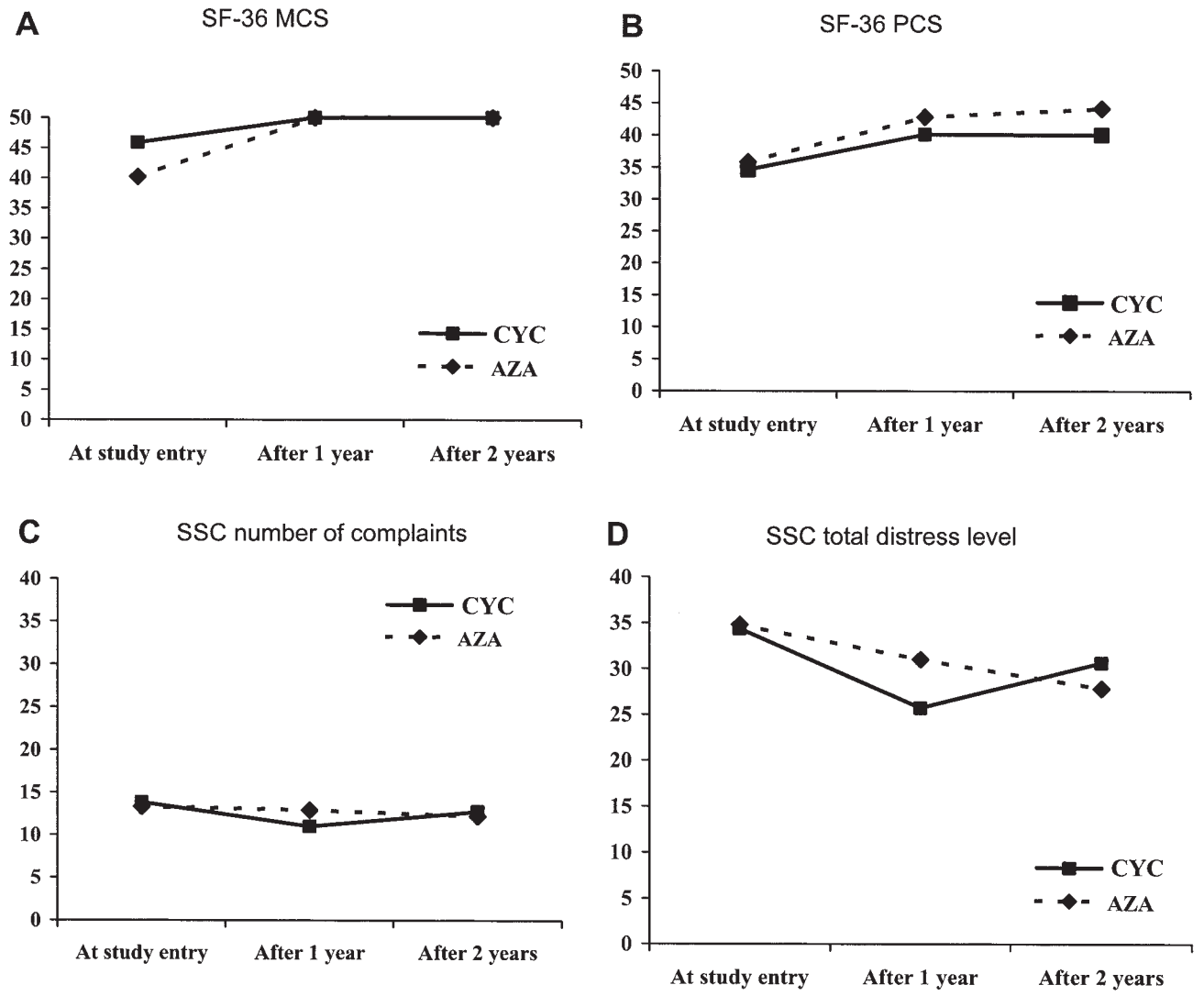

Figure 3. Comparison of SF-36 MCS (A), SF-36 PCS (B), SSC number of complaints (C), and SSC total distress level (D) between patients treated with CYC and AZA.

peutic option for proliferative lupus nephritis. However, we think that this treatment could be an alternative for women who wish to become pregnant and are willing to take the higher risks of renal relapse and infections. Further, MMF or low doses of CYC should also be considered as an alternative to 2 years of CYC treatment.

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REFERENCES

1. Abu-Shakra M, Mader R, Langevitz P, et al. Quality of life in systemic lupus erythematosus: a controlled study. J Rheumatol 1999;26:306-9.
2. Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? J Rheumatol 2005;32:1706-8.
3. Wysenbeek AJ, Leibovici L, Weinberger A, Guedj D. Fatigue in systemic lupus erythematosus. Prevalence and relation to disease expression. Br J Rheumatol 1993;32:633-5.
4. Wang B, Gladman DD, Urowitz MB. Fatigue in lupus is not correlated with disease activity. J Rheumatol 1998;25:892-5.
5. Bruce IN, Mak VC, Hallett DC, Gladman DD, Urowitz MB. Factors associated with fatigue in patients with systemic lupus erythematosus. Ann Rheum Dis 1999;58:379-81.
6. Krupp LB, LaRocca NG, Muir J, Steinberg AD. A study of fatigue in systemic lupus erythematosus. J Rheumatol 1990;17:1450-2.
7. Hanly JG. Disease activity, cumulative damage and quality of life in systematic lupus erythematosus: results of a cross-sectional study. Lupus 1997;6:243-7.
8. Boumpas DT, Austin HA III, Fessler BJ, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. Part 1: Renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease. Ann Intern Med 1995;122:940-50.

9. Berden JH. Lupus nephritis. Kidney Int 1997;52:538-58.
10. Fine DM. Pharmacological therapy of lupus nephritis. JAMA 2005;293:3053-60.
11. Cameron JS. Lupus nephritis. J Am Soc Nephrol 1999;10:413-24.
12. Grootscholten C, Ligtenberg G, Hagen EC, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney Int 2006;70:732-42.
13. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
15. Churg J, Bernstein J, Glassock RJ. Lupus nephritis. Renal disease: classification and atlas of glomerular diseases. New York: Igaku-Shoin; 1995:151-80.
16. de Glas-Vos JW, Krediet RT, Weening JJ, Arisz L. Treatment of proliferative lupus nephritis with methylprednisolone pulse therapy and oral azathioprine. Neth J Med 1995;46:4-14.
17. Boumpas DT, Austin HA III, Vaughn EM, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 1992;340:741-5.
18. Balow JE, Austin HA III, Muenz LR, et al. Effect of treatment on the evolution of renal abnormalities in lupus nephritis. N Engl J Med 1984;311:491-5.
19. Ponticelli C. Current treatment recommendations for lupus nephritis. Drugs 1990;40:19-30.
20. Liebling MR, McLaughlin K, Boonsue S, Kasdin J, Barnett EV. Monthly pulses of methylprednisolone in SLE nephritis. J Rheumatol 1982;9:543-8.
21. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630-40.
22. Ware JE. SF-36 Health Survey. Manual and interpretation guide. Boston: The Health Institute, New England Medical Center; 1993.
23. Aaronson NK, Acquadro C, Alonso J, et al. International Quality of Life Assessment (IQOLA) Project. Qual Life Res 1992;1:349-51.
24. van der Zee K, Sanderman R, Heyink J. De psychometrische kwaliteiten van de MOS 36-item Short Form Health Survey (SF-36) in een Nederlandse populatie. [The psychometric qualities of the MOS 36-item Short Form Health Survey (SF-36) in a Dutch population.] T Soc Gezondheidsz 1993;71:183-91.
25. Pouchot J, De Bandt M, Guillevin L, et al. Psychometric properties of the SF-36 and the AIMS2-SF in patients with systemic lupus erythematosus (SLE). Qual Life Res 1999;8:A153.
26. Gladman D, Urowitz M, Fortin P, et al. Systemic Lupus International Collaborating Clinics conference on assessment of lupus flare and quality of life measures in SLE. Systemic Lupus International Collaborating Clinics Group. J Rheumatol 1996;23:1953-5.
27. Strand V, Gladman D, Isenberg D, Petri M, Smolen J, Tugwell P. Outcome measures to be used in clinical trials in systemic lupus erythematosus. J Rheumatol 1999;26:490-7.
28. Ware JE, Kosinski M, Keller SD. SF-36 Physical and Mental Health Summary Scales: a user's manual. Boston: The Health Institute, New England Medical Center; 1994.
29. Wald FD, Mellenbergh GJ. De verkorte versie van de Nederlandse vertaling van de Profile of Mood States (POMS). [The shortened version of the Dutch translation of the Profile of Mood States (POMS).] Nederlands Tijdschrift voor de Psychologie en haar Grensgebieden 1990;45:86-90.
30. de Groot MH. Psychometrische aspecten van een stemmingsschaal (Verkorte POMS). [Psychometric characteristics of a mood states inventory: Shortened POMS.] Gedrag en Gezondheid 1992;20:46-51.
31. Reddon JR, Marceau R, Holden RR. A confirmatory evaluation of the Profile of Mood States: convergent and discriminant item validity. J Psychopathol Behav Assess 1985;7:243-59.
32. Huiskes CJAE, Kraaimaat FW, Bijlsma JWJ. De ontwikkeling van de IRGL. Een instrument om gezondheid te meten bij patiënten met reuma. [Development of a Dutch health status measure for patients with arthritis.] Gedrag en Gezondheid 1990;18:78-89.
33. Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis. The Arthritis Impact Measurement Scales. Arthritis Rheum 1980;23:146-52.
34. Grootscholten C, Ligtenberg G, Derksen RH, et al. Health-related quality of life in patients with systemic lupus erythematosus: development and validation of a lupus specific symptom checklist. Qual Life Res 2003;12:635-44.
35. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-68.
36. Clarke AE, Petri MA, Manzi S, et al. An international perspective on the well being and health care costs for patients with systemic lupus erythematosus. Tri-Nation Study Group. J Rheumatol 1999;26:1500-11.
37. Vu TV, Escalante A. A comparison of the quality of life of patients with systemic lupus erythematosus with and without endstage renal disease. J Rheumatol 1999;26:2595-601.
38. Wang C, Mayo NE, Fortin PR. The relationship between health related quality of life and disease activity and damage in systemic lupus erythematosus. J Rheumatol 2001;28:525-32.
39. Abu-Shakra M, Keren A, Livshitz I, et al. Sense of coherence and its impact on quality of life of patients with systemic lupus erythematosus. Lupus 2006;15:32-7.
40. Snoek FJ. Quality of life: a closer look at measuring patients' well-being. Diabetes Spectrum 2000;13:24-8.
41. Burckhardt CS, Archenholtz B, Mannerkorpi K, Bjelle A. Quality of life of Swedish women with fibromyalgia syndrome, rheumatoid arthritis or systemic lupus erythematosus. J Musculoskeletal Pain 1993;1:199-207.
42. Greco CM, Rudy TE, Manzi S. Effects of disease activity, pain, and distress on activity limitations in patients with systemic lupus erythematosus. J Rheumatol 2004;31:260-7.
43. Leong KP, Kong KO, Thong BY, et al. Development and preliminary validation of a systemic lupus erythematosus-specific quality-of-life instrument (SLEQOL). Rheumatology Oxford 2005;44:1267-76.
44. Dorsey RR, Andresen EM, Moore TL. Health-related quality of life and support group attendance for patients with systemic lupus erythematosus. J Clin Rheumatol 2004;10:6-9.
45. Tse KC, Tang CS, Lio WI, Lam MF, Chan TM. Quality of life comparison between corticosteroid and mycofenolate mofetil and corticosteroid and oral cyclophosphamide in the treatment of severe lupus nephritis. Lupus 2006;15:371-9.
46. Grootscholten C, Bajema IM, Florquin S, et al. Treatment with cyclophosphamide delays the progression of chronic lesions more effectively than does treatment with azathioprine plus methylprednisolone in patients with proliferative lupus nephritis. Arthritis Rheum 2007;56:924-37.