

Induction therapy with short-term high-dose intravenous cyclophosphamide followed by mycophenolate mofetil in proliferative lupus nephritis

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ABSTRACT

Background: For decades, high-dose intravenous cyclophosphamide (ivCY) given for 24-30 months was regarded as the standard therapy for proliferative lupus nephritis, despite serious side effects. Our aim was to evaluate the effect of induction therapy with short-term high-dose ivCY followed by mycophenolate mofetil (MMF) on disease parameters, mortality and health-related quality of life (HRQoL) in patients with proliferative lupus nephritis.

Methods: Between January 2003 and November 2006, 71 patients with biopsy-proven proliferative lupus nephritis were included in the second Dutch Lupus Nephritis Study. All patients were treated with ivCY (750 mg/m², six monthly pulses) plus oral prednisone, followed by MMF (2000 mg/day) plus oral prednisone for 18 months, and then azathioprine (2 mg/kg/day) plus oral prednisone. Study endpoints included the occurrence of renal relapse, end-stage renal disease (ESRD) and mortality.

Results: After a median follow-up of 3.8 years (range 0.1-4.5), four (5.6%) of the 71 patients had a renal relapse, one (1.4%) failed treatment, one (1.4%) reached ESRD, and two (2.8%) died. Systemic lupus erythematosus (SLE) Disease Activity Index, serum creatinine, proteinuria and antibodies against anti-dsDNA decreased significantly

during treatment and serum levels of complement factor 3 and 4 increased significantly. Furthermore, six of eight domains of the Short Form-36 as well as the number of symptoms and total distress level according to the SLE Symptom Checklist improved significantly over time.

Conclusions: This open-label study shows that induction therapy with short-term (six monthly pulses) high-dose ivCY followed by MMF is effective in preventing renal relapses, ESRD and mortality and improving HRQoL in patients with proliferative lupus nephritis.

KEYWORDS

Cyclophosphamide, lupus nephritis, mycophenolate mofetil, renal relapse, quality of life

INTRODUCTION

For decades, high-dose intravenous cyclophosphamide (ivCY) given for 24-30 months was regarded as standard therapy for systemic lupus erythematosus (SLE) patients with proliferative lupus nephritis. This treatment has been

proven to be highly effective with a renal survival after ten years of approximately 80%.^{1,2} However, long-term high-dose ivCY treatment is burdensome for patients and leads to an increased risk of infections, malignancies and infertility, partly depending on the cumulative dose and age of the patient.^{3,4} Since patients with lupus nephritis are usually young women of childbearing age, infertility is a serious complication which can greatly affect health-related quality of life (HRQoL). Therefore, it is important to search for alternative treatments that are equally effective with respect to renal outcome, but with fewer side effects.

The second Dutch Lupus Nephritis study, which started in 2003, was originally designed as a randomised controlled trial (RCT) comparing induction treatment with short-term high-dose ivCY (750 mg/m², six monthly pulses) followed by mycophenolate mofetil (MMF; 18 months) to the standard regimen consisting of 24 months of high-dose ivCY. Short-term ivCY preceding MMF was chosen because at that time the efficacy of MMF as induction therapy was not established. Furthermore, at the start of the study, long-term follow-up data of low-dose ivCY, as used in the Euro-Lupus Nephritis Trial, were not available. Treatment was continued with MMF for 18 months as the high-dose ivCY National Institute of Health (NIH) scheme also spanned a period of 24 months. After 24 months, immunosuppression was continued with azathioprine.

However, the first data from the Euro-Lupus Nephritis Trial challenged long-term treatment with high-dose ivCY.^{5,6} Moreover, maintenance treatment with MMF was shown to be superior to ivCY, although this was mainly due to a higher than generally observed mortality rate in the ivCY-treated patients.⁷ Hence, the RCT design of the second Dutch Lupus Nephritis study was changed into an open-label cohort design, evaluating the effects of six monthly pulses of ivCY followed by MMF for 18 months. The aim of this open-label study was to investigate the effect of induction therapy with short-term high-dose ivCY followed by MMF on renal function, mortality and HRQoL in patients with proliferative lupus nephritis.

METHODS

Patients

Between January 2003 and November 2006, 71 patients from 20 hospitals in the Netherlands were included in the second Dutch Lupus Nephritis study. All patients were aged between 18 and 70 years, fulfilled ≥ 4 American College of Rheumatology (ACR) criteria for SLE and had active proliferative lupus nephritis, defined as biopsy-proven lupus nephritis (WHO class III or IV, in combination with class V in seven patients; renal biopsy had to be performed less than one year before inclusion), active urinary sediment (> 5 dysmorphic erythrocytes per

high-power field and/or presence of cellular casts) and proteinuria > 0.5 g/day. Patients with active infection, malignancy < 5 years before inclusion (except basal cell carcinoma), pregnancy or refusal to use reliable contraceptives during the first 2.5 years of treatment, or known allergy for the study medication were excluded.

The study was approved by the ethics committee (METC Utrecht) and all patients provided written informed consent according to the Declaration of Helsinki.

Treatment

All patients were treated with ivCY (750 mg/m²) every month for a total of six pulses, in combination with mesna (natrium-2-mercapto-ethane sulphonate) to prevent bladder toxicity (60% of ivCY dose given in three infusions of 100 ml, NaCl 0.9% at -30, 240 and 360 minutes after ivCY). Oral prednisone was added (first month 1 mg/kg/day, second month 0.75 mg/kg/day, third month 0.50 mg/kg/day and then tapered by 5 mg/day every month to 10 mg/day). After six months, treatment was continued with MMF (1000 mg/twice daily) plus oral prednisone (10 mg/day) for 18 months. Subsequently, treatment was continued with azathioprine (2 mg/kg/day) plus oral prednisone (10 mg/day).

All patients were treated with angiotensin-converting enzyme (ACE) inhibitors (preferably enalapril ≥ 10 mg/day or in case of side effects angiotensin-II receptor antagonists; preferably losartan ≥ 50 mg/day), calcium (500 mg/day) and colecalciferol (800 IE/day) supplementation.

Study endpoints

Patients were evaluated monthly during the first five months and then every three months, with a maximum follow-up of four years. The primary study endpoint was the occurrence of a renal relapse. A renal relapse could occur after week 12 and was defined as a nephritic flare: doubling of the lowest obtained serum creatinine so far, and/or a proteinuric flare: development of either nephrotic syndrome (proteinuria > 3.5 g/day) while the lowest protein excretion so far had been repeatedly ≤ 2.0 g/day, or proteinuria > 1.5 g/day without other causes in a previously non-proteinuric patient. Secondary endpoints included treatment failure, end-stage renal disease (ESRD), mortality, treatment toxicity and adverse events (especially infections resulting in hospitalisation and herpes zoster virus infections). Treatment failure was defined as doubling of baseline serum creatinine confirmed on two consecutive visits excluding other causes. Treatment toxicity was defined as discontinuation of treatment due to adverse events which made appropriate dosing of the drug impossible.

In addition, the number of patients achieving response was analysed. Complete response included no disease activity, defined as proteinuria < 0.5 g/24 hours and serum

creatinine within 125% of the baseline value at 5-12 months after the start of induction therapy. Partial response was defined as an improvement not sufficient for the definition of complete response, i.e. reduction of proteinuria of > 50% (and at least < 3 g/24 hours) and serum creatinine within 125% of the baseline value at 5-12 months after the start of induction therapy.⁸

Clinical, laboratory, and HRQoL assessments

At all visits, serum creatinine, proteinuria, anti-double-stranded DNA antibodies (anti-dsDNA), complement factor 3 (C3), complement factor 4 (C4) and current medication were recorded. Anti-dsDNA positivity was assessed according to local standards. Disease activity was measured using the SLE Disease Activity Index (SLEDAI), ranging from 0 to 105.⁹ Furthermore, physicians were asked to score disease activity on a visual analogue scale (VAS; ranging from 0 to 10) at baseline. For both measures, a lower score denotes less disease activity.

HRQoL was assessed yearly with several questionnaires. The SLE Symptom Checklist (SSC) was used to study the presence and perceived burden of both disease-related and treatment-related symptoms. The SSC refers to the past month and consists of 38 symptoms. Each item is scored on a frequency scale, and if the symptom is present, also on a discomfort scale: 4-point Likert scale, ranging from 1 = present, but not burdensome to 4 = extremely burdensome. The total distress level is calculated as the sum of the perceived burden of each symptom present (range 0-152).¹⁰ The Short Form-36 Health Survey (SF-36) was used as a generic measure of HRQoL. It contains 36 questions, evaluating eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. For each domain, the scores are summed and recoded into a scale from 0 to 100, with a higher score representing better functioning and/or fewer limitations.^{11,12} Physical component summary and mental component summary are calculated as summary health scores.¹³

The Dutch shortened version of the Profile of Mood States (POMS) was used to measure emotional well-being. It refers to the past days, including today, and covers one positive and four negative mood states: vigour (5 items), depression (8 items), fatigue (6 items), anger (7 items) and tension (6 items). For each mood state, the scores on a 5-point response format, ranging from 0 = not at all to 4 = extremely, are summed.^{14,15}

An adapted version of the Influence of Rheumatic Diseases on General Health and Lifestyle (IRGL) questionnaire, based on the Arthritis Impact Measurement Scale (AIMS), was used to study the effect of SLE on activities of daily life. For the present study, only the subscales mobility (six items) and impact of disease (ten items) were used. The IRGL refers to the past month. For each subscale,

the scores on a four-point Likert scale, ranging from 1 = almost never to 4 = almost always, are summed. A higher score represents better mobility and more effect of disease, respectively.¹⁶

Statistical analysis

Results were expressed as mean $\pm$ standard deviation (SD) or median (range) for normally distributed and non-normally distributed data, respectively. Generalised estimating equations (GEE) with exchangeable correlation structure were used to analyse clinical, laboratory and HRQoL assessments within subjects over time. GEE is a technique for longitudinal analysis which makes use of all available longitudinal data and allows unequal numbers of repeated measurements.¹⁷ If residuals were

Table 1. Baseline characteristics of 71 patients with proliferative lupus nephritis

Female gender	55 (77%)
Caucasian	53 (75%)*
Age (years)	36.6 $\pm$ 11.7
Time since diagnosis SLE (years)	0.2 (0.0-16.0)
LN as first manifestation	37 (53%)
Hypertension ^a	50 (74%)
Systolic blood pressure (mmHg)	140 (100-190)
Diastolic blood pressure (mmHg)	82 (55-120)
Biopsy WHO class III / IV	18 [†] (25%) / 53 [‡] (75%)
SLEDAI	17 $\pm$ 6
Physician's VAS	7 (0-10)
Serum creatinine (μ mol/l)	93 (53-435)
Anti-dsDNA positivity	57 (89%)
Serum C3 (g/l)	0.55 (0.20-1.66)
Serum C4 (g/l)	0.09 (0.01-0.53)
Low C3/C4	55 (85%)
Proteinuria (g/24h)	2.87 (0.51-19.00)
Hematuria (> 5 RBC/hpf)	64 (91%)
Leukocyturia (> 5 WBC/hpf)	44 (65%)
Cellular casts present	35 (58%)

Values are number (percentage), mean $\pm$ SD or median (range). SLE = systemic lupus erythematosus; LN = lupus nephritis; SLEDAI = SLE disease activity index; WHO = World Health Organisation; VAS = visual analogue scale; anti-dsDNA = anti-double-stranded DNA antibodies; C3 = complement factor 3; C4 = complement factor 4; RBC = red blood cells; hpf = high power-field; WBC = white blood cells; ^asystolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg, or the use of antihypertensive drugs; *non-Caucasian patients were Asian (n = 11) or Black (n = 7); [†]2/18 patients had class III in combination with class V changes; [‡]5/53 patients had class IV in combination with class V changes.

non-normally distributed, parameters were transformed (log, square root or logit) before being entered into the equation. P values < 0.05 were considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA).

RESULTS

The mean age of the 71 patients with proliferative lupus nephritis was 36.6 years (SD±11.7), 77% were female and median time since diagnosis of SLE was 0.2 years (range: 0.0-16.0). All baseline characteristics are shown in *table 1*.

Study endpoints

In February 2009, the median follow-up was 3.8 years (range 0.1-4.5). In total, five (7.0%) of the 71 patients were lost to follow-up (week 13 to 186). During follow-up, four (5.6%) patients had a renal relapse (week 68 to 124), which consisted of doubling of the lowest serum creatinine (nephritic flare) in two patients and of proteinuric flares in two patients. Furthermore, one (1.4%) patient failed treatment (week 117), one (1.4%) reached ESRD (week 87) and two (2.8%) died. Causes of death were sepsis (week 5) and cancer (week 36) (*table 2*). Of note, four of the eight patients with renal relapse, treatment failure, ESRD or mortality were non-Caucasian.

In total, ten patients experienced treatment toxicity from CY (n = 1, patient quit the study; week 3), MMF (n = 1, patient switched to azathioprine), or azathioprine (n = 8, seven patients switched back to MMF and one patient continued with oral prednisone alone). Serious infections occurred in 15 patients, of which eight had a herpes zoster virus infection. In addition to the patient who died from cancer (anaplastic T-cell lymphoma), one other patient developed cancer (testicular seminoma) and five patients suffered from avascular necrosis of the hip (n = 3) or knee (n = 2) during follow-up.

Of the 71 patients, 42 achieved complete response, 15 achieved partial response and six did not achieve complete or partial response after short-term high-dose ivCY. The remaining patients reached a study endpoint within the first five months (n = 2), had no available data on both serum creatinine and proteinuria at baseline and after 5-12 months (n = 4), or were lost to follow-up (n = 2).

After high-dose ivCY, 65 patients switched to MMF plus oral prednisone. After two years, 57 patients switched to azathioprine plus oral prednisone, one patient switched to oral prednisone alone, and two patients stayed on MMF plus oral prednisone (reasons unknown) (*figure 1*).

Clinical and laboratory assessments

SLEDAI score, serum creatinine and proteinuria decreased significantly and serum levels of C3 and C4 increased

Table 2. Proportion of 71 patients with proliferative lupus nephritis reaching study endpoints

Years of follow-up	3.8 (0.1-4.5)
Lost to follow-up	5 (7.0%)*
Renal relapse	4 (5.6%)
- Doubling of lowest serum creatinine	2
- Proteinuric flare	2
- Both	-
Renal relapse rate ^a	1.8
ESRD	1 (1.4%)
Death	2 (2.8%)
Infection rate ^a	7.8
- HZV infection rate ^a	3.8
Responders after 5-12 months ^b	
- Complete response	42 (64.6%)
- Partial response	15 (23.1%)
- No response / study endpoint reached	8 (12.3%)

Values are number (percentage) or median (range) unless otherwise indicated. LN = lupus nephritis; ESRD = end-stage renal disease; ^anumber of patients with a renal relapse or serious infection / 100 patient years; ^bno data were available for six patients; *reasons for lost to follow-up: withdrawal of informed consent; afraid of infertility (week 13), severe psychosis (week 16), protocol violation (week 27), unknown (week 38), and immigration (week 186).

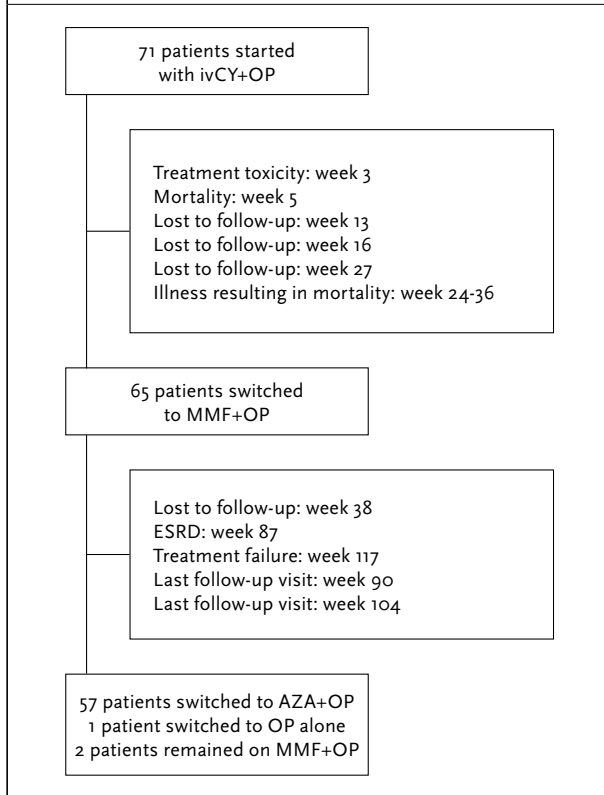
significantly during treatment (*figure 2*). At baseline, 89% of patients had antibodies against anti-dsDNA and this percentage decreased significantly over time (51% after four years of treatment).

The changes in generic and disease-specific HRQoL during follow-up are shown in *figures 3* and *4*, respectively. Data on at least one time point were available for 62 of the 71 (87%) patients, with a median follow-up of 3.0 years (range 0.0-4.1).

Six of the eight domains of the SF-36 (physical functioning, role-physical, bodily pain, social functioning, role-emotional and mental health) as well as the physical component summary improved significantly over time. No overall significant effect of treatment was found on vitality, general health or the mental component summary. For the POMS, tension decreased significantly during treatment, but no significant effect was found on the other mood states.

The number of symptoms and total distress level according to the SSC improved significantly during treatment. Fatigue (92%), painful joints (78%) and chubby cheeks/face (75%) were the most frequently reported complaints at baseline. The percentage of patients who reported to be fatigued decreased only slightly over time (85% after four years of

Figure 1. Flow diagram, showing the number of patients starting intravenous cyclophosphamide (ivCY) plus oral prednisone (OP) for six months, followed by mycophenolate mofetil (MMF) plus OP for 18 months, and then azathioprine (AZA) plus OP



treatment), whereas painful joints and chubby cheeks/face occurred less frequently over time (58% and 46% after four years, $p < 0.01$). Both subscales of the IRGL (mobility and impact of disease) improved significantly over time.

DISCUSSION

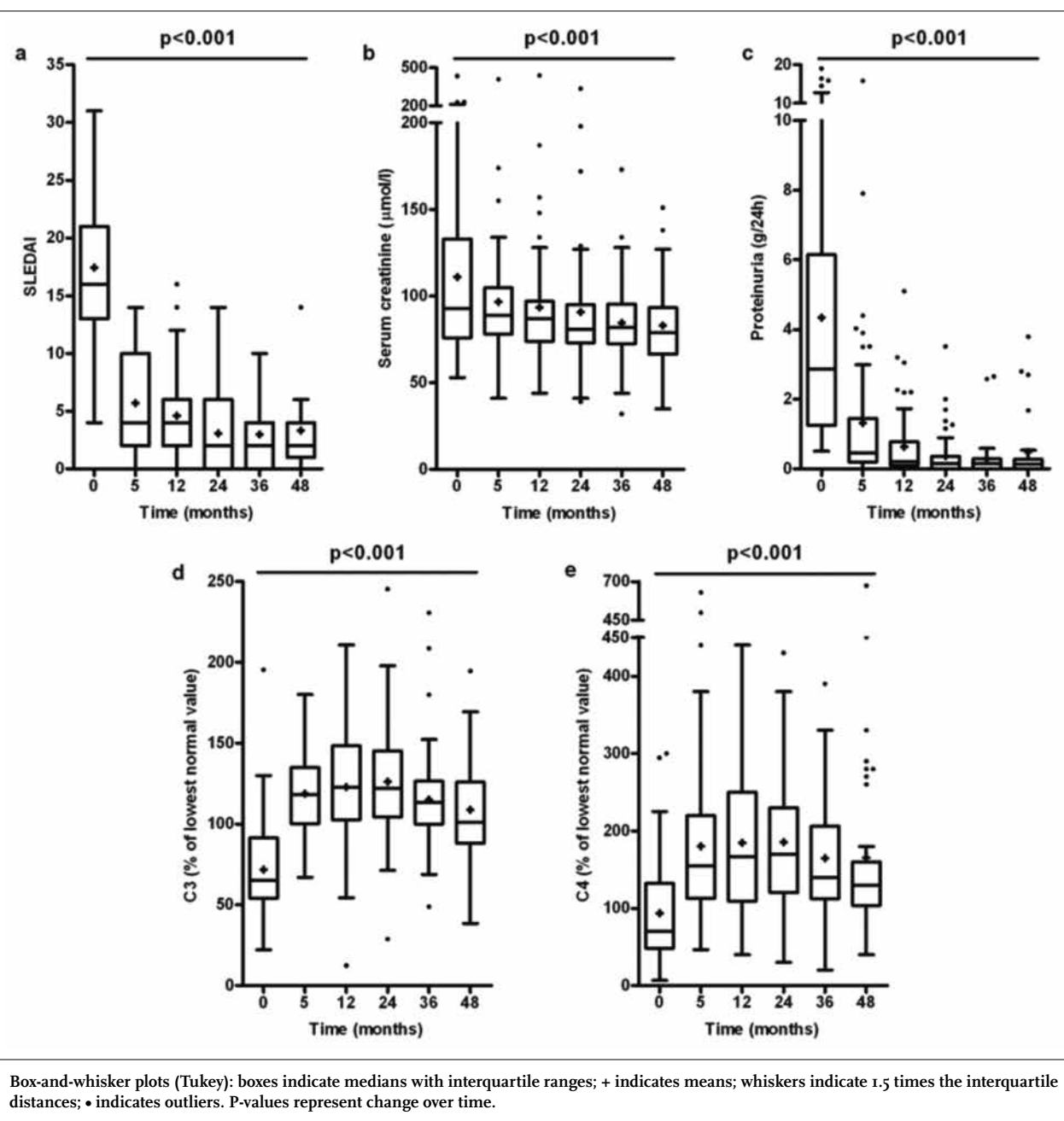
In this report, we present the 45-month follow-up data of the second Dutch Lupus Nephritis study, an open-label study evaluating the efficacy of short-term ivCY (750 mg/m², six pulses) followed by MMF (18 months) and azathioprine in patients with proliferative lupus nephritis. During follow-up, 5.6% of patients had a renal relapse, 1.4% reached ESRD and 2.8% died. In comparison, 4.0% had a renal flare, 0% reached ESRD and 4.0% died during the 5.5 years of follow-up of the first Dutch Lupus Nephritis study, in which patients received ivCY for 24 months (six monthly pulses, as in the present study, and thereafter every three months; in total 13 pulses) followed by azathioprine. All these endpoints were reached within four years. The occurrence of serious infections was also comparable between the two studies.¹⁸

In contrast, Contreras *et al.* reported that short-term ivCY (500-1000 mg/m², median six pulses) followed by MMF or azathioprine was more efficacious and safer than long-term ivCY (median 25 months). During 25-30 months of treatment, renal relapses (based on doubling of the urinary protein : creatinine ratio), ESRD, and mortality occurred in 40%, 10%, and 20% of the patients in the long-term CY group, respectively, compared with 15%, 5%, and 5% in the CY/MMF group and 32%, 0%, and 0% in the CY/azathioprine group.⁷ It is important to note that this study included predominantly Hispanic and Black patients, while our study included mainly Caucasians.

In the last decade, several alternative treatment regimens have been evaluated. The Euro-Lupus Nephritis Trial compared high-dose (500 mg/m² escalating to maximum 1500 mg per pulse, eight pulses) and low-dose (fixed dose 500 mg, six pulses) ivCY followed by azathioprine. During 41 months of follow-up, 29% experienced a severe renal flare (defined as renal impairment based on > 33% increase in serum creatinine within one month, increase in proteinuria, or severe systemic disease), 4% reached ESRD, and 0% died after high-dose ivCY, while this was the case in 27%, 2% and 5%, respectively, of the patients receiving low-dose ivCY.⁵ The ten-year follow-up data confirmed that low-dose ivCY followed by azathioprine is an alternative for the long-term high-dose NIH regimen.¹⁹ The Aspreva Lupus Management Study (ALMS) demonstrated that 24 weeks of induction therapy with MMF was as effective as high-dose ivCY.²⁰ Subsequently, maintenance treatment with MMF was shown to be superior to azathioprine in maintaining renal response and preventing relapses. During the 36-month maintenance phase, renal relapses, ESRD, and mortality occurred in 13%, 0%, and 0%, respectively, of the patients treated with MMF and in 23%, 3%, and 1% treated with azathioprine.²¹ However, one should realise that only patients with a favourable response on induction treatment were randomised at 24 weeks. Our approach of treating all patients with MMF is clinically more relevant, since not all patients will have achieved a therapeutic response at six months. The MAINTAIN Nephritis trial showed comparable efficacy of maintenance treatment with MMF and after short-term ivCY (500 mg, six pulses) combined with methylprednisolone (MP). During 48-month follow-up, renal flares occurred in 19% of the patients in the MMF group compared with 25% in the azathioprine group.²² Therefore, in Caucasian patients, long-term treatment with azathioprine is a good option, as was also observed in our study.

Overall, the percentage of patients who reached ESRD or died during 2-4 years of follow-up was low and comparable between the different ivCY regimens and induction treatment with MMF. The results regarding the occurrence of renal relapse are difficult to compare between the

Figure 2. Clinical and laboratory values during follow-up: (a) SLE Disease Activity Index (SLEDAI), (b) serum creatinine, (c) proteinuria, (d) complement factor 3 (C3), (e) complement factor 4 (C4)

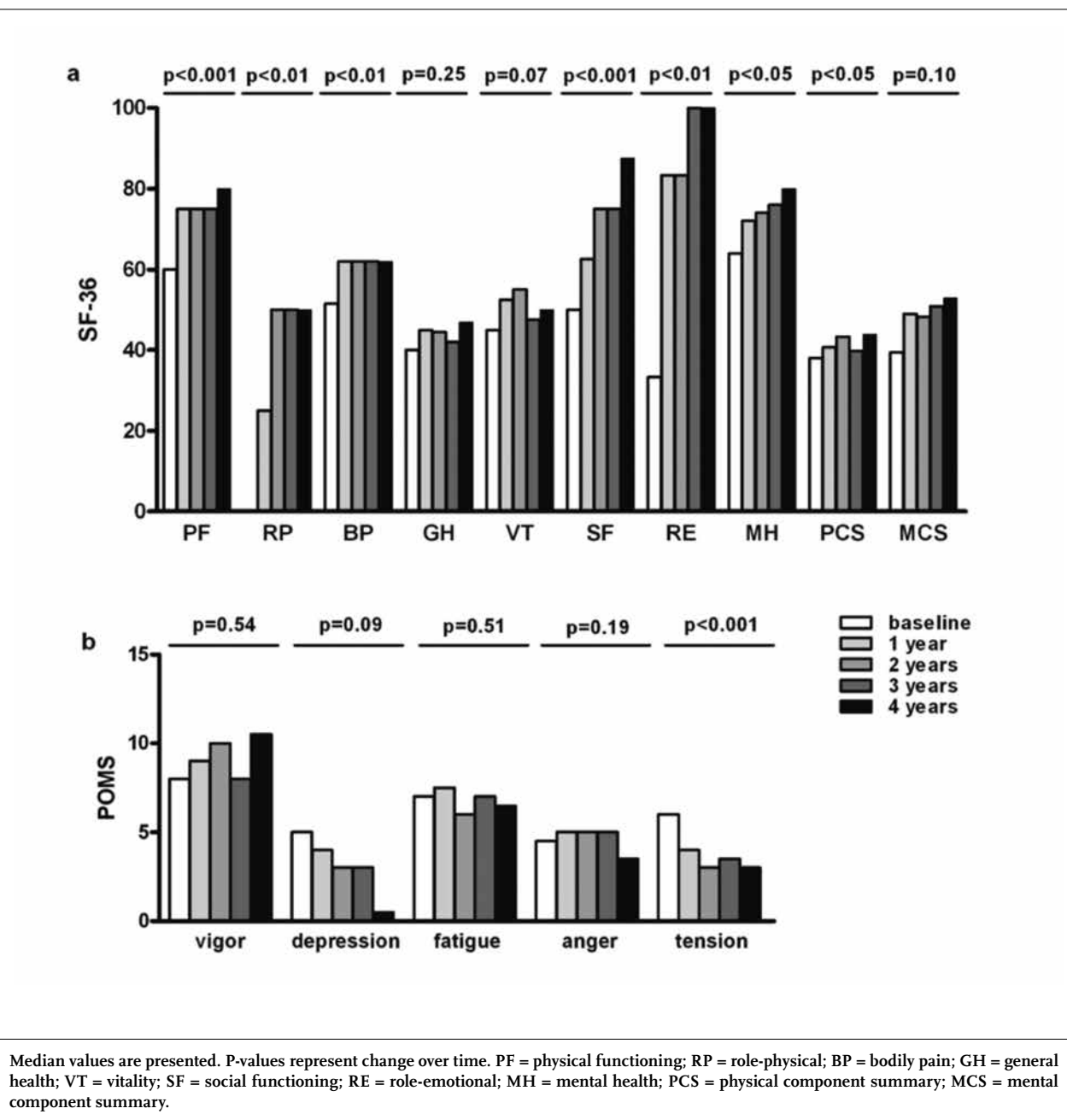


studies due to differences in definitions. All recently published guidelines indicate that induction therapy with ivCY or MMF along with glucocorticoids is recommended for patients with class III or IV lupus nephritis. MMF (2000-3000 mg daily for six months) is preferred over ivCY in African Americans and Hispanics as well as in patients who wish to preserve fertility. Furthermore, low-dose ivCY (500 mg every two weeks for six pulses) is preferred over high-dose ivCY (500-1000 mg/m² once a month for six pulses) in whites with European background.^{8,23,24}

Azathioprine is not recommended as first choice for induction therapy in patients with proliferative lupus nephritis.^{8,23,25} However, our previously published data regarding long-term renal function showed that induction therapy with azathioprine/MP can serve as an alternative for CY in patients with proliferative lupus nephritis who wish to avoid infertility or who have a high risk of premature ovarian failure.²⁶ Furthermore, azathioprine allows pregnancy in contrast to MMF.

Besides the low proportion of patients who reached the study endpoints, we found that short-term ivCY followed by

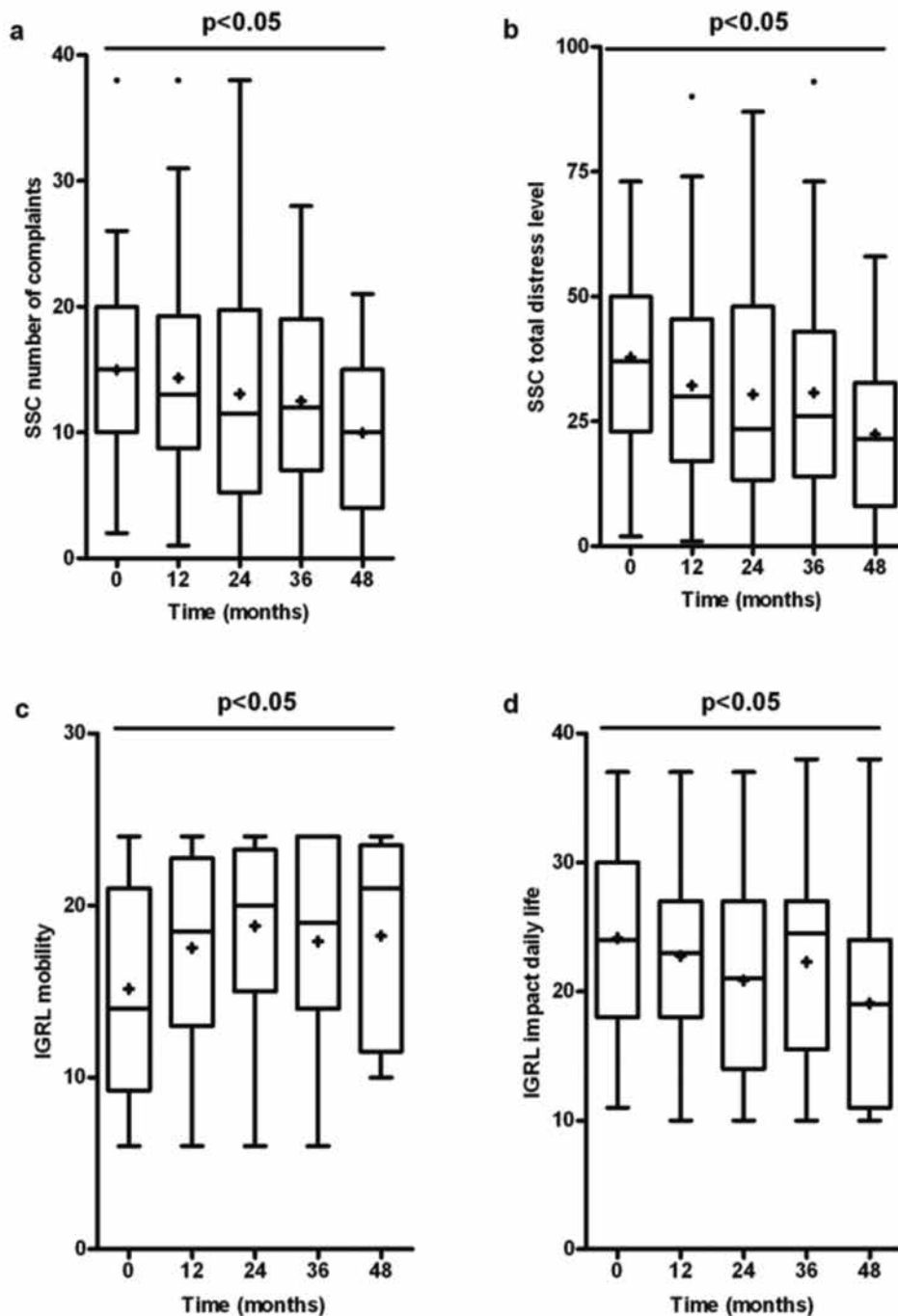
Figure 3. Generic HRQoL during follow-up: (a) Short Form-36 Health Survey (SF-36), (b) Profile of Mood States (POMS)



MMF resulted in significant improvements in all laboratory parameters. But what could be the place for short-term ivCY treatment followed by MMF? On the basis of the current knowledge, one could argue that short-term ivCY/MMF could be given to patients in whom MMF induction treatment fails or to patients who experience a relapse during MMF maintenance treatment. Nowadays, the use of high-dose steroids, as used in the present study, is debated. The recent rituxilup protocol showed good results without the use of oral steroids. This protocol consisted of two doses of rituximab (RTX; 1 g) and MP (500 mg) on days 1 and 15

followed by MMF maintenance treatment (initially 500 mg twice a day, titrated (to a maximum dose of 1.5 g twice a day) to 12 h trough mycophenolic acid levels of 1.2-2.4 mg/l, providing the leukocyte count and gastrointestinal symptoms allowed this).²⁷ The relatively high proportion of patients suffering from avascular necrosis in our study may be related to the high dose of steroids. However, one should realise that osteonecrosis is not uncommon in SLE. In a prospective MRI study, the incidence of steroid-associated osteonecrosis was 37% in the hip and knee joints of SLE patients.²⁸

Figure 4. Disease-specific HRQoL during follow-up: (a, b) SLE Symptom Checklist (SSC), (c, d) Influence of Rheumatic Diseases on General health and Lifestyle (IRGL) questionnaire



Median values are presented. P-values represent change over time.

The Outcome Measures in Rheumatology (OMERACT) recommended that both generic and disease-specific HRQoL instruments should be included in RCTs and longitudinal observational studies in SLE.²⁹ In the present study, we found that short-term ivCY followed

by MMF resulted in a significant improvement in most domains of the SF-36, the most commonly used generic instrument in SLE, as well as in disease-specific QoL measured by the SSC and the IRGL. In agreement with previous studies,³⁰⁻³² fatigue was the most disturbing

symptom and remained present in most patients during treatment.

Three previous studies have investigated the effect of treatment on HRQoL in patients with lupus nephritis. The first Dutch Lupus Nephritis study showed that induction treatment with long-term ivCY or azathioprine resulted in significant improvement of HRQoL. Overall, the scores at baseline as well as the improvement after treatment were comparable with those found in the present study.³¹ Tse *et al.* found that HRQoL, as measured by the SF-36 and World Health Organisation QoL (WHOQoL), was higher during induction treatment with MMF compared with oral CY.³³ Recently, Dalebout *et al.* reported that the Euro-Lupus protocol tends to result in better HRQoL, as measured by SF-36 and SSC, than the NIH protocol.³² In these last two studies, patients were asked to fill in the questionnaires on the basis of recall about the first six months of treatment. Therefore, comparison of the HRQoL scores with those found in our study is difficult.

A limitation of this study is the relatively short follow-up time (median 3.8 years). However, two recent analyses in patient cohorts with comparable ethnic background and clinical characteristics showed that the ten-year follow-up data did not differ from those observed after four years.^{19,26} An additional limitation was that the interpretation of QoL data with respect to the different phases of treatment was limited by the timing of the questionnaires. The questionnaires were sent every 12 months and related to the past months or days (depending on the questionnaire). Therefore, no information was available at six months, prohibiting an evaluation of short-term ivCY on the different domains of HRQoL.

In conclusion, this open-label study shows that induction therapy with short-term (six monthly pulses) high-dose ivCY followed by MMF is effective in preventing renal relapses, ESRD and mortality in patients with proliferative lupus nephritis. The relatively low proportion of patients reaching these study endpoints, together with the significant improvements in laboratory parameters and HRQoL, confirms that induction therapy with short-term high-dose ivCY followed by MMF can be considered in patients with proliferative lupus nephritis. In the current guidelines for treatment of proliferative lupus nephritis, treatment with low-dose ivCY or MMF is first choice. For those who do not adequately respond to induction treatment with these regimens, RTX is recommended. If RTX is unavailable, the current data suggest that high-dose ivCY followed by MMF might be an alternative.

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DISCLOSURES

Competing interests

The authors declare that they have no competing interests.

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