

Oral Cyclophosphamide for Lupus Glomerulonephritis: An Underused Therapeutic Option

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Background and objectives: In our center, systemic lupus erythematosus nephritis is routinely treated with an oral cyclophosphamide (POCY) regimen. PO CY is easy to administer and less expensive than intravenous cyclophosphamide (IVCY) as it is currently used in the United States; however, the use of PO CY has declined in favor of IVCY. Our experience with PO CY suggests that it is well tolerated and consistently associated with good long-term outcomes. Here we report this experience to build a case for maintaining PO CY as a therapeutic option in lupus nephritis.

Design, setting, participants, & measurements: This is a single-center, retrospective analysis of the outcome of 46 patients who had systemic lupus erythematosus with nephritis and were treated with PO CY between 1995 and 2006. PO CY was given for 2 to 4 mo at a dosage of 1.0 to 1.5 mg/kg ideal body weight. After completing PO CY, the patients received either azathioprine or mycophenolate mofetil.

Results: Median follow-up was 23.5 mo, and median duration of PO CY was 4 mo (range 1 to 16 mo). Durable complete or partial remission of proteinuria was achieved in 32 (70%) patients, whereas 5 (11%) progressed to ESRD. Outcomes were comparable in black and white individuals. Adverse effects occurred in fewer than 10% of the cohort, and only four patients discontinued PO CY.

Conclusions: These results suggest that sequential therapy of PO CY followed by azathioprine or mycophenolate mofetil is comparable to IVCY regimens but that efficacy may not be affected by race.

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In the United States, induction therapy for the treatment of severe systemic lupus erythematosus (SLE) nephritis is mainly done with intravenous pulses of cyclophosphamide (IVCY) or oral mycophenolate mofetil (MMF). There seems to be no difference between IVCY or MMF for induction (1). Oral cyclophosphamide (POCY) is generally not considered for routine clinical use for lupus nephritis, although PO CY is routinely used by both nephrologists and rheumatologists in the treatment of ANCA-associated renal vasculitis. The scientific basis of this practice is not clear (2). The original direct comparison between IVCY ($n = 20$) and PO CY ($n = 18$) for lupus nephritis was a small study and showed no significant difference in outcome but did find that 17% of the PO CY patients developed cystitis, whereas none of the IVCY arm had this complication (3). PO CY was thus perceived as having greater toxicity than IVCY; however, the dosage and the duration of cyclophosphamide therapy in the original trial of IVCY versus PO CY were far greater than those currently recommended for either IVCY or PO CY.

A potential advantage of PO CY over IVCY is its greater convenience of administration and less cost. In the United States, PO CY costs approximately \$340 per month or \$1000 per course, compared with approximately \$1400 per month or \$9800 per course for IVCY. The direct cost of IVCY includes the drug, intravenous equipment, nursing care, and physician supervision (4). IVCY can also incur indirect costs, such as loss of a day's work to come to an infusion center.

Once IVCY is given, its effects are large, irreversible, and present for a prolonged period. Although the white blood cell nadir is generally manageable, in the setting of reduced kidney function, as often occurs in lupus nephritis, IVCY administration is more difficult. It is suggested that the dosage of IVCY be reduced by 20 to 30% in patients with moderate to severe renal insufficiency, but even with this adjustment, the clearance of cyclophosphamide is variable (5), and increased exposure could lead to serious leucopenia. By contrast, PO CY can be stopped promptly and its effects reversed more quickly. This is a major advantage if an infection or severe leucopenia develops.

In this report, we present our single-center experience with 46 patients to demonstrate that PO CY is clinically effective and has manageable adverse effects. We suggest that a short course of PO CY is a relevant but underused therapy for SLE nephritis, especially in black patients, who seem to respond less well than white patients to IVCY (1,3,6).

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Materials and Methods

Study Design

This is a retrospective analysis of patients who were prescribed POCY by the Ohio State University Nephrology Division for lupus nephritis between 1995 and 2006. Patients gave informed consent, and the Declaration of Helsinki guidelines were observed. Efficacy of POCY was determined by changes in serum creatinine and proteinuria during the entire period of follow-up after the start of POCY. Return of serum creatinine to normal (≤ 1.0 mg/dl in women; 1.2 mg/dl in men) or to the patient's baseline serum creatinine was defined as a creatinine remission. Baseline serum creatinine was defined as the average of all of the values (minimum of two values) in the 6 mo preceding the renal flare. A decline in serum creatinine $\geq 25\%$ but not to normal was defined as a creatinine improvement. Proteinuria rate was measured as the protein-to-creatinine (PC) ratio of a 24-h urine collection. Remission of proteinuria was defined as a PC ratio < 0.5 . Improvement in proteinuria was defined as a decrease in PC ratio of $\geq 50\%$ but not to < 0.5 . For those with nephrotic-range proteinuria (PC ratio ≥ 3), improvement required a $\geq 50\%$ reduction in PC ratio and a PC ratio < 3.0 but > 0.5 . For complete remission of the flare, the PC ratio had to decrease to < 0.5 and the serum creatinine had to return to normal or the patient's preflare baseline.

Patients

Between 1995 and 2006, 46 patients with severe, biopsy-proven SLE glomerulonephritis were treated with POCY to induce remission of their kidney disease. At our institution, POCY has been the standard treatment for severe SLE nephritis, and all patients were offered this regimen without selection. Some patients refused cyclophosphamide and were given other initial therapies. The cohort treated with POCY consisted of 43 women and was 52% black, 43% white, 2% Hispanic, and 2% Asian. The median follow-up was 23.5 mo (range 6.0 to 31.0 mo). The majority (87%) of these patients also had data from 1 to 6 mo before POCY was given, so baseline serum creatinine and proteinuria levels could be established. All of these patients had serum creatinine data for the duration of follow-up, but four patients did not have sufficient proteinuria data during follow-up to judge the effect of therapy on proteinuria.

Treatment Regimen

Oral prednisone was begun usually at 1 mg/kg ideal body weight (IBW) per d, with a maximum dosage of 80 mg/d. For those who were judged to have particularly severe disease, with a rapid decline in renal function (an increase in serum creatinine of > 1 mg/dl, or 1.5 mg/dl if baseline was > 2 mg/dl), intravenous bolus methylprednisolone was used for the first 1 to 3 d. The prednisone dosage was tapered as described previously (7). POCY was started at 1.0 to 1.5 mg/kg IBW per d (maximum dosage 150 mg/d) and continued usually for 2 to 4 mo, depending on the response at 2 mo. If patients were not improving by 2 mo, then POCY was continued for another 1 to 2 mo, although a handful of patients received POCY for > 4 mo. In many of these patients, compliance was an issue, and the POCY was taken only intermittently or not at all, despite its being prescribed. After stopping POCY, the patients were continued on MMF (1.5 to 2.0 g/d) or azathioprine (AZA; 1.5 to 2.0 mg/kg IBW per d) as maintenance therapy. Maintenance therapy was continued until the patients were in complete remission for at least 1 yr. At that point, the drugs were tapered slowly during the next 2 yr if the patient remained in complete remission.

To protect fertility during POCY, women were offered prophylaxis with leuprolide and men were offered prophylaxis with testosterone (8,9). Leuprolide was given intramuscularly at a dosage of 3.75 mg

every 4 to 6 wk. Testosterone was given at a dosage of 100 mg intramuscularly every 2 wk, both for the duration of cyclophosphamide therapy. When gonadal suppression was used, the start of POCY was delayed until the suppression had been in place for approximately 2 wk; however, when it was determined that the SLE nephritis was too severe to delay cyclophosphamide therapy ($n = 6$ in this cohort), the patient was given an initial dose of IVCY (500 to 750 mg/m²), and hormonal therapy was started 3 d later, after 15 cyclophosphamide half-lives had elapsed. POCY was then started 3 to 4 wk later.

For mitigation of cyclophosphamide-associated bladder toxicity (cystitis and cancer), the dosage and duration of cyclophosphamide were limited (10). In addition, patients were instructed to take cyclophosphamide in the morning and to drink an extra glass of fluid with each meal and at bed time. Patients also received kidney and cardioprotective therapies, including strict BP control, renin-angiotensin system blockade, statin therapy, and dietary sodium and protein restriction (11,12).

Statistical Analysis

Comparison of proteinuria and serum creatinine data between responders and nonresponders was done by the Mann-Whitney test. Survival analysis by the log-rank method of χ^2 calculation was used to analyze differences in time to improvement between black and white patients. Evaluation of the proportion of black or white patients in the responder and nonresponder groups was done by Fisher exact test.

Results

Patient Characteristics

Baseline clinical characteristics and a treatment summary of the patients are given in Table 1. There were no significant differences between ethnic groups except that white patients had a significantly lower level of complement component 4 (C4) than did black patients. The higher frequency MMF after POCY in the white patients mainly reflected insurance disparities for the coverage of MMF. The 10 patients with class V glomerulonephritis were treated before we and others showed that MMF could be used successfully to treat membranous lupus nephritis (13,14).

Proteinuria and Serum Creatinine Responses

The proteinuria and serum creatinine responses are summarized in Table 2. The time course of improvement in renal function and proteinuria is shown in Figure 1. Comparison between the white and black cohorts is shown in Figure 2. All patients had abnormal proteinuria levels at treatment initiation, and most improved with therapy. Specifically, 76% showed an improvement in PC ratio, whereas 14.6% maintained a stable level of proteinuria long term. Of the patients who improved, 61% (45% of total cohort) had a complete proteinuria remission. Only 54% of the cohort began therapy with an elevated serum creatinine, and 72% of these improved with treatment. Of the patients who improved, 72% (28% of total cohort) had a complete serum creatinine remission. A number of patients ($n = 18$; 39%) had at treatment initiation a normal serum creatinine level that remained stable over time. This was also considered a positive outcome. Complete SLE nephritis remission required that both the PC ratio and serum creatinine criteria of complete remission be met. This occurred in 35% of the cohort.

Table 1. Clinical characteristics of the cohort at initiation of POCY

Characteristic	White	Black	Asian	Hispanic
Male (<i>n</i> [%])	20 (2)	24 (1)	1	1
Age (yr; median [range])	33.0 (20.0 to 67.0)	29.5 (20.0 to 49.0)	32.0	22.0
Biopsy, WHO class (<i>n</i> [%])				
III	5 (25.0)	2 (8.3)		
IV	10 (50.0)	14 (58.0)	1	1
V	3 (15.0)	7 (29.0)		
unknown	2	1		
SCr (mg/dl; median [range])	0.94 (0.60 to 4.40)	1.18 (0.52 to 5.50)	1.49	2.15
PC ratio	3.60 (0.98 to 10.10)	3.10 (0.74 to 16.50)	6.30	2.50
C3 (mg/dl; median [range])	71.0 (27.0 to 126.0)	66.5 (5.0 to 208.0)	58.0	68.0
C4 (mg/dl; median [range])	9.5 (2.0 to 21.0)	13.0 (5.0 to 55.0) ^a	11.0	8.0
Initial dosage of CYC (mg/kg per d; median [range])	1.3 (0.7 to 1.9)	1.4 (0.5 to 1.7)	1.2	1.5
Duration of CYC (mo; median [range])	3.5 (1.0 to 8.0)	4.0 (1.0 to 16.0)	5.0	2.0
Total dosage of CYC (g; median [range])	9.0 (3.0 to 22.0)	10.5 (3.0 to 38.0)	15.0	6.0
MMF after CYC (% of patients)	71	55	0	100
AZA after CYC (% of patients)	29	45	100	0

CYC, cyclophosphamide; SCr, serum creatinine; WHO, World Health Organization.

^a*P* = 0.04 between black and white patients

Short- and Long-Term Follow-up

During follow-up, only six patients experienced renal flares, as previously defined (15). In these six patients, the median time to flare was 16 mo (range 9 to 29 mo). The rest remained in complete or partial remission throughout the duration of observation (4 to 31 mo). Kidney function deteriorated in six patients, and five of these went on to hemodialysis. Each of the patients with ESRD was highly noncompliant with medications. Seven patients did not improve but did maintain stable serum creatinine and proteinuria for a median of 21 mo (range 8 to 31 mo). Of these, four had normal serum creatinine values.

Several patients from this cohort had more recent serum creatinine and proteinuria data available. Those with long-term observations (3 to 10 yr after the data reported in Figure 1) are shown in Figure 3. As can be seen, the initial improvement was generally maintained.

Clinical and Demographic Factors and Outcome

Age at the time of treatment initiation did not influence outcome. The number of patients who worsened was small, making it difficult to determine the effect of baseline proteinuria and serum creatinine on outcome with certainty. Nonetheless, serum creatinine and the level of proteinuria at the beginning of treatment did not seem to be different between the group that showed improvement in proteinuria and the group that showed worsening of proteinuria (Mann-Whitney test). Similarly, the initial levels of serum creatinine and proteinuria did not seem to be different between the group that showed an improvement in serum creatinine and the group that showed a decline in kidney function (Mann-Whitney test). With respect to immunosuppression after POCY, 70% of patients who received AZA and 65% of patients who received MMF had a

complete or partial remission (not significantly different, Fisher exact test).

Black and white patients responded equally well in terms of improvement and remission of serum creatinine and proteinuria (Table 2, Figure 2). Twelve months after treatment initiation, 54% of black patients and 60% of the white patients had achieved a complete or partial remission. Using the log-rank method of χ^2 calculation, survival analysis across race shows no statistical difference between months to improvement for black versus white patients (*P* = 0.68). Although the majority of patients whose disease worsened over time were black, the total number of patients whose disease worsened was small, and compared with patients whose disease improved, there was not a significant association between outcome and race (Fisher exact test).

Adverse Events

The adverse events encountered during follow-up are presented in Table 3. As expected, leucopenia and infections were the most frequent adverse events, followed by gastrointestinal intolerance. Nevertheless, POCY was discontinued in only four patients. The indications for discontinuation were pneumonia (1), anemia (1), thrombocytopenia (1), and gastrointestinal intolerance (1). In six patients, POCY was temporarily held and restarted, or the dosage was decreased. The reasons for temporarily holding or decreasing the dosage were pneumonia (1), gastrointestinal intolerance (1), viral syndrome (1), and leucopenia (3). Amenorrhea occurred in only 2.2%. No hemorrhagic cystitis or malignancies occurred. One patient died 9 mo after completing cyclophosphamide, while receiving AZA and prednisone. Death was the result of severe pulmonary hypertension attributed to antiphospholipid syndrome.

Table 2. Changes in proteinuria and serum creatinine after induction with POCY

Change in Proteinuria or SCr	n	Age (yr; Median [Range])	% White	% Black	Duration of CYC (mo; Median [Range])	Total Dosage of CYC (g; Median [Range])	SCr (Median [Range]) ^a	PC Ratio (Median [Range]) ^b	Time to Improvement (mo; Median [Range]) ^c	Time to Remission (mo; Median [Range]) ^d
Proteinuria improved	32	29.5 (20.0 to 59.0)	38	56	4.0 (1.0 to 8.0)	10.0 (3.0 to 19.5)	1.07 (0.52 to 4.40)	3.4 (0.9 to 16.5)	5 (1 to 16)	9 (2 to 26); n=19 ^e
Proteinuria remained stable	6	33.0 (24.0 to 46.0)	66	33	3.5 (2.0 to 8.0)	8.3 (4.5 to 12.0)	0.85 (0.60 to 1.07)	2.3 (0.7 to 9.1)		
Proteinuria worsened	4	25.0 (20.0 to 32.0)	25	75	5.5 (4.0 to 16.0)	13.3 (10.5 to 38.3)	2.30 (0.60 to 5.50)	1.9 (1.0 to 6.9)		
SCr improved	18	35.0 (20.0 to 67.0)	50	44	3.5 (1.0 to 8.0)	10.3 (3.0 to 19.5)	1.60 (0.70 to 2.60)	3.7 (1.2 to 15.2)	4.5 (1 to 16)	7 (2 to 19); n=13 ^f
SCr remained stable	22	31.0 (20.0 to 59.0)	45	55	3.0 (1.0 to 9.0)	9.0 (3.0 to 22.5)	0.81 (0.50 to 4.40)	3.3 (0.7 to 16.5)		
SCr worsened	6	26.0 (20.0 to 45.0)	17	83	5.8 (4.0 to 16.0)	13.3 (9.0 to 38.3)	1.80 (0.60 to 5.50)	2.2 (1.0 to 6.9)		

^aSCr (mg/dl) at the time CYC was started.
^bTwenty-four-hour urine PC ratio at the time CYC was started.
^cTime to improvement in proteinuria or SCr (see the Materials and Methods section for definition of improvement).
^dTime to complete remission of proteinuria or renal insufficiency (see the Materials and Methods section for definition of complete remission).
^eNumber of improved patients who also met the definition of complete remission of proteinuria.
^fNumber of improved patients who also met the definition of complete remission of renal insufficiency.

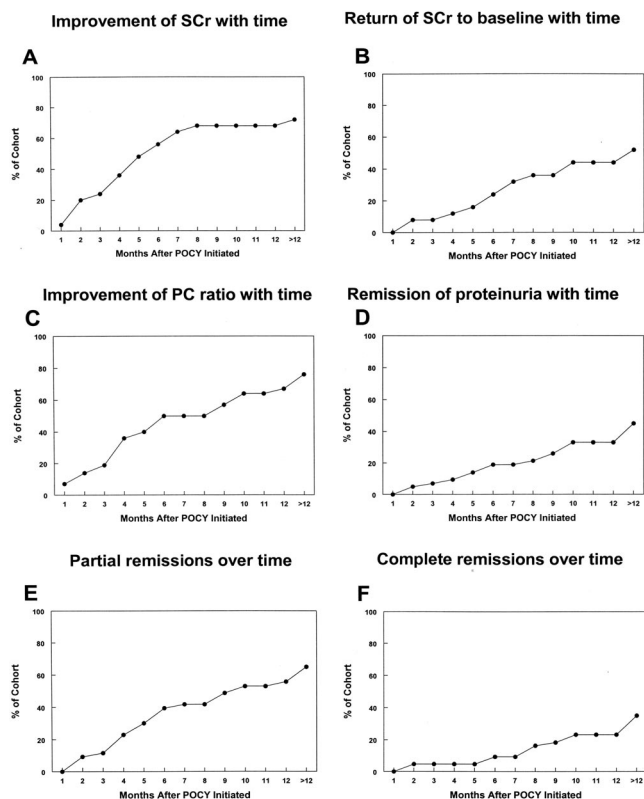


Figure 1. (A through F) Time course of improvement in serum creatinine and proteinuria after starting POCY. The results are expressed as the percentage of the cohort that had either improved (A, C, and E) or entered remission (B, D, and F) as a function of duration of cytotoxic therapy. The time point >12 mo indicates the interval between 13 and 26 mo after the initial dose of cyclophosphamide. SCr, serum creatinine.

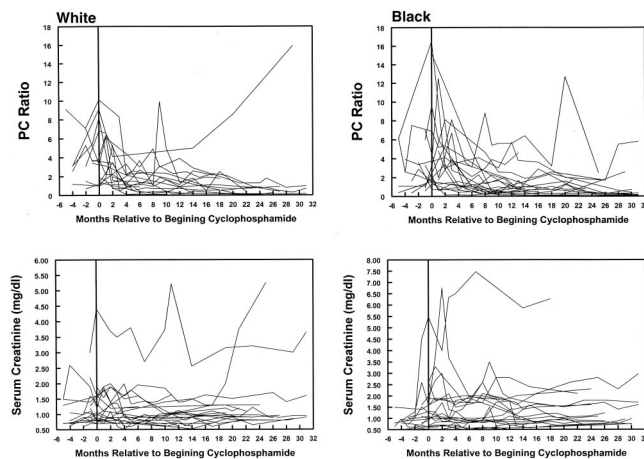


Figure 2. Trends in proteinuria and renal function for individual patients. The cohort is divided into white and black groups. The response to sequential therapy with POCY and MMF/AZA was comparable in white and black patients.

Discussion

This is one of the largest reported single-center experiences on the use of POCY in the management of SLE nephritis. It is

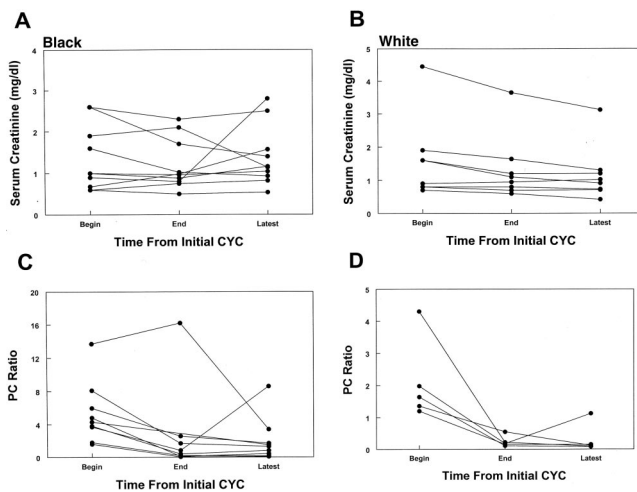


Figure 3. (A through D) Individual long-term serum creatinine and proteinuria outcomes in the black (A and C) and white (B and D) groups of this study. Long-term refers to serum creatinine and PC ratios measured ≥ 3 yr (range 3 to 10 yr) beyond the last measurements shown in Figure 2, designated “End.” Black and white patients have similar long-term outcomes to sequential therapy with POCY and MMF/AZA. CYC, cyclophosphamide.

Table 3. Adverse events during treatment

Adverse Event	N	% of Cohort
Leucopenia	4	8.7
Nausea/anorexia/diarrhea	3	6.5
Pneumonia	2	4.3
Viral syndrome	2	4.3
Anemia	1	2.2
Thrombocytopenia	1	2.2
Amenorrhea	1	2.2

different from most other studies of oral cyclophosphamide because the regimen used a lower dosage and a shorter duration of POCY, similar to the regimen used by the Lupus Nephritis Collaborative Study Group (16). Although a small number of patients were outliers in terms of duration and cumulative dosage of POCY, the intended short course, lower dosage regimen was achieved in the majority of patients. Our experience suggests that this regimen is effective in inducing complete or partial remission of proteinuria and renal dysfunction and does not seem to depend on age, race, baseline level of proteinuria, or serum creatinine. Furthermore, adverse events that required discontinuation of POCY occurred in fewer than 10% of the patients. Hemorrhagic cystitis and malignancy were not seen, and no deaths were attributable to POCY.

These data provide a timeline for the expected therapeutic responses in SLE nephritis to sequential therapy with POCY and MMF or AZA. In general, improvement in proteinuria and serum creatinine is seen by 4 to 5 mo, and improvement tends to continue during the maintenance phase. Only 15% of the

cohort experienced an increase in serum creatinine. ESRD was observed but only in the few patients who were severely non-compliant with POCY. Noncompliance was not generally attributable to intolerance of POCY. Noncompliant patients who require cyclophosphamide therapy should be considered for IVCY to ensure that treatment is received.

Treatment of lupus nephritis with POCY is common in other countries. Complete responses are reported in 57 to 82% of patients at 12 to 24 mo (10,17–20). This is higher than the complete remissions of 23% at 12 mo in this cohort; however, it is difficult to make direct comparisons among these studies because the definitions of complete and partial remission differ and sometimes were less stringent (17,18). Also, these studies involved Asian patients, whose SLE nephritis may respond more favorably to therapy. Another difference is that the previously reported POCY regimens continued for ≥ 6 mo *versus* our usual course of 2 to 4 mo and at dosages up to 2.5 mg/kg per d, as opposed to 1.5 mg/kg per d. Not surprising, serious adverse events that were attributable to cyclophosphamide were higher in previous POCY studies, which reported a 10 to 30% incidence compared with $<10\%$ of our cohort.

The most common current practice in the United States for treating severe SLE nephritis is to use IVCY monthly at 0.5 to 1 g/m² for 6 mo, followed by AZA or MMF. The outcome of our POCY regimen compares favorably to this IVCY regimen. In five IVCY trials, the proportion of complete and partial responders at 6 mo was approximately 45% (range 25 to 83%) (1,21–24), similar to the 42% 6-mo and the 60.5% 12-mo responses seen in this study. The types of adverse events with IVCY that were observed in these studies were similar to POCY, but, in general, the IVCY regimens were associated with a higher incidence of severe infection (5 to 8%), gastrointestinal disturbances (25 to 46%), and leucopenia (20%).

A true low-dosage IVCY regimen developed in Europe also compares favorably to the standard US IVCY protocol (25,26) but thus far has not been widely used in the United States. In this Euro-Lupus regimen, IVCY is given at a dosage of 500 mg every 2 wk for six doses, and then patients are switched to AZA. Euro-Lupus resulted in a higher percentage of remissions and a lower incidence of severe infections than standard IVCY, although the differences were NS (25). Importantly, the Euro-Lupus regimen was not inferior to standard IVCY, and long-term outcomes were similar (26). In both Euro-Lupus and our POCY regimen, patients are given more intense cytotoxic therapy at the beginning of treatment, when the disease is presumably most active. It is interesting to speculate that this may be why these regimens are successful.

With regard to race and the efficacy of cyclophosphamide in SLE nephritis, several investigations showed better outcomes for white compared with black or Hispanic patients (1,6,27); however, these studies used IVCY. The patients in the Euro-Lupus trial were mainly white, so differential efficacy according to race cannot be assessed (25). Using short-course POCY, our black patients responded as well as the white patients. Although this study was not powered to show this outcome conclusively, it raises the question of whether POCY may be superior to IVCY in black patients with lupus nephritis.

Induction therapy with oral MMF has recently challenged sequential cyclophosphamide therapies for the initial management of severe lupus nephritis. Prospective studies that compared cyclophosphamide with MMF have thus far demonstrated no benefit of MMF over IVCY (1) or POCY (19,20), as measured by complete or partial remissions or time to response. Also, MMF and IVCY cohorts showed similar profiles and incidences of serious adverse events (*e.g.*, infections, mortality). By contrast, POCY at 2.5 mg/kg per d for 6 mo was associated with a significantly greater incidence of serious adverse events than MMF, including leucopenia, all infections, and serious infections. Furthermore, both the POCY and IVCY groups tended to have more adverse effects overall than the MMF groups. The unfavorable adverse event profiles of IVCY and POCY seem to be major factors in the emerging preference of MMF over any form of cyclophosphamide for the initial treatment of SLE nephritis; however, although there have been no direct comparisons of MMF with the POCY regimen used here, our data suggest that this regimen would be comparable to MMF. Also, it cannot be assumed that short-course POCY will have less efficacy than a traditional POCY regimen. Indeed, traditional POCY (and IVCY; see Euro-Lupus discussion) regimens may provide more cyclophosphamide than is needed, exposing patients to increased risk without increased benefit (2,25,26).

Conclusions

We provide evidence that short-course POCY followed by AZA or MMF is an effective sequential treatment regimen for severe SLE nephritis. Black and white patients respond equally well, as do patients with impaired renal function and heavy proteinuria. Furthermore, the adverse effect profile of POCY is comparable to MMF. These findings, coupled with the ease of administration and lower cost, suggest that limited-dosage, short-course POCY is a relevant treatment option for SLE and may be a superior choice for black patients than IVCY. We acknowledge that this study is limited because it is retrospective and did not directly compare POCY with IVCY; however, given the recent failures of several large, randomized clinical trials to find more effective new therapies for SLE nephritis, it will be important to learn how best to use available treatments such as cyclophosphamide. In this regard, we suggest that further study of POCY to determine optimal dosage and duration is warranted.

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Disclosures

None.

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