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Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide

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Background. Long-term intravenous cyclophosphamide (IVC) in combination with corticosteroids is standard therapy for proliferative lupus nephritis, but it has limitations. There are few data on long-term remission rates, predictors of relapse, and the ability to achieve a second remission with currently recommended IVC regimens.

Methods. A cohort of 85 patients with proliferative lupus glomerulonephritis (focal $N = 33$, diffuse $N = 52$) treated with IVC was assembled in three institutions. Timing and predictors of remission, relapse, and re-remission were evaluated with Kaplan–Meier analyses and Cox models.

Results. The median time to remission was 10 months, whereas an estimated 22% of patients had not remitted after 2 years. The median time to relapse among 63 patients who had achieved remission was 79 months. In multivariate models, adverse predictors of remission were a delay in the initiation of therapy from the time nephritis was clinically diagnosed [hazard ratio (HR) 0.58, $P = 0.063$] and a higher amount of proteinuria (HR 0.86 per 1 g/24 hours, $P = 0.014$). Predictors of earlier relapse for patients entering remission included a longer time to remission (HR 1.029 per month, $P = 0.025$), a history of central nervous system involvement (HR 8.41, $P = 0.002$), and World Health Organization histology ($P = 0.01$). Among the 23 patients who relapsed during follow-up, the median time to re-remission was 32 months, and with three exceptions, all patients took substantially longer time to remit the second time compared with their first remission ($P = 0.01$). The time to re-remission was longer in patients who had taken longer to remit the first time (HR 0.979 per month, $P = 0.16$), in patients who had relapsed earlier after the first remission (HR 1.071 per month, $P = 0.002$), and in those with evidence of chronicity in the original kidney biopsy ($P = 0.015$).

Conclusions. Prolonged courses with a cumulative risk of toxicity are needed to achieve remission in many first-treated patients and in most patients treated for a second time. The optimal management of patients with identified adverse predictors of response needs further study.

Key words: lupus nephritis, systemic lupus erythematosus, cyclophosphamide.

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Nephritis is one of the most important causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE) [1]. The most popular therapeutic regimen, particularly for proliferative glomerulonephritis, consists of long-term pulses of intravenous cyclophosphamide (IVC) [2–6] in combination with corticosteroids. This regimen has been shown to be effective in both observational studies and randomized trials, and most patients respond initially to this regimen. However, some investigators have also drawn attention to the limitations of IVC, including toxicity during long-term use [7] and the possibility of relapses [8, 9]. The optimal duration of therapy that would minimize relapses without substantially increasing toxicity is not known. More importantly, there is little evidence on how soon patients who relapse may enter into remission for a second time. Although there are several reports on predictors of long-term outcomes [including end-stage renal disease (ESRD) and death] [10–13], there is inadequate knowledge about predictors of relapse and the ability to achieve a second remission among patients with proliferative nephritis treated with currently recommended IVC regimens. Such information would be important to obtain because it would offer some guidance on what a clinician could expect in trying to establish a second remission in patients who have relapsed after IVC therapy. In order to yield insight into these issues, this study performed predictive modeling in a large cohort of patients with proliferative lupus nephritis treated with IVC.

METHODS

Study cohort

All patients with biopsy-documented diagnosis of proliferative lupus nephritis (World Health Organization types III or IV [14]) treated with IVC at the Department of Pathophysiology, University of Athens, the affiliated Eugenidion Hospital, and the University Hospital of the University of Ioannina School of Medicine until December 1998 were included in this analysis. Additional detailed information on patients who had started IVC elsewhere before their first visit was obtained from medical records.

The typical regimen used in the study cohort was prednisone (0.5 mg/kg daily) for four weeks, with gradual tapering to the minimum dose required for control of extrarenal manifestations and intravenous infusions of cyclophosphamide (0.75 to 1.0 g/m^2) monthly for up to six months and then once every two months for 12 months and then every three months for another 18 months. Continuation of treatment beyond the three years was up to the physician's discretion. Upon signs of relapse or deterioration, monthly administration of IVC was reintroduced. Deviations from this regimen could be due to patient preferences, toxicity, and noncompliance.

Definitions

Clinical evidence of nephritis required the presence of proteinuria ($\geq$0.5 g/24 hours) or an active urine sediment (>8 to 10 erythrocytes per high power field; or casts). The diagnosis was documented by biopsy (light microscopy and immunofluorescence). Lupus nephritis was classified by the World Health Organization classification criteria [14].

Remission was defined by the presence of all of the four following criteria in at least two determinations one month apart: (*a*) absence of active urine sediment, (*b*) proteinuria of non-nephrotic range (<3 g/24 hours), (*c*) a reduction by at least 30% in the level of proteinuria, and (*d*) stable or improving creatinine clearance, an improvement of creatinine clearance by at least 30% if the baseline creatinine was $\geq$2.5 mg/dL or stable creatinine clearance if the baseline creatinine was <2.5 mg/dL.

Relapse was defined as the presence of any of the following criteria in at least two determinations: (*a*) increase in proteinuria by more than 2 g/24 hours, (*b*) active urine sediment, or (*c*) increase in creatinine by >30%.

Database

The following data were collected and considered as predictors of the time to remission: age at the time of SLE onset and age at the time of diagnosis of nephritis; sex; the presence of mucocutaneous involvement, arthritis, serositis, central nervous system (CNS) disease (including psychosis, seizures, paresis or paralysis, and cranial nerve involvement), autoimmune hemolytic anemia (defined as hemoglobin below 12 g/dL and reticulocytosis along with positive Coombs test), other anemia (defined as hemoglobin below 12 g/dL without hemolysis), leukopenia (defined as <3000 leukocytes per cubic millimeter), and thrombocytopenia (defined as platelet count <100,000 per cubic millimeter) separately at any point up until the clinical diagnosis of nephritis and specifically at the time of the diagnosis of nephritis; hypertension, low C4 or C3 complement levels, amount of proteinuria, creatinine level and creatinine clearance at the time of diagnosis of lupus nephritis; activity and chronicity index in the renal biopsy [11]; prior therapy including per os cyclophosphamide, azathioprine, pulse corticosteroids, corticosteroids at daily doses exceeding the equivalent of 30 mg methylprednisolone; and delay for initiation of IVC from the time nephritis was diagnosed clinically and from the time the renal biopsy was performed. The same variables were also considered as potential predictors of the time to relapse (for patients who did remit) and of the time from relapse to second remission (for patients who relapsed), with the exception that for the latter analysis, we considered variables such as creatinine, proteinuria, complement levels, and hypertension at the time of the relapse. For the time-to-relapse analysis, we also considered the time it took to reach remission as a potential predictor. For the time-to-second remission analysis, we also considered the time it took to reach remission the first time and the time it took to relapse after the first remission as a potential predictor.

Statistical analysis

Time to event analyses were performed according to the Kaplan–Meier method, and comparisons involved the log-rank test [15]. Predictive modeling was performed with Cox proportional hazards models [16]. Multivariate models used a step-wise backward elimination procedure based on a likelihood ratio test with $P > 0.10$ for removal and $P < 0.05$ for entry of variables. To avoid using too many variables given the limited number of events and observations, in the initial multivariate models, we considered only the six variables with lowest P values in univariate analyses (generally $P < 0.15$) in the modeling of time to remission and time to relapse and the three variables with the lowest P values in univariate analyses (generally $P < 0.25$) in the modeling of time to re-remission. Clinical site was not a significant predictor in any of the models, and site-adjusted estimates were similar (data not reported). Analyses were conducted in Advanced SPSS [17]. All P values are two-tailed.

Table 1. Characteristics of the patient population

Age at SLE onset, mean (SD) *years*	28.7 (14.3)
Age at nephritis onset, mean (SD) *years*	32.9 (14.7)
Creatinine at time of IVC initiation, mean (SD) *mg/dL*	1.3 (0.8)
Proteinuria at time of IVC initiation, mean (SD) *g/24 hours*	2.2 (2.0)
Low complement at time of IVC initiation	59/80
Hypertension at time of IVC initiation	36/82
Chronicity index on renal biopsy, mean (SD)	3.0 (2.5)
Activity index on renal biopsy, mean (SD)	7.5 (3.6)
Number of patients with other abnormalities at onset (at any other time)	
CNS disease	6 (17)
Serositis	12 (18)
Arthritis	31 (61)
Mucocutaneous involvement	53 (64)
Leukopenia	16 (24)
Autoimmune hemolytic anemia	8 (11)
Other anemia	48 (50)
Thrombocytopenia	5 (11)
Prior therapy for SLE and complications	
Oral cyclophosphamide	13
Azathioprine	23
Pulse corticosteroids	6
Corticosteroids >30 mg/day MPE	37
Patients switching to other regimens to achieve first remission	2

Abbreviations are: CNS, central nervous system; IVC, intravenous cyclophosphamide; MPE, methylprednisone equivalent; SLE, systemic lupus erythematosus.

RESULTS

Patient population

A total of 85 patients (69 female and 16 male) with proliferative lupus nephritis were included in the analysis. Thirty-three patients had focal proliferative nephritis (type III), and 52 had diffuse proliferative nephritis (type IV). Eight patients reached ESRD during follow-up, and two of them died; four more patients died from other causes. All patients with ESRD and four of six patients who died had type IV glomerulonephritis. Other characteristics of the patient population are shown in Table 1. Sixty-three of the 85 patients entered into remission during follow-up. Of those, 23 had relapsed during follow-up, and 15 of them had already entered into a second remission at the time data were censored for analysis. Fifteen patients started IVC more than two months after having a renal biopsy, and 30 patients had delayed the onset of IVC therapy for more than three months from the time kidney disease was clinically detected for the first time. In the majority of cases in which therapy was delayed, the delay was due to the time it took for primary care physicians to document the diagnosis and refer the patient for treatment or hesitation by the patient to start therapy. The median time from clinical detection to onset of IVC was two months (interquartile range 1 to 8 months).

Treatment experience

The median duration of treatment in our cohort was 31 months. Forty-six of the 85 patients had stopped IVC. Thirty-four patients stopped IVC before completing the typical three-year regimen. Of those, 24 stopped before completing at least two years of treatment, and 15 stopped even before completing one year. The reasons for these early discontinuations were rapid progression to irreversible kidney damage ($N = 4$), poor response with a decision to change to oral cyclophosphamide and azathioprine ($N = 1$), peripheral neuropathy ($N = 1$), recurrent infections in the setting of neutropenia ($N = 1$), patient decision in the setting of good response ($N = 4$), and erratic follow-up ($N = 4$).

Time to remission

Two patients had to use a different regimen (cyclosporine 3 mg/kg per day and azathioprine in combination with oral cyclophosphamide 1 mg/kg per day of each, respectively) to achieve remission. As shown in Figure 1A, the vast majority of patients seemed to enter remission eventually, but some patients may take a long time. The median time to remission was 10 months. The estimated proportions entering into remission at 6 months, 12 months, and 2 years were 33, 58, and 78%, respectively. Table 2 shows the important predictors of the time to remission in univariate and multivariate Cox models. Remission took longer to reach in patients who had delayed the onset of IVC for more than three months after clinical diagnosis, were younger at the time SLE and nephritis were diagnosed, and had more pronounced proteinuria. There was also a suggestion that patients whose nephritis was accompanied by autoimmune hemolytic anemia took longer to remit. In the multivariate regression, the most important independent predictors were the level of proteinuria and a delay of more than three months from the clinical diagnosis. The rate of remission was almost half among patients who had delayed therapy for more than three months and decreased by 14% for each increase of 1 g/24 hours in the level of proteinuria. Of note, even though patients with histologic type IV were modestly slower to remit (hazard ratio 0.80), this finding was not statistically significant ($P = 0.4$). Nevertheless, at 50 months, all patients with type III histology were expected to have entered remission, as compared with only 81.8% of patients with group IV histology.

Time to relapse

The median time to relapse was 79 months from the time of remission. In Kaplan–Meier analysis (Fig. 1B), the risk of relapse seemed to slightly decrease over time; that is, patients who had stayed in remission for longer had a lesser risk of relapsing in the immediate future. Table 3 shows the important predictors of relapse for patients who had entered into remission. In both univariate and multivariate analyses, the coexistence of CNS disease at the time of the diagnosis of nephritis and the

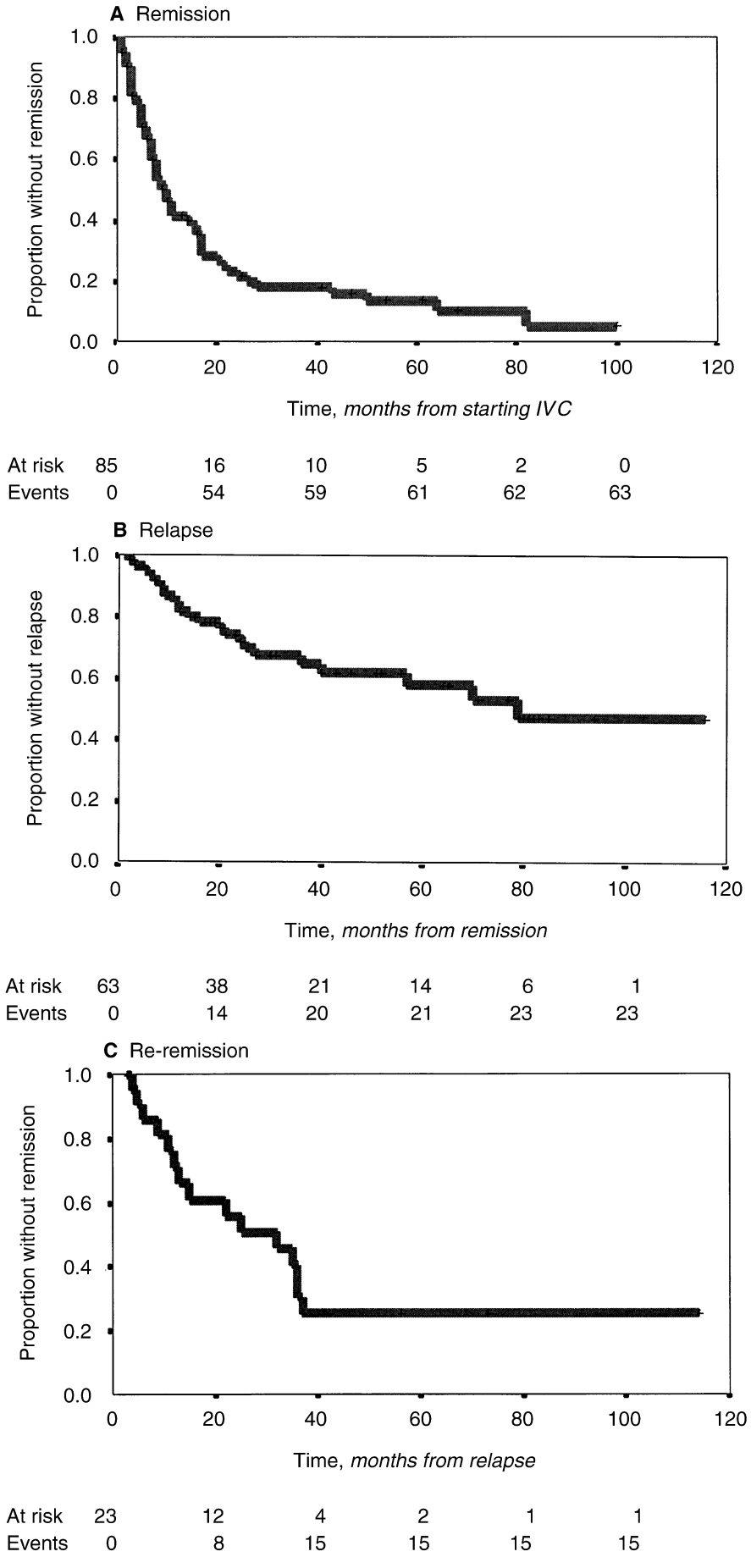

Fig. 1. Kaplan–Meier curves for (*A*) the time to remission after the start of intravenous cyclophosphamide (IVC; *N* = 85), (*B*) the time to relapse after remission (*N* = 63 with remission), and (*C*) the time to re-remission after relapse (*N* = 23 with relapse). Each patient censored without an event is shown by a cross in the Kaplan–Meier curves. The number of patients at risk and the cumulative number of events at 0, 20, 40, 60, 80, and 100 months are also shown under each Kaplan–Meier plot.

Table 2. Predictors of remission

Predictor	Hazard ratio (*P* value)	
	Univariate	Multivariate
Delay >3 months from clinical diagnosis	0.56 (0.046)	0.58 (0.063)
Proteinuria *per 1 g/24 hours*	0.85 (0.024)	0.86 (0.014)
Age at nephritis onset *per year*	1.0145 (0.090)	NS
Age at SLE onset *per year*	1.0182 (0.046)	NS
AHA at nephritis onset	0.44 (0.082)	NS
Activity index *per point*	0.936 (0.121)	NS

Abbreviations are: NS, not selected in the multivariate model; SLE, systemic lupus erythematosus; AHA, autoimmune hemolytic anemia. A hazard ratio <1 denotes a longer time to remission.

Table 3. Predictors of relapse

Predictor	Hazard ratio (*P* value)	
	Univariate	Multivariate
CNS disease at nephritis onset	3.61 (0.025)	8.41 (0.002)
Time to remission *per month*	1.017 (0.145)	1.029 (0.025)
WHO type IV	0.47 (0.080)	0.28 (0.01)
Delay >2 months from biopsy	2.10 (0.120)	NS
Creatinine when IVC started *per 1 g/dL*	1.38 (0.120)	NS
History of leukopenia	2.31 (0.062)	NS

Abbreviations are: CNS, central nervous system; IVC, intravenous cyclophosphamide; NS, not selected in the multivariate model; SLE, systemic lupus erythematosus. A hazard ratio <1 denotes a longer time to relapse.

time that it had originally taken to reach remission were predictive of relapse. Patients with group IV histology seemed to take longer on average to relapse, if they reached remission. There was a suggestion that patients who had delayed IVC initiation after biopsy documentation, those with a higher level of creatinine and those with a history of leukopenia were more likely to relapse, but none of these predictive factors remained significant in the multivariate analysis. Of note, the risk of relapse among patients who entered into remission was not statistically significantly associated with the delay in initiation of therapy from the time of clinical documentation ($P = 0.74$), a high activity index ($P = 0.66$), a high chronicity index ($P = 0.84$), or the patient's age at SLE or nephritis onset ($P = 0.74$ and 0.95, respectively).

Time to re-remission

Fifteen of the 23 patients who relapsed entered into a second remission during follow-up. Of the 23 patients, 15 used IVC alone. One patient used both IVC and intravenous immunoglobulin, and one patient used both IVC and azathioprine. Two patients used oral cyclophosphamide 2 mg/kg per day, and 4 patients used azathioprine. As shown in Figure 1C, the median time from relapse to re-remission was 32 months. The probability of entering re-remission gradually decreased over time.

Table 4. Predictors of second remission

Predictor	Hazard ratio (*P* value)	
	Univariate	Multivariate
Time to relapse from first remission *per month*	1.053 (0.004)	1.071 (0.002)
Chronicity index = 0	20.5 (0.033)	56.2 (0.015)
Time to first remission *per month*	0.981 (0.223)	0.979 (0.160)

A hazard ratio <1 denotes a longer time to second remission.

Patients not entering a second remission after three years were very unlikely to ever remit.

Among the 15 patients who entered a second remission, the time to re-remission was longer on average than the time that these same patients had taken to enter remission originally (median 15 months vs. 5 months); 12 out of 15 took longer to enter remission the second time than it had taken to enter remission the first time. Of the remaining eight patients who had not yet entered a second remission, six had already been followed for a longer time after their relapse than it had taken for the first remission ($P = 0.01$).

Table 4 shows the important predictors of second remission among patients who had relapsed. In both univariate and multivariate analyses, the time to re-remission was longer if the relapse had occurred earlier after the first remission and was probably also more prolonged if the time it had taken to enter into remission the first time was longer. Patients with no chronic damage in the original kidney biopsy were more likely to enter again into remission. The time to re-remission was not significantly associated with the creatinine level, level of proteinuria, or the presence of hypertension or hypocomplementemia at the time of relapse.

DISCUSSION

In this study, we analyzed the timing and predictors of remission, relapse, and second remission of proliferative glomerulonephritis in SLE patients treated with long-term IVC. In concordance with previously published experience [1, 18], we observed that most patients enter into remission with IVC therapy. However, many patients may take very long to remit. Moreover, relapse was very common in our study cohort. On average, patients on IVC seemed to gain a little more than six years (median 79 months) of remission. The rate of relapses seemed to decrease the longer patients stayed in remission. Relapses occurred earlier in patients with evidence of severe SLE such as CNS disease and in patients who had taken longer to remit. Finally, achieving a second remission in patients who had relapsed was far more difficult than achieving remission the first time. Re-remission was less likely to occur among patients who had taken longer to remit the first time and those who

had relapsed sooner after achieving remission the first time. The probability of a second remission diminished over time and seemed to become negligible three years after the relapse.

Several studies have assessed predictors of long-term outcomes, especially end-stage renal disease in patients with SLE glomerulonephritis [1]. These predictors include an elevated creatinine, nephrotic-range proteinuria, low levels of complement, severe anemia, hypertension, diffuse proliferation on kidney biopsy, a high activity and chronicity index, male gender, black race, young age, and low socioeconomic status [1]. These factors may also be important for long-term outcomes in the context of currently recommended long-term IVC regimens, although most previous studies collected data on patients with various histologic types and various treatment modalities, including short-term courses of IVC. There are even more limited data on the predictors of immediate responses to current long-term IVC regimens and the propensity of proliferative glomerulonephritis to relapse and re-remit with IVC treatment.

One team of investigators reported that young age and a higher chronicity and activity index, as well as a delay in initiation of therapy, were associated with a higher probability of relapse [19]. In our study, we observed that a delay in initiation of therapy as well as proteinuria and, in univariate associations at least, probably a higher activity index and younger age were predictors of slower remission rather than faster relapse. Nevertheless, the risk of relapse seemed to correlate inversely with the time it took to remit. Some of the predictors of relapse that we observed, namely CNS disease and leukopenia, may be surrogates for the presence of more severe SLE disease. The reason why patients with type IV glomerulonephritis seemed to have a lower risk of relapsing once entering remission is not obvious. The effect may be spurious. It may reflect the fact that all eight patients who suffered irreversible renal damage and four of six patients who died had type IV disease. Thus, the remaining patients who did remit may have been selected to have a seemingly more favorable prognosis. Still, relapses are a serious problem for both type III and type IV glomerulonephritis. One recent study reported that a one third of patients with proliferative lupus nephritis relapsed at a median of 21 months after remission (abstract; Illei et al, *Arthritis Rheum* 41:S242, 1998). In other studies, rates of relapse have ranged from 25% at 5 years and 46% at 10 years to 36% early after discontinuation of therapy [8, 9, 19]. Our estimate (50% at 79 months) is based on one of the largest ICV-treated cohort of proliferative nephritis in the literature and is well within this range.

Differences in associations and in rates of relapse in various studies may be also dependent on the criteria used to define relapse and remission as well as on the retrospective character of most studies in this field, including the present report. Criteria of remission based on proteinuria and creatinine clearance are less satisfactory than criteria incorporating an inactive urine sediment. Definitions of relapse are even more difficult to validate, as there is even more limited comparative evidence. For example, simple changes in creatinine may not necessarily reflect lupus-related activity in the kidneys. Nevertheless, all relapses in our cohort were also associated with an active urine sediment. There is a need for developing uniformly accepted criteria for defining remission and relapse in the short term and validating these criteria on long-term hard outcomes [20]. Prospective, preferably randomized, studies of an adequately large sample size would be needed to overcome the biases stemming from variability in the therapeutic management of patients and accompanying selection biases [21]. Finally, although retrospective in nature, our study had the advantage of assembling the largest population of IVC-treated patients with proliferative nephritis in the literature, to our knowledge. Patients had a common racial background and were recruited from three hospitals sharing a standardized therapeutic approach, which obviates strong selection biases.

The median time of first remission in our study was 10 months. Although typically the response to IVC has been thought to be fairly swift, often occurring within 2 to 6 months, a previous study also reported that the mean time to reach renal remission was 21 months, whereas the number of IV CY pulses averaged to 10 (abstract; Pando et al, *Arthritis Rheum* 37:S179, 1994). Many patients may take a very long time to enter into remission. This translates into a substantial cumulative dose of IVC that increases the risk for serious subsequent toxicity. It is thus very important to know which patients are then likely to respond a second time, if they relapse. Our data suggest that patients who relapse take on average 32 months to re-remit. Apparently, some of them will never enter remission again, especially those who took longer to remit the first time and/or relapsed rapidly. With an average treatment experience of 31 months during the first remission and maintenance phase, two or more additional years of IVC could create a substantial load of cumulative toxicity. Based on our study results, we recommend that patients who have adverse prognostic factors for re-remission, such as difficult remission and early relapse, should be considered for treatment with alternative regimens.

In fact, our study offers further evidence about the limitations of IVC and the need for developing and evaluating alternative regimens. Fifteen of 85 patients in our cohort stopped IVC before completing one year of therapy, usually because of lack of efficacy, side effects, and patient noncompliance, the latter often also reflecting toxicity concerns. A much larger number of pa-

tients did not complete a three-year course. Candidate alternative agents include azathioprine and intravenous immunoglobulin. Preliminary experience with azathioprine is promising [22], but definitive data are lacking. In a pilot randomized trial, we recently demonstrated that intravenous immunoglobulin pulses may have similar success in sustaining remission in patients with lupus nephritis [23]. Clinical development of these and other agents and their incorporation in the management of lupus nephritis may need to target those who need long-term maintenance hemodialysis therapy and those with adverse predictors for response to IVC, especially in cases of relapse.

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