Retrospective analysis of outcome in a cohort of patients with lupus nephritis treated between 1977 and 1999

J. R. MacGowan, S. Ellis, M. Griffiths¹ and D. A. Isenberg

The Centre for Rheumatology, Middlesex Hospital, Arthur Stanley House, 40–50 Tottenham Street, London, W1P 9PG and ¹The Department of Histopathology, University College Hospital, University Street, London W1N 8AA, UK

Abstract

Objective. To review the development, histological type and outcome of a cohort of patients with lupus nephritis who were managed and followed up by the specialist Bloomsbury Rheumatology Unit between 1977 and 1999.

Patients and methods. Seventy-eight of the 280 (28%) patients with systemic lupus erythematosus (SLE) developed nephritis. Occurrence of end stage renal disease (ESRD) according to World Health Organization (WHO) class was analysed, and patients were subdivided according to whether treatment included at least six pulses of intravenous (i.v.) cyclophosphamide (CYC) once a month.

Results. For patients with WHO class III nephritis, three out of five treated with i.v. CYC developed ESRD compared with none out of 10 not treated with i.v. CYC (P < 0.02). There was no significant difference between these subgroups in terms of a variety of parameters with good prognostic value, except anti-dsDNA titre at time of biopsy (which was greater in the former). For patients with WHO class IV nephritis, three out of 16 treated with i.v. CYC developed ESRD, compared with five out of 20 not treated with i.v. CYC (no significant difference).

Conclusion. These data suggest that there may be a subgroup of patients with lupus nephritis (WHO class III) whose long-term outcome is not adversely affected by the omission of i.v. CYC.

Key words: Lupus nephritis, Cyclophosphamide, WHO class.

In the past 50 yr there has been a substantial improvement in the survival of patients with systemic lupus erythematosus (SLE), with 5-yr survival increasing from 50% in 1955 to 94% in 1994 [1]. This improvement has been attributed to a number of different factors, including the more judicious use of corticosteroids, refinements in immunosuppressive therapy, more effective treatment of hypertension and cardiovascular disease, and greater availability of dialysis and renal transplantation. This improvement in overall survival is also reflected in the 5-yr survival data of patients with diffuse proliferative lupus nephritis (>80% during the past two decades compared to just 17% before 1970 [2]). Nevertheless, recent studies show that these patients remain at substantial risk of developing end stage renal disease (ESRD), with estimates varying from 10 to 70% after 5 yr [3–10]. Nossent’s recent review of the literature indicates that this complication develops in ~20% of patients with lupus nephritis, a proportion not significantly different from three decades ago [11]. Studies have, therefore, focused on the prognostic value of various clinical, demographic and histological features so as to enable the development of rational guidelines for the use of potentially toxic immunosuppressive therapies in the management of lupus nephritis.

The histological findings in lupus nephritis are categorized into six classes according to World Health Organization (WHO) classification. Various studies of the prevalence of ESRD in lupus nephritis make it clear that those patients at highest risk of progression to ESRD have proliferative, WHO classes III and IV nephritis [10]. It has been suggested, therefore, that it is in these patients that the potential benefits of aggressive therapeutic intervention are most likely to outweigh the risks. In general, patients with mesangial (WHO class II) nephritis do not require treatment beyond therapy directed at the extra-renal manifestations. While patients with nephrotic syndrome due to pure membranous (WHO class V) nephritis are at particular risk of cardiovascular events and thromboembolism, the renal
prognosis is more favourable than for proliferative nephritis. Treatment recommendations for both class II and V nephritis are largely based on empirical grounds and open studies. It is recommended that the focus of therapy for patients with advanced glomerulosclerosis (WHO class VI) be directed to the management of extra-renal disease, in addition to renal replacement and alleviation of the consequences of chronic renal insufficiency.

The role of intermittent, longer course cyclophosphamide in the treatment of lupus nephritis was established by two prospective, controlled clinical trials performed at the National Institutes of Health (NIH) [12, 13] and the Mayo clinic [14] in the 1970s, and more recently again at the NIH [15]. The NIH studies showed that a regimen of monthly intravenous pulses of cyclophosphamide was comparable to oral cyclophosphamide in terms of efficacy, but was less toxic [16]. Although the optimal duration and frequency of pulse i.v. cyclophosphamide therapy have yet to be determined, the currently preferred regimen is monthly pulse intravenous cyclophosphamide for 6 months (CYC) followed by quarterly pulses for 2 yr.

Justifiably, concerns remain about the toxicity associated with long-term CYC, in particular premature ovarian failure (frequency increasing from 17% in patients aged <25 yr receiving >15 doses of pulse therapy to 100% in patients aged >31 yr) [16], infection (most commonly herpes zoster) and possible malignancy. Further research is clearly needed to facilitate improved targeting of toxic therapy towards those patients at highest risk of poor outcome.

In view of the current interest in the use of i.v. CYC in the management of lupus nephritis and the relative paucity of long-term follow-up data, we have examined the outcome of patients with lupus nephritis managed by this unit since 1978. Particular attention has been paid to the relationship between outcome (ESRD and death) and therapy involving i.v. CYC, with patients being analysed according to WHO class.

Patients and methods

Patients

Patients included in the present analysis had four or more revised criteria of the American College of Rheumatology for the classification of SLE [17] and lupus nephritis. The onset of lupus nephritis was defined as the date at which sustained proteinuria (>2+ on urinary dipstick testing)/active urinary-sediment or impairment of renal function (rise in serum creatinine) occurred. Between January 1977 and June 1999, 78 patients (28%) out of 280 with SLE managed by this unit developed lupus nephritis. Demographic factors that were defined at time of onset of lupus nephritis in all patients were age, ethnicity, sex, and duration of follow-up. Where tissue was available the histologic pattern of disease on renal biopsy and the activity and chronicity indices were recorded. All available renal biopsy specimens not previously examined by our histopathologist (M. Griffiths) were re-analysed by her. Patients with WHO class III and IV disease were also characterized for C3 complement (C3) level (by laser nephelometer; normal range 0.9–1.8 g/l), antibodies to double-stranded DNA (dsDNA) (Shield Diagnostic ELISA kit, Dundee; normal range <50), serum creatinine (µM) and proteinuria on urinalysis (1+ to 3+) at the time of biopsy. Assessment of disease activity at the time of renal biopsy was made using the ‘BILAG’ (British Isles Lupus Assessment Group) index. This scoring system was originally developed in 1984 in an attempt to move away from the global disease activity score approach [typified by the Systemic Lupus Erythematosus Disease ‘Activity Index (SLEDAI)’], and is based upon the ‘intention to treat’ premise. The BILAG index is described in detail elsewhere [18, 19]. In essence, it includes a total of 86 items in eight organs or systems. Each system is allocated alphabetic scores (A–E) according to the presence or absence of a variety of clinical features (mostly) in each organ/system. A = disease that requires urgent disease-modifying therapy; B = disease that demands close attention and perhaps modification of minor therapy; C = stable mild disease; D = disease that previously affected but currently inactive; and E = system never involved. Global disease activity was calculated for each assessment, using the system A = 9, B = 3, C = 1, D = 0 and E = 0. The BILAG index has been shown to have a high degree of inter-rater variability and validity [19].

Renal biopsy

The histological pattern of disease was established using WHO criteria [20], and where tissue was available for further analysis it was scored for activity and chronicity indices (AI and CI) as described by the NIH [21].

Treatment regimens

This is a retrospective, observational study and consequently therapeutic regimens were not standardized. Patients received varying combinations of prednisolone, azathioprine and i.v. CYC. A minority received additional treatments such as mycophenolate mofetil, cyclosporin A, tacrolimus and plasma exchange. Patients were stratified according to whether or not their treatment protocols included at least six, monthly pulses of CYC (patients receiving no i.v. CYC were assigned to group A, patients receiving i.v. CYC were assigned to group B). It is recognized that such stratification necessarily introduces a degree of bias and therefore caution is required in the interpretation of our results. However, as far as it is possible in an observational study, we have attempted to control for this by comparing the aforementioned baseline laboratory and clinical prognostic parameters in each group.

Outcome measures

The primary outcome measure was ESRD, defined by a need for renal replacement in the form of dialysis or
transplantation. Death was analysed as a secondary outcome measure.

**Statistical analysis**

Statistical advice was taken from the statisticians based in the Department of Research and Development, University College Hospital, London. Two-tailed tests were used to estimate P-values throughout. Differences in outcome between the two groups treated with and without CYC (limited to patients with WHO class III and IV disease) were analysed by $\chi^2$ tests using Fisher’s exact two-tailed test.

**Results**

In 21 years of follow-up, 78 (28%) of 280 SLE patients managed by our unit have developed lupus nephritis. A total of 54 out of 78 (69%) patients with lupus nephritis were treated with regimens that did not include i.v. CYC (group A) and 24 out of 78 (31%) patients were treated with regimens that did include i.v. CYC (group B). Breakdown by WHO class of both groups is illustrated in Fig. 1.

Renal biopsy was either not performed, or the results lost, in three and one patients, respectively, of the 54 patients in group A, but in none of those in group B. AI and CI scores were not available for 13 out of 54 (24%) group A patients and four out of 22 (18%) group B patients.

During this period of follow-up, 10 out of 54 (18.5%) patients from group A and three out of 24 (12.5%) patients from group B have died. Causes of death are recorded in Tables 1 and 2.

The total number of patients who progressed to ESRD is small, occurring in just 12 out of 54 (22.2%) patients in group A and six out of 24 (25%) patients in group B. Of those patients not treated with i.v. CYC, six out of 12 had class IV disease and none had class III disease. Of those who were treated with i.v. CYC, three out of six had class IV disease and three out of six had class III disease. A breakdown of patients who progressed to ESRD by WHO class is illustrated in Fig. 2.

**Subgroup analysis of patients with WHO class III disease**

Characteristics of patients with WHO grade III lupus nephritis whose treatment did (group $B^{III}$) and did not include i.v. CYC (group $A^{III}$) are shown in Table 1. Information was incomplete in one of the patients in group $A^{III}$, and in no patients in group $B^{III}$.

There was no significant difference between sex, age at onset of renal disease, mean AI and mean CI between the two subgroups. Although there was a trend for group $B^{III}$ to have higher C3 and serum creatinine, and lower haemoglobin at time of renal biopsy, this did not reach statistical significance. However, group $B^{III}$ did have significantly higher anti-dsDNA antibodies at time of renal biopsy ($P < 0.02$). The mean duration of follow-up is significantly longer in group $A^{III}$ compared with group $B^{III}$ (mean ± s.d. 15.2 ± 9 yr compared with 4.0 ± 2.7 yr; $P < 0.03$).

![Fig. 1. Breakdown of patients with lupus nephritis by WHO class.](image-url)
Three out of five patients treated with i.v. CYC in addition to corticosteroids and azathioprine developed ESRD compared with none out of 10 of those whose treatment regimens did not include i.v. CYC (statistically significant, $P < 0.02$).

Two out of five patients (40%) treated with i.v. CYC died compared with two out of 10 (20%) not treated with i.v. CYC (not statistically significant).

Subgroup analysis of patients with WHO grade IV disease
Characteristics of patients with WHO class IV lupus nephritis whose treatment did (group B$^{IV}$) and did not include i.v. CYC (group A$^{IV}$) are shown in Table 2. Information was missing or incomplete in four out of 20 patients in group A$^{IV}$, and three out of 16 in group B$^{IV}$.
Again there was no significant difference between the two subgroups in terms of sex, age at onset of renal disease, mean AI or mean CI. Mean (± S.D.) duration of follow-up was 12.6 yr (± 7.5) in group A IV compared with 6.7 yr (± 4.5) in group B IV ($P < 0.008$). There was no significant difference in baseline parameters of disease severity at time of renal biopsy [complement (C3) level, anti-dsDNA antibody titre, urinary dipstick protein, serum creatinine and global BILAG score] between the two subgroups.

Three out of 16 (18.7%) patients treated with i.v. CYC in addition to corticosteroids and azathioprine developed ESRD, compared with five out of 20 (25%) of those whose treatment regimens did not include i.v. CYC (not statistically significant).

Three out of 20 patients (15%) treated without i.v. CYC died, compared with one out of 16 (6.2%) whose treatment included i.v. CYC (not statistically significant).

Discussion

Since the number of patients assessed is relatively small, our analysis has been restricted to patients with WHO class III and IV nephritis. As well as being the largest subgroups, these patients are also deemed to be at highest risk of progression to ESRD [10] and, therefore, are most likely to warrant consideration of aggressive therapy.

We observed that patients with WHO class IV disease whose therapeutic regimens included i.v. CYC fared better in terms of progression to ESRD, although there were insufficient numbers to demonstrate statistical significance.

Our data also suggested that there may be a subgroup of patients with proliferative lupus nephritis (WHO class III) for whom the use of therapeutic regimens, including at least six, monthly pulses of i.v. cyclophosphamide, is not associated with an improved renal outcome; in fact, the risk of developing ESRD was greater in these patients ($P < 0.02$). This finding was unexpected, although the fact that patients whose treatment included i.v. CYC had significantly higher anti-dsDNA antibodies and tended to have higher serum creatinine and lower C3 levels at time of renal biopsy, might indicate that these patients had more aggressive disease per se.

The fact that there was no statistically significant difference between serum creatinine and C3 levels in the two groups at baseline may relate to the small number of patients in our series. Interestingly, however, the duration of nephritis was longer in the group of patients with class III disease who were not treated with i.v. CYC ($P < 0.03$). One study has identified this parameter as an adverse prognostic indicator [25].

The literature cites a number of clinical, laboratory and demographic factors that increase the risk for ESRD in patients with lupus nephritis, many of which we have attempted to define in our population with class III nephritis. Austin et al. [22] demonstrated by multivariate analysis that the strongest combination of clinical predictors of renal insufficiency was serum creatinine, haematocrit and race. No other clinical feature (including age and C3, which only had prognostic significance by univariate analysis) contributed significantly to prediction of renal outcome. McLaughlin et al. [23] identified serum creatinine level and lupus activity, as measured by the global SLEDAI index, as the clinical and laboratory factors most closely related to renal outcome.
associated with risk of dying. Other parameters identified by some, but not all studies as having useful value in indicating poor outcome include nephrotic-range proteinuria [24–26], hypertension [28], low socioeconomic status [28], male sex [23], age < 24 yr [23, 24] and anaemia [23].

The precise role of renal biopsy in providing additive predictive value remains a subject of debate. However, it is generally accepted that outcome predictions based on clinical information alone are significantly enhanced by information obtained from renal biopsy [22, 23].

Goulet et al. [25] used regression tree techniques to show that combinations of serum creatinine, 24-h urine protein levels, nephrotic syndrome and duration of prior renal disease provide accurate prognostic information about lupus nephritis without recourse to biopsy. Whiting-O’Keefe et al. [29] applied a stepwise regression analysis to data collected over a 12-month period after renal biopsy in 130 patients to see if biopsy added any useful information to the clinical data. They found that the histological classification did not add significantly to the predictive power of the ‘before biopsy’ model. However, certain features, notably the percentage of glomeruli that had undergone sclerosis in the presence of subendothelial deposits on electron microscopy, did increase the ability to predict the effect of 12 months of treatment of lupus nephritis. The contribution of activity and chronicity indices to the predictive value of clinical and demographic data has been examined by a number of investigators. The presence of severe active histological change, resulting in an activity index > 12/24 (most notably due to cellular crescents and fibrinoid necrosis) [21, 28] or a chronicity index > 3/15 (i.e. extensive glomerular sclerosis, interstitial fibrosis and atrophy) [21, 24, 27], and the combination of active and chronic renal parenchymal injury all provide additive prognostic information [22, 27, 29]. However, McLaughlan et al. [23] reported that the chronicity index was not helpful in assessing prognosis in patients with an elevated serum creatinine. The patients in our series with class III and IV nephritis were matched for both activity and chronicity indices. With the exception of anti-dsDNA antibody titres at time of renal biopsy, which were significantly higher in those patients who progressed to ESRD, the group of patients with class III nephritis were apparently matched for several parameters recognized as having good prognostic value.

In terms of long-term outcome we have recently reported that, to date, the use of cyclophosphamide in this group of patients has not been associated with excess development of any malignancy [30].

We remain cautious about over-interpreting our data regarding the merits of i.v. CYC in the management of proliferative, particularly WHO class III nephritis as our numbers are small. Moreover, this is an observational study in which treatment regimens were not strictly standardized. Clearly, however, there remains a need to examine further the outcome of patients in this subclass in order to refine the risk/benefit ratios of their therapeutic regimens. Large prospective, randomized, controlled trials are urgently needed to help clarify these issues.

Acknowledgement

We gratefully acknowledge the long-term help of Professor G. Neild and his colleagues at the Renal Unit, UCL, in managing our patients with lupus nephritis.

References

15. Boumpas DT, Austin HA 3rd, Vaughan EM et al. Controlled trial of pulse methylprednisolone versus two


