Review

THE PROGNOSTIC MARKERS, CURRENT TREATMENT STRATEGIES AND THE LONG TERM PROGNOSIS FOR PROLIFERATIVE FORMS OF LUPUS NEPHRITIS

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ABSTRACT

Renal manifestations of systemic lupus erytematosus (SLE) are highly variable in clinical presentation, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis leading to end stage renal disease.

Renal biopsy evaluated by light microscopy, immunofluorescence and electron microscopy where possible, provides invaluable information for the proper histopathological classification and for assessing the disease activity and chronicity. The World Health Organization (WHO) classification of lupus nephritis is a practical and widely accepted system for categorizing the main renal lesions observed on biopsies of patients with lupus nephritis(Table I) (1). The focal and diffuse proliferative forms of lupus nephritis corresponding to WHO class III and IV have the worst prognosis, leading to ESRD in 20-30% of the cases (2). A substantial proportion of patients with class III nephritis progress to class IV disease and it has been suggested that these two classes are qualitatively similar and simply reflect milder or more severe stages respectively (3).

The aim of this article is to overview the prognostic markers, the current treatment strategies and the long term prognosis for the latter forms of lupus nephritis.

PROGNOSTIC MARKERS

The proliferative forms of lupus nephritis are characterized with endocapillary proliferation, capillary loop necrosis and wire loop formation on light microscopy and abundant deposits of all classes of immunoglobulins along the capillary walls on immunoflourescent microscopy. These features are considered potentially active but reversible (3).

Clinical studies have demonstrated the utility of the WHO classification in stratifying patients according to risk of renal disease progression. However, in addition to this classification, further emphasis on the potential roles of the diverse glomerular, tubular, interstitial and vascular lesions have demonstrated that better prediction for renal survival can be made with subclassification of the WHO system aiming to include the extent of the injury to the various

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components of the kidney listed above. These subclassifications provide a semiquantitative analysis of acute and chronic renal injury. Markers of acute injury (activity index (AI)) include intracapillary proliferation, epithelial crescents, glomerular polymorphonuclear infiltration, wire loop lesions, intracapillary thrombi, fibrinoid necrosis and/or karyorrhexis, hematoxylen bodies, vasculitis and diffuse interstitial inflammation. Activity index ranges from 0-24 depending on the presence and extent of the above stated lesion. Chronic changes (chronicity index (CI)) include glomerular obsoloscence, segmental glomerular hyalinosis, interstitial fibrosis, tubular atrophy and arteriolar hyalinosis. CI reflects the features of chronic irreversible damage and the score ranges from 0-12. It should, nevertheless, be emphasized that the biopsy provides information regarding acute and chronic renal injury at a single time point. Transformation of renal lesions for better or worse can occur both spontaneously or as a result of treatment. Reproducibility of the activity and chronicity indices in experienced hands has been considered excellent (3). Aggressive therapy may alter the prognostic significance of a high activity index (4). However, patients with a high chronicity index, are at risk for developing progressive renal disease, despite aggressive immunosuppressive treatment (5,6). On the other hand, the extent of chronic irreversible renal injury should be considered when weighing the costs and benefits of aggressive immunosuppression.

NIH studies have revealed that an elevated AI (>12/24) and CI (>2/12) is associated with a poor renal prognosis: Long term renal survival with CI<2/12 corresponding to a 10yr survival of 100%, while CI from 2-4/12 had a 10yr survival of 70% and a CI>4/12 had a 10 yr survival of only 35%. In other studies, including the recent article by Ilei et al. addressing a large population of patients with severe diffuse proliferative disease, neither AI nor CI predicted renal outcome.

Studies investigating the prognostic role of renal flares in patients with lupus nephritis are limited. Moroni et al (7) have evaluated the prognostic role of the renal flares in 70 patients with lupus nephritis followed for 5-30 years. The end-point of the study was the persistent doubling of plasma creatinine. Patients who developed renal flares had significantly more probability of reaching the end point than patients who had never had flares (P=0.03; RR:6.8). Among the patients with proteinuric flares, none eventually doubled his or her plasma creatinine after a median follow-up of 10 years. In contrast, the probability of reaching the end-point was significantly higher in patients who had nephritic flares (P<0.00001; RR:27). The hazard of irreversible renal function deterioration was higher when plasma creatinine did not return to the basal levels within 2 months after treatment (p< 0.0001)

Other clinical and pathological correlates with renal flares have been reported as high AI at initial biopsy(>9) (8), age under 29yrs at onset of renal disease, treatment with corticosteroids alone (9), a delay of more than 5 months from the onset of nephritis to initiation of cytotoxic therapy (10) and a short duration of high-dose IV cyclophosphamide (11), male sex, presence of arterial hypertension at presentation (7), and duration of the disease (12). There was a significant reduction of renal flares after the 10th year from the clinical onset of lupus nephritis when compared to the first 10 years.

Since renal flares seem to be strongly correlated with long-term renal prognosis, close monitorization of these patients for early detection and treatment of any exacerbation of lupus activity is essential. Serum complement levels, inreased levels of C1q antibodies (13), increased anti-DNA antibodies (14) have been suggested to predict the onset of renal flares. However, these immunological markers may also have fluctuations without heralding the exacerbation of disease activity. Increasing the corticosteroid and/or immunosuppressive treatment based only on these markers may expose the patients to overtreatment, which will in turn be associated with increased iatrogenic toxicity. Therefore Ponticelli et al have suggested the intensification of therapy on the basis of double-checked consistent increase in serum creatinine and/or daily proteinuria (12).

TREATMENT STRATEGIES

Data provided by several studies, especially NIH, have made prednisone in combination with cytotoxic immuno-suppressives, either

cyclophosphamide or azathioprine, the main stay of the current treatment for LN WHO Classes III and IV (11,15).

The results of several studies proved prednisone monotherapy to be insufficient for the proliferative forms of LN. Bansal and Beto (16) reported a 29% higher chance of developing ESRD if treated with prednisone alone. Data from the NIH study have demonstrated that prednisone was not able to prevent the development of chronic lesions(17) while in patients treated with cyclophosphamide or azathioprine there was no progression of chronicity over time (18). The chronicity index has proved itself to be one of the strongest indicators of a poor outcome.

On the other hand, the difference in renal survival between cyclophosphamide and azathioprin treated groups failed to reach statistical significance in the well-known study of Steinberg et al (19). In fact a direct prospective randomized comparison between azathioprin and cyclophosphamide is unfortunately lacking. Cameron gathered data from the literature in 1993, comparing the renal survival in patients treated with cyclophosphamide with data obtained retrospectively in patients treated with azathioprine (20). There were no differences between the two drugs. However, the fact that this was not a prospective analysis and since patients with a less severe disease may have been treated with azathioprine while cyclophosphamide may have been reserved for more severe cases, these results cannot be considered conclusive.

The Dutch working party on SLE started a randomised controlled trial in 1995 to compare the NIH cyclophosphamide regimen with a regimen containing azathioprine (2 milligrams per kilogram) together with methylprednisolone pulses on week 0, 2 and 6 together with prednisone (20 millligrams/day for 5 months, then tapered to 10 milligrams/day) per day. NIH cyclophosphamide regimen consisted of initially 3 methylprednisolone pulses on days 1-3 and 6 cyclophosphamide pulses/monthly, and thereafter every 3 months together with 1 mg/kg of prednisone tapered until 6 months at a dose of 10 milligrams.

As for the entry characteristics of 87 patients treated according to this protocol; they had a rather severe form of lupus nephritis as indicated by the serum creatinine, all had low C-3 levels, high levels of anti-double stranded DNA antibodies, and a significant proteinuria of 4.8 grams. There were no statistically significant differences between the two groups for these parameters.

At 6 months, there were no significant differences between the number of relapses, failures, renal failures, discontinuation of treatment, development of end stage renal disease, or death. Furthermore, the serum mean creatinine came down from 135mmol/L to 97mmol/L in both groups; the proteinuria decreased; the systolic blood pressure became lower; the SLEDAI score as a measure of disease activity also decreased. The complement C3 levels normalised and the level of anti-DNA antibodies also significantly decreased in both groups at 6 months.

Recently, the results of the Euro-Lupus trial have been published by Houssiau et al (21). In the latter trial, high dose cyclophosphamide was compared to low dose cyclophosphamide. The high dose group received cyclophosphamide at 500mg/m2 (max 1500mg) monthly for 6 months and tri-monthly twice thereafter. The low-dose group also received cyclophosphamide intravenously but at a fixed dose of 500 milligrams fortnightly for 6 months and every 2 weeks for 3 months thereafter. Both groups received 750 mg pulse methylprednisone on three successive days at the start of the trial and continued with prednisone 0.5mg/kg tapered every two weeks with 2.5 to finally 5-7.5 mg at 30 months. Both groups were converted to prednisone and azathioprine 2mg/day after stopping cyclophosphamide pulses. This study included 90 patients of which 40 remained on a high dose of cyclophosphamide and 38 on a low dose. There was no significant difference for treatment failure, between the low dose and high dose of cyclophosphamide. The incidence of renal flares was comparable in both groups,with comparable serum creatinine levels and proteinuria at 5 years follow up.

According to the currently available data, intravenous cyclophosphamide is of proven efficacy, but based on the Euro lupus trial, it may

be true that we do not need high doses for induction. The preliminary results of the Dutch trial suggets that IV methylprednisolone is probably less toxic, and an effective alternative.

Mycophenolate mofetil (MMF) is another promising yet unproven alternative. Its efficacy has been demonstrated in an animal model of lupus nephritis in MRC/lpr mice with reduction in proteinuria, decrease in histological severity and glomerular immunoglobulin ad C3 deposition (22). Chan et al have recently reported the results of a randomized trial of 42 patients with diffuse proliferative glomerulonephritis comparing the effect of MMF (1000 mg bid decreased to 500mg bid at 6 months) and prednisolone with cyclophosphamide (2.5mg/kg po daily) and prednisolone followed by azathioprine and prednisolone at 6 months (23). Limitations of this study were that only 42 patients were included,most had minor renal impairment, the follow-up period was relatively short (12 months) and the patients with poorer prognostic markers were not included. In fact both groups had comparable results for serum creatinine, C3 and albumin levels and proteinuria. However, the relapse of nephritis occurred in 46% of MMF-treated patients compared to only 17% of patients treated with cyclophosphamide. Further prospective randomized long-term studies are needed to prove the beneficial effect of MMF in remission induction and/or maintenance phase of treatment in proliferative lupus nephritis.

Cyclosporine A (CycA), a calcineurin inhibitor, inhibiting the production of IL-2, has been efficacious in the treatment of several forms of glomerulonephritis such as membraneous glomerulonephritis and focal segmental glomerulosclerosis. Its use in lupus nephritis has, however, been limited to small numbers of patients unresponsive to standard regimen. In a two years trial of CycA, 26 SLE patients unresponsive to standard therapy showed decreased activity and proteinuria, improved renal morphology and a stable creatinine. A randomized trial of CycA for membranous LN at the NIH is currently underway.

Biological response modifiers (BRM) are another group drugs of promising yet unproven efficacy in the treatment of proliferative lupus nephritis.

LJP 394 is a small molecule composed of polyglycol platform with 4 attached DNA polymers. LJP 394 produced decreased anti-DNA Ab production in SLE prone mice along with improved renal histology and function. This new BRM has been used in a recent large, multicenter, controlled randomized trial where it decreased anti-DNA Ab production but did not prevent flares of lupus nephritis.

Anti-C5A, a monoclonal antibody is currently being studied in a randomized trial in idiopathic membranous nephritis but not yet in proliferative lupus nephritis.

Anti-CD40L, a monoclonal antibody blocking the communication between B and T cells has been potent and successful in improving renal histology, decreasing proteinuria and prolonging survival in murine models.

Bindarit, an imidazole molecule, blocks the production of MCP-1. This agent has been successful in animal models and randomized controlled trial of Lupus nephritis is currently on the way.

Rituximab is a chimeric mouse-human monoclonal antibody against the B cell-specific antigen CD20, which selectively and profoundly depletes B lymphocytes and has been widely used to treat B cell lymphomas. Recent open-label studies indicate that rituximab is safe and may be efficacious in the treatment of recalcitrant lupus nephritis, and continued study with randomized clinical trials is justified (24).

Apart from the specific immunosuppressive therapy directed to the treatment of lupus nephritis, an important issue which should not be overlooked from the renal and sytemic point of view is the general management guidelines that apply to all forms of glomerulonephritis and chronic renal disease. Vigorous treatment of hypertension, and hyperlipidemia has proved itself to be very important in all forms of glomerulonephritis. Use of angiotensin converting enzyme inhibitors has become the first choice in patients with glomerulonephritis due to their additional antiproteinuric effect.

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