Preventing renal failure in patients with severe lupus nephritis

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Background and Methods. Advances in immunosuppressive treatment regimens, with increased efficacy, while minimizing the treatment-related toxicities, and better prevention and treatment of complications, have resulted in improved patient and renal survival in subjects with severe proliferative lupus nephritis over the past few decades. This review discusses the issues that are pertinent to the preservation of renal function in these patients.

Results and Conclusion. Treatment of severe proliferative lupus nephritis can be divided into an initial phase of induction followed by a prolonged maintenance phase, both of which impact upon the long-term renal and patient survival. The immunosuppressive potency of the treatment required for disease control varies according to the disease activity during the different phases. Despite variations in the choice, duration, and route of administration of antiproliferative agents, data to date suggest that immunosuppressive treatments combining cyclophosphamide or mycophenolate mofetil with corticosteroid appear to have similar efficacy in terms of inducing immunologic remission. In this regard, the immunologic efficacy of treatment is prerequisite to the prevention of irreversible loss of nephrons, but long-term renal outcome is also dependent on factors other than treatment efficacy, such as preexisting renal parenchymal damage and blood pressure control. Prompt diagnosis, early effective therapy, and reducing the risk of relapses are the disease specific measures that are essential to long-term renal preservation and the prevention of renal failure in subjects with severe proliferative lupus nephritis.

The outcome of patients with severe proliferative lupus nephritis has improved considerably over the past few decades. Patient survival rate was 70% at 5 years during the 1960s [1], but has been reported to exceed 90% at 10 years in recent series [2, 3]. Factors contributing to this improvement include advancements in immunosuppressive therapy, as well as better prevention and management of complications, such as infection or hypertension. Immunosuppressive treatment regimens with enhanced efficacy but reduced adverse effects have evolved from clinical studies. While the immunosuppressive regimens remain varied, the commonly adopted immunosuppressive treatments appear to have comparable short-term efficacy in inducing remission. In contrast, the long-term outcome after treatment is less well defined. Despite a general trend toward progressive improvement in long-term renal survival, independent investigators have reported different rates of renal failure. The variation in immunosuppressive treatments represents only one of many factors that can influence the longitudinal evolution of renal function.

OUTCOME INDICATORS OF CLINICAL TRIALS IN LUPUS NEPHRITIS

The incidence of renal failure associated with different treatments, as indicated by doubling of baseline serum creatinine level and/or end-stage renal failure, is commonly used as the principal end point of studies. In accordance with the progressive nature of renal function deterioration, it has been shown that prolonged follow-up exceeding 5 years is required to discern different treatment outcomes [4]. While these end points have obvious clinical relevance, it is imperative to note that the ultimate renal outcome is also under the influence of factors other than immunosuppressive efficacy. These modulating factors include the extent of irreversible renal parenchymal damage before and after induction therapy, blood pressure control, and the number and severity of subsequent nephritic relapses, which also relate to the efficacy of maintenance immunosuppression. Therefore, while long-term renal survival is the ultimate aim of clinical management, it is actually a composite end point subject to the influence of multiple confounding factors.

Prompt induction of remission is the major short-term objective of immunosuppressive treatment in severe lupus nephritis. The definition of remission varies between investigators, and commonly adopted criteria include a significant reduction of proteinuria, reversal of renal failure or preservation of baseline renal function, and improvement of serologic parameters such as the titre of anti-DNA antibodies and complement components. It should be noted, however, that the lack of improvements in proteinuria or renal function after treatment may be due to delayed treatment and irreversible scarring rather than inadequate immunosuppressive potency. The efficacy of immunosuppressive treatment per se is evident.

Key words: cyclophosphamide, mycophenolate mofetil, remission.

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from abatement of serologic activity, which usually precedes end-organ manifestations. Immunologic remission is prerequisite to interruption of the damaging inflammatory processes. Prompt induction of remission is, thus, essential to the preservation of a critical renal mass, and the prevention of progressive renal failure [2].

TREATMENT OUTCOME WITH DIFFERENT IMMUNOSUPPRESSIVE REGIMENS

Immunosuppressive medications remain the mainstay of treatment for lupus nephritis. In general, the intensity of immunosuppressive therapy should be tailored according to the serologic and histologic activity. Treatment of severe proliferative lupus nephritis can be separated into an initial phase of induction followed by a prolonged maintenance phase. The aim of induction treatment is to induce remission and preserve renal parenchyma, while that of maintenance therapy is to prevent relapses. Maximizing patient and renal survival, minimizing complications, and avoiding treatment-related adverse effects remain the unifying themes throughout the course of management. The induction phase lasts 4 to 6 months, and the immunosuppressive treatment usually comprises corticosteroid and an antiproliferative agent [3, 5–7]. After the disease activity is under control, the dose of corticosteroid is reduced and potent immunosuppressive agents can be replaced by less toxic alternatives.

Prednisolone combined with cyclophosphamide, the latter either as intermittent intravenous pulses or as daily oral treatment, has been commonly used as initial treatment [6, 8]. The inclusion of cyclophosphamide has been associated with better renal preservation and more stable remissions compared with corticosteroid treatment alone. A series of clinical trials from investigators at the NIH have shown that induction treatment with intravenous cyclophosphamide pulses was more effective than pulse methylprednisolone alone, and was associated with fewer side effects compared with prolonged (often exceeding 1 year) daily oral cyclophosphamide treatment [4, 9, 10]. In addition, extending the duration of intravenous cyclophosphamide treatment with quarterly pulses for 2 years reduced the relapse rate but increased the risk of ovarian failure, compared with treatment that included only the initial 6 monthly pulses [10]. Recently, the Euro-lupus Nephritis Trial showed that low-dose intravenous cyclophosphamide pulses of 500 mg fortnightly for 6 doses followed by azathioprine maintenance was as effective as the NIH regimen and might be associated with fewer infections [11]. Our own data showed that sequential immunosuppression with prednisolone and oral cyclophosphamide followed by low-dose prednisolone and azathioprine maintenance was associated with a complete remission rate of 77%, and that severe toxicities such as hemorrhagic cystitis or permanent amenorrhea could be obviated by limiting the duration of cyclophosphamide treatment to 6 months [12]. For comparison, a remission rate of 78% at 2 years has been reported in patients treated with prednisone and intravenous cyclophosphamide [13], and a complete remission rate of around 50% has been observed in patients treated with pulse cyclophosphamide, pulse methylprednisolone, or the combination of both [14]. A retrospective study on 43 subjects over 24 months has reported comparable remission rates of 73% and 90% in patients treated with intravenous or oral cyclophosphamide, respectively [15]. While patient characteristics and the definitions of remission differed between the various series, these data suggest that the duration of cyclophosphamide treatment is more important than its route of administration on the incidence of severe adverse effects.

Our previous studies on sequential immunosuppression with prednisolone and oral cyclophosphamide for 6 months followed by azathioprine maintenance showed that renal function remained stable during 35 months of follow-up [12]. In a follow-up study involving 66 patients with follow-up of more than 7 years, we have observed that the promising short-term outcome was associated with long-term stability of renal function in the majority of patients, so that chronic renal failure was noted in 6% of patients, and there was no death or end-stage renal failure [16]. In this context, other investigators have reported that 20% to 30% of patients treated with corticosteroid and intravenous cyclophosphamide pulses showed doubling of baseline serum creatinine after 36 months [10], and after 117 months, 21.4% of patients had died or developed end-stage renal failure, while another 11.7% showed chronic renal failure [14]. Another study reported that 12.8% of patients developed end-stage renal failure, and 8.1% had chronic renal failure after 2.6 years of follow-up following treatment with prednisone and 8 weeks of oral cyclophosphamide [5]. A study on 21 Chinese patients treated with a similar sequential immunosuppression regimen showed that 9.5% of patients had treatment failure or doubling of serum creatinine by 24 months [15]. These differences may be related to variations in clinical or histologic characteristics, sample size, ethnicity, and other factors that can influence long-term outcome.

More recently, we have shown that mycophenolate mofetil provides an equally effective alternative to cyclophosphamide, but with distinctly fewer and less severe side effects [17]. Patients treated with sequential immunosuppression and those treated with prednisolone and mycophenolate mofetil had similar remission rates of around 80%, and similar renal function during 12 months of follow-up. Mycophenolate mofetil treated subjects had fewer infections, no significant alopecia, or leukopenia, compared to those treated with cyclophosphamide. A follow-up study with a bigger sample size and follow-up
Table 1. Immunosuppressive treatment algorithm for severe proliferative lupus nephritis

<table>
<thead>
<tr>
<th>Induction</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>Agent</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.8 mg/kg/day, tapered to 7.5–10 mg/day</td>
</tr>
<tr>
<td></td>
<td>after 4–6 months</td>
</tr>
<tr>
<td>Mycophenolate mofetil or Cyclophosphamide</td>
<td>1.0–1.5 g b.i.d. for 6 months</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>7.5 mg/day gradually reduced to 5 mg/day</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2–2.5 mg/kg/day gradually reduced to 1 mg/kg/day, optimal duration not well defined</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td>Mycophenolate mofetil or Cyclophosphamide</td>
<td>1.0 g b.i.d. gradually reduced to 0.5 g b.i.d., optimal duration not well defined</td>
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<tr>
<td></td>
<td>or</td>
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<tr>
<td></td>
<td>i.v. 0.5–1 g/m²/month for 6 months or 500 mg fortnightly for 6 doses, or p.o. 2–2.5 mg/kg/day for 4–6 months</td>
</tr>
</tbody>
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Factors that Influence Long-Term Renal Survival

Factors that have been reported to adversely affect renal survival in patients with severe proliferative lupus nephritis include a high chronicity index and impaired renal function at baseline, failure to achieve complete remission after treatment, and serum creatinine concentration exceeding 2.0 mg/dL after treatment [2, 14, 19]. Lower remission rates have been observed in patients of African origin compared with Caucasians [2, 14]. In addition, there is an association between lower socioeconomic status and inferior long-term outcome, which may be related at least in part to the timeliness of diagnosis (and thus treatment) and drug compliance [2, 14, 19, 20]. Similar to others, we have noted no association between baseline activity score and long-term renal outcome [14]. This underscores the importance of reversibility and remission as critical determinants of final renal outcome. Our data show an association between the latest renal function and the renal function both at baseline and at 1 year after treatment, and that the chronicity index at baseline is also an independent predictor of latest creatinine clearance. Together these findings corroborate the important long-term implications of established renal parenchymal damage, and the critical need to preserve nephrons by prompt induction of remission. While focal proliferative and diffuse proliferative types of lupus nephritis have long been regarded as belonging to the same continuum, the Lupus Nephritis Collaborative Study Group has recently presented data to suggest that the two might have distinct pathogenetic mechanisms, so that focal proliferative lesions were associated with a lower likelihood of complete remission and a higher risk of renal failure compared with diffuse proliferative disease [21].

Relapses are common in systemic lupus erythematosus, and nephritic relapses adversely affect long-term renal outcome because with each relapse there is immune-mediated renal damage [14, 22]. It is therefore imperative to watch out for impending relapse by regular monitoring of serologic and clinical parameters. It remains controversial whether to increase the dose of immunosuppression preemptively should there be serologic reactivation in the absence of clinical manifestations. Such decisions should be individualized, taking into account the previous history of relapses. Our own data on patients treated with sequential immunosuppression show that 39% of patients relapsed over 7 years. This relapse rate appears comparable to that observed in patients who have received intravenous cyclophosphamide as induction therapy [13]. The relatively late occurrence (median of 79 months) of relapses in the latter study could be attributed to the long duration of cyclophosphamide treatment lasting 3 years. A relapse rate of 45% was reported in another study that included patients treated with pulse cyclophosphamide, pulse methylprednisolone, or the combination of both [9]. Similar to our findings, this study also reported an increased risk of relapse in patients who failed to achieve complete remission. Although nephritic relapses might result in reduced renal reserve, it is of interest to note that the latest renal function is similar between relapsers and nonrelapsers in our own series. This apparent paradox may be explained by the mild nature of the relapses, their early detection, and prompt reinduction of remission. The optimal rate of dose tapering, and the relative merits of low-dose prednisolone with or without mycophenolate mofetil or azathioprine as maintenance treatment, all require further investigation.

Hypertension and hyperlipidemia affect about one third and one fifth of patients with a history of lupus nephritis, respectively. The detrimental effect of uncontrolled hypertension on accelerating renal deterioration is well recognized. There is increasing evidence that heavy
proteinuria per se can exacerbate tubulointerstitial inflammation and fibrosis [23–25]. Although there is little data on the effect of angiotensin II blockade on proteinuria or renal protection in patients with lupus nephritis, this seems a reasonable approach in patients with persistent proteinuria despite optimal control of disease activity. It is imperative that these complications are rigorously prevented and controlled, since these patients show accelerated atherosclerosis and coronary vascular disease, which lead to premature vascular morbidity and mortality [26, 27]. Cardiovascular events have been reported to account for 48% of deaths in patients with a history of lupus nephritis [19, 28].

CONCLUSION

Management of patients with lupus nephritis encompasses both immunosuppressive therapy and the prevention and treatment of complications related to disease or treatment, with the ultimate aim of maximizing patient survival, renal survival, quality of life, and rehabilitation. With the advent of potent immunosuppressive agents, death from uncontrolled lupus activity is increasingly uncommon, although severe extrarenal involvements, such as pulmonary or cerebral lupus, are still associated with considerable morbidity and mortality. A recent report has shown that the outcome of patients with lupus nephritis who presented during the last decade was better than those who presented in the 1980s [29], and that such improvement was related to shorter time to diagnosis, less severe proteinuria, and fewer chronicity features at diagnosis. These findings exemplify the importance of early diagnosis and early intervention with effective but safe immunosuppression, before the disease activity has culminated in significant irreversible end-organ damage.

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REFERENCES