Current therapy of lupus nephritis. Which is the best option?

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Renal involvement in systemic lupus erythematosus (SLE) is an important cause of morbidity and mortality, reaching a prevalence of 39% during the course of the disease. Currently, the therapy for severe lupus nephritis is based on the use of high-dose corticosteroids and immunosuppressive drugs, being traditionally cyclophosphamide the most frequently used agent. Recent studies have demonstrated the efficacy of mycophenolate mofetil as induction therapy for lupus nephritis. Azathioprine, a safe drug during pregnancy, has not been demonstrated to be as effective as mycophenolate or cyclophosphamide as induction therapy, although it is an effective drug for maintenance of remission.

KEY WORDS: systemic lupus erythematosus, lupus nephritis, therapy, micophenolate mofetil.


Systemic lupus erythematosus (SLE) is an autoimmune systemic disease that predominantly affects young women. The prevalence of nephropathy at onset of SLE has been estimated at 16%, reaching 39% during the evolution of the disease. Furthermore, renal involvement in SLE is a relevant cause of morbidity and mortality. In fact, after 10 years, 5-10% of patients have died and a further 5-15% have developed end-stage renal failure, even with standard of care treatment. There have been several attempts to classify lupus nephritis. The World Health Organization (WHO) classification is the most extensively used both in clinical trials and routine clinical practice, although it has been recently modified and made more complex, subdividing the former classes. The pathologic classification of lupus nephritis has an outstanding importance in defining the outcome and the intensity of therapy required to prevent the evolution to end-stage renal disease. Diffuse proliferative glomerulonephritis is a term used to describe a distinct histological form of glomerulonephritis common to various types of systemic inflammatory diseases, including SLE. When more than 50% of the glomeruli demonstrate increased mesangial, epithelial, endothelial (proliferative) and inflammatory cells, it is called diffuse glomerulonephritis; in contrast, when less than 50% of the glomeruli are involved, the condition is termed focal proliferative glomerulonephritis, an entity that can potentially progress to diffuse proliferative glomerulonephritis. Currently, it is accepted that focal proliferative glomerulonephritis requires the same therapeutic approach as diffuse proliferative glomerulonephritis.

The aim of the treatment in lupus nephritis is to suppress the inflammation in renal tissue and to preserve the structure and function of the kidney, avoiding the progression to renal failure. This objective must be achieved without developing significant adverse events. Currently, the therapy for severe lupus nephritis is based on the use of high-dose corticosteroids and immunosuppressive drugs. Several randomized controlled studies demonstrated that, for patients with severe lupus nephritis, a regimen including cyclophosphamide (CYC) is more effective than treatment with only glucocorticoids. Noteworthy, these randomized...
zed trials of the United States National Institutes of Health (NIH) failed to demonstrate significant differences among the different regimens containing immunosuppressive drugs (daily oral CYC, monthly intravenous (IV) CYC, daily oral azathioprine (AZA), combined low-dose oral CYC plus AZA). Nevertheless, monthly IV CYC became the gold standard of treatment for severe lupus nephritis since then. A recent study by Houssiau et al. has shown that, as far as induction of remission and prevention of end-stage renal failure is concerned, a 12-week course of IV CYC given at a fixed dose of 500 mg fortnightly and followed by AZA for 2 years is as effective as an abbreviated NIH protocol consisting on six monthly IV CYC pulses of 0.5 g/m² (increasing the dose according to the leucocyte count) followed by two quarterly pulses, after a median follow-up of 72 months. Unfortunately, the use of IV CYC is not exempt from pitfalls. Despite the treatment with CYC, a significant proportion, up to 50%, of patients with lupus nephritis do not achieve a complete remission. In the studies of the United States NIH, a longer duration of the therapy with CYC reduced the cumulative probability of relapse, when comparing 24 versus 6 months of treatment, but longer therapy with CYC was associated with increased gonadal toxicity. In addition, CYC, even with intravenous administration, has a significant toxicity in terms of hemorrhagic cystitis, gonadal failure and infections.

For the above mentioned reasons, the need for less toxic and more effective alternatives to CYC in the treatment of lupus nephritis is clear. Mycophenolate mofetil (MMF) is a powerful immunosuppressant that exerts a reversible inhibitor of inosine monophosphate dehydrogenase, the rate-limiting step in de novo purine synthesis, which is essential for lymphocyte proliferation. MMF has been approved for the prevention of allograft rejection, an indication for which it has been demonstrated to be superior to AZA. Although several uncontrolled studies had suggested the safety and efficacy of MMF in lupus nephritis, only recently has solid evidence on the role of MMF in comparison with CYC been published (table 1).

### Table 1

Randomized clinical trials comparing mycophenolate mofetil versus cyclophosphamide in the treatment of proliferative lupus nephritis

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Number of patients</th>
<th>WHO class</th>
<th>Follow-up</th>
<th>Regime</th>
<th>Drug doses</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al., 2000</td>
<td>42</td>
<td>III, IV, Vb</td>
<td>12 months</td>
<td>Induction of remission</td>
<td>Oral CYC 2.3 mg/kg/d vs oral MMF up to 3 g/d</td>
<td>Equal</td>
<td>MMF less toxic</td>
</tr>
<tr>
<td>Chan et al., 2005</td>
<td>64</td>
<td>IV</td>
<td>63 months</td>
<td>Induction of remission</td>
<td>Oral CYC 2.5 mg/kg 6 months followed by oral AZA 1.5-2 mg/kg vs oral MMF 2 g/d</td>
<td>Equal</td>
<td>MMF less toxic</td>
</tr>
<tr>
<td>Hu et al., 2002</td>
<td>46</td>
<td>IV</td>
<td>6 months</td>
<td>Induction of remission</td>
<td>IV CYC 0.75-1 g/m² monthly vs oral MMF 0.5-1.5 g/d</td>
<td>MMF more effective</td>
<td>MMF less toxic</td>
</tr>
<tr>
<td>Ong et al., 2005</td>
<td>44</td>
<td>III, IV</td>
<td>6 months</td>
<td>Induction of remission</td>
<td>IV CYC 0.75-1 g/m² monthly vs oral MMF 2 g/d</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Ginzler et al., 2005</td>
<td>140</td>
<td>III, IV, V</td>
<td>6 months</td>
<td>Induction of remission</td>
<td>IV CYC 0.5-1 g/m² monthly vs oral MMF up to 3 g/d</td>
<td>MMF more effective</td>
<td>MMF less toxic</td>
</tr>
<tr>
<td>Contreras et al., 2004</td>
<td>59</td>
<td>III, IV, Vb</td>
<td>1-3 years</td>
<td>Maintenance of remission</td>
<td>IV CYC 0.5-1 g/m² quarterly; oral AZA 1-3 mg/kg/d; or oral MMF up to 3 g/d</td>
<td>MMF and AZA more effective</td>
<td>MMF and AZA less toxic</td>
</tr>
</tbody>
</table>

AZA: azathioprine; CYC: cyclophosphamide; MMF: mycophenolate mofetil; WHO: World Health Organization.
Hu et al. conducted a clinical trial comparing MMF versus IV CYC in 46 patients with diffuse proliferative lupus nephritis WHO class IV for 6 months. All the 23 patients receiving MMF had failed or relapsed after treatment with CYC and steroids. They compared the clinical efficacy and the difference in histological alterations after each treatment. Significant differences in reduction in proteinuria and hematuria favouring the treatment with MMF were found. After 3-6 months, repeated renal biopsies demonstrated that the activity index was substantially reduced after MMF treatment compared with CYC. With regard to side effects, MMF was found to be safer than CYC. Ong et al. also compared MMF versus IV CYC as induction therapy for proliferative lupus nephritis. They included 44 patients with newly diagnosed lupus nephritis WHO class III or IV, who were randomly assigned to receive either MMF 2 g/day for 6 months or IV CYC 0.75-1 g/m² monthly for 6 months, both immunosuppressants in addition to corticosteroids. Remission occurred in 52% of patients in the CYC group and in 59% of patients in the MMF group (p = 0.70). Complete remission was achieved in three patients (12%) in the CYC group and five patients (26%) in the MMF group (p = 0.22). Proteinuria decreased and serum creatinine remained stable in both groups. Twenty-four follow-up renal biopsies at the end of therapy showed a significant reduction in the activity score in both groups. The chronicity index increased significantly over the 6 months in the IV CYC group but not in the MMF group. There was no difference (p = 0.18) in the rate of adverse events between groups.

Recently, the efficacy of MMF in the maintenance of response after an induction regime with IV CYC in severe lupus nephritis has also been studied. Contreras et al. included 59 patients with lupus nephritis (12 in WHO class III, 46 in class IV, and 1 in class Vb) who received induction therapy with IV monthly CYC (0.5 to 1 g/m²) plus corticosteroids. Subsequently, the patients were randomly assigned to one of three maintenance therapies: quarterly intravenous injections of CYC (0.5 to 1 g/m²), oral AZA (1 to 3 mg/kg/day), or oral MMF (500 to 3000 mg/day) for one to three years. During the follow-up, four patients died in the CYC group and one in the MMF group. Three patients in the CYC group and one each in the AZA and MMF groups developed chronic renal failure. The 72-month event-free survival rate for the composite end point of death or chronic renal failure was significantly higher in the MMF and AZA groups than in the CYC group (p = 0.05 and p = 0.009, respectively). Furthermore, the rate of relapse-free survival was also significantly higher in the MMF group than in the CYC group (p = 0.02). With respect to the incidence of adverse events, hospitalizations, amenorrhea, infections, nausea, and vomiting were significantly higher in the CYC group. The authors concluded that, in proliferative lupus nephritis, the maintenance therapy with MMF or AZA appears to be more efficacious and safer than long-term therapy with IV CYC.

AZA is a relatively safe immunosuppressant extensively used as a corticosteroid-sparing agent in different manifestations of SLE, including lupus nephritis. Furthermore, AZA can be used during pregnancy, in contrast to CYC or MMF. Recently, Grootscholten et al. have shown the results of a randomized trial comparing AZA (2 mg/kg/day for 2 years combined with intravenous pulses of methylprednisolone) vs IV CYC pulses (0.75 g/m², 13 pulses in 2 years) as induction regime in 87 patients with proliferative lupus nephritis. With a median follow-up of 5.7 years, doubling of serum creatinine was more frequent in the AZA group, although without reaching statistical significance. Relapses occurred significantly more often in the AZA group, with a relative risk of 8.8 (95% confidence interval: 1.5-31.8). Furthermore, the kidney biopsies obtained after two years of treatment showed that CYC delayed the progression of chronic lesions more effectively than AZA.

Concluding remarks

In 1981, Alfred D. Steinberg wrote in the first edition of Kelley’s Textbook of Rheumatology «Despite wi-
despread interest and a large literature, the optimal treatment for kidney disease (in SLE) remains controversial, if not unknown. A quarter of a century after, his words are still true but new insights from the randomized clinical trials on lupus nephritis have added light into the scene and have helped us to formulate new and relevant questions about the optimal therapy for proliferative lupus nephritis.

After analyzing the different randomized controlled clinical trials recently published on proliferative lupus nephritis, the conclusions could be that the induction of remission can be achieved with oral MMF (up to 3 g/day) or with IV CYC in its different ways of administration (monthly 0.5 to 1 g/m² x 6 doses or fortnightly 500 mg x 6 doses). After achieving remission, both AZA and MMF are effective and relatively safe agents for maintenance of remission.

Nevertheless, many essential questions remain to be elucidated as to the optimal type and duration of therapy for inducing and maintaining remission, the optimal treatment of relapses, the need for repeated biopsies, the need for stratification of patients based on the risk of end-stage renal failure and tailoring of the therapy, or the role of new biologic agents, such as anti-CD20 or anti-BLyS antibodies, in the treatment of lupus nephritis.

REFERENCES