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, mycophenolate mofetil.

Tratamiento actual de la nefritis lúpica. ¿Cuál es la mejor opción?
La afectación renal en el lupus eritematoso sistémico (LES) es una causa importante de morbilidad y mortalidad, llegando a afectar hasta al 39% de los pacientes diagnosticados de LES durante su evolución. Actualmente, el tratamiento de la nefritis lúpica grave se basa en el uso de dosis altas de corticosteroides y fármacos inmunosupresores, de entre los cuales, tradicionalmente, la ciclofosfamida ha sido el más utilizado. Estudios recientes han demostrado la eficacia del micofenolato de mofetilo como terapia de inducción para la nefritis lúpica. La azatioprina, de uso seguro durante la gestación, no ha demostrado ser tan eficaz como el micofenolato o la ciclofosfamida como terapia de inducción, aunque sí ha resultado ser efectiva para el mantenimiento de la remisión.

PALABRAS CLAVE: lupus eritematoso sistémico, nefritis lúpica, terapia, micofenolato mofetilo.

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 randomi-
TABLE 1

<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 (extended study)</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.

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 leukocyte 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 NH, 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 (14,22-25).

Chan et al. randomized 42 patients with diffuse proliferative lupus nephritis to be treated with prednisolone and MMF for 12 months (21 patients) or prednisolone and CYC for 6 months followed by prednisolone and AZA for another 6 months (21 patients). Complete remission was defined as urinary protein excretion less than 0.3 g per 24 hours, with normal urinary sediment, normal serum albumin concentration, and values for both serum creatinine and creatinine clearance less than 15 percent above the baseline values. Partial remission was defined as proteinuria within the range of 0.3 to 2.9 g per 24 hours, with a serum albumin concentration of at least 30 g/L and stable renal function. The incidence of complete or partial remission and the duration of treatment before a complete remission was achieved were similar in the two groups. Of the 21 patients treated with MMF and prednisolone, 81% had a complete remission and 14% had a partial remission, compared with 76% and 14%, respectively, of the 21 patients treated with CYC and prednisolone followed by AZA and prednisolone. The improvement in the degree of proteinuria and the serum albumin and creatinine concentrations were similar in both groups. Infections developed with a similar incidence in the two groups, occurring in 19% of the patients in the MMF group and in 33% of those in the CYC group (p = 0.29). Other adverse effects, including amenorrhea (23%), alopecia (19%), leukopenia (10%) and death (10%), were seen only in patients treated with CYC. The rates of relapse were 15% in the MMF group and 11% in the CYC-AZA group, all occurring after nine months, when the patients were receiving maintenance therapy. Later, the same authors...
published an extended long-term study with 64 patients and a median follow-up of 63 months. More than 90% of subjects in each group responded favourably (complete or partial remission) to induction treatment and both groups showed stable and comparable serum creatinine over time. Proteinuria decreased in the two groups without significant differences. There was no significant difference in the rates of either doubling of serum creatinine, end-stage renal failure or renal relapses. Significantly, fewer MMF treated patients developed infections that required antibiotic treatment or hospitalization, despite an identical corticosteroid regimen. And, again, end-stage renal failure, death, leukopenia and alopecia were observed only in the CYC-AZA group. The authors concluded that MMF and prednisolone were a safe, well-tolerated and effective continuous induction-maintenance treatment for diffuse proliferative lupus nephritis.

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 58% 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.

The largest to date induction study in proliferative lupus nephritis, Ginzler et al. compared oral MMF (initial dose, 1000 mg/d, increased to 3000 mg/d) with monthly IV CYC (0.5 g/m² of body-surface area, increased to 1 g/m²) as induction therapy for active lupus nephritis over a 6-month period. In the intention-to-treat analysis, 16 of the 71 patients (22.5%) receiving MMF and 4 of the 69 patients receiving IV CYC (5.8%) had complete remission (defined as a return to within 10% of normal values of serum creatinine levels, proteinuria and urine sediment), for an absolute difference of 16.7 percentage points (p = 0.005), fulfilling the criteria for non-inferiority and demonstrating the superiority of MMF to CYC. There was no difference in the rate of partial remissions (29.6% vs 24.6%, respectively; p = 0.51) and, on follow-up, there were no significant differences in the rates of renal relapse, end-stage renal failure or death. Interestingly, there were fewer severe infections and hospitalizations in patients receiving MMF. The investigators concluded that MMF was more effective than IV CYC in inducing remission of lupus nephritis and had a more favourable safety profile.

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 also was 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 AZC 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 × 6 doses or fortnightly 500 mg × 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 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


