Treatment of Lupus Nephritis

Lucía Silva Fernández, a José Luis Andréu Sánchez, b and Ellen M. Ginzler c

a Servicio de Reumatología, Complexo Hospitalario de Pontevedra, Pontevedra, Spain
b Servicio de Reumatología, Hospital Universitario Puerta de Hierro, Madrid, Spain
c Rheumatology Division, SUNY Downstate Medical Center, New York, NY, USA

Lupus nephritis is a relevant source of morbidity and mortality in patients with systemic lupus erythematosus. The standard therapy of remission induction in severe lupus nephritis is based on the use of monthly intravenous cyclophosphamide. Recent data have established that the maintenance of remission in lupus nephritis can be achieved with azathioprine or mycophenolate mofetil, with less adverse effects than quarterly intravenous cyclophosphamide. In recent years, a number of controlled randomized clinical trials have been published, opening new therapeutic options in the induction of remission in lupus nephritis, such as less aggressive regimens of intravenous cyclophosphamide or mycophenolate mofetil. Further studies are needed for establishing the optimal therapy of lupus nephritis patients.

Key words: Lupus nephritis. Mycophenolate mofetil. Cyclophosphamide. Systemic lupus erythematosus.

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a prevalence that varies with the age, sex, and race, affecting young women, predominantly in fertile age, particularly of Afro-Caribbean origin.1-2 The prevalence of kidney involvement at the time of diagnosis of SLE is 16%, reaching 39% during the evolution of the disease.3 Renal involvement in SLE is an important cause of morbidity and mortality.4,5 In fact, after 10 years from the diagnosis, 5%-10% of the patients have died and another 5%-15% have developed end-stage renal failure, even with standard cyclophosphamide therapy.6,7 There have been several attempts to classify lupus nephritis (LN). The most commonly used classification is that of the World Health Organization (WHO), applied both in clinical trials and in routine clinical practice.8 This classification is based on the histologic findings in the glomerulus and kidney interstitium, and its progression. The pathological classification of LN is of outstanding relevance for defining the prognosis, and the intensity and duration of the therapy needed to prevent the evolution to end stage renal disease (ESRD). Mild renal disease (classes II and IIIa) affects approximately 35%-50% of patients, while the classes IIIB, IV, and V affect 45%-60%. In a significant
minority of patients with LN class III (focal and segmental proliferative glomerulonephritis), renal function worsens and progresses to class IV. The objective in the treatment of LN is to suppress the inflammation and to preserve the structure and renal function to avoid the progression to ESRD. It is also very important to minimize the secondary effects. In a first induction phase an early remission should be achieved avoiding the chronicity of renal disease. In the maintenance phase the development of new renal flares should be avoided during the course of the disease. Currently the therapy for serious LN is based on the use of high dose of corticosteroids (CS) and immunosuppressive drugs, being traditionally cyclophosphamide (CYC).

**Treatment of Remission Induction With Cyclophosphamide**

Traditionally, the National Institutes of Health (NIH) regimen with intermittent intravenous (IV) CYC has been considered the standard of care for proliferative LN. This regimen involves the use of IV CYC dosages of 0.5-1 g/m² body surface area for 6 months, followed by quarterly dosages until completing 2 years of treatment, and oral CS in tapering doses. Initially, several randomized and controlled clinical trials of the NIH demonstrated that oral or IV CYC was an effective therapy for the treatment of severe LN. The results of these studies showed that the treatment regimens that included CYC preserved renal function and more successfully reduced the probability of progression to ESRD than monotherapy with CS, although IV CYC did not increase the global survival of the patients. This superiority of CYC to other treatments (CS alone or CS plus azathioprine) could be observed only after 5 years of follow-up. The best regimen for CYC therapy in LN has not been completely defined yet. In the studies of NIH it was demonstrated that IV administration had better long term effectiveness than oral continuous administration, but the difference was not significant. In another study in which 2 cohorts of LN patients treated with oral continuous CYC or with IV pulses were prospectively compared, it was demonstrated that 6 and 24 months after treatment, oral administration tended to be more effective, but conclusions were limited by sample size and the short period of observation. Studies comparing the toxicity of oral and IV CYC are also scarce. In the NIH study it was demonstrated that IV administration was associated with a lower incidence of amenorrhea, haemorrhagic cystitis and tumours when compared with oral administration. A more recent study compared the 2 modes of administration in 29 patients with LN without finding significant differences in effectiveness and toxicity, probably due to the reduced size of the sample. In the last years a new administration regimen of IV CYC has been introduced. It reduces the accumulated dose of CYC to 3 g, reducing also its secondary effects. In 2002 the results of the Euro-Lupus Nephritis Trial (ELNT) were published. In this study the NIH regimen was compared with another IV CYC regimen, consisting of the administration of 500 mg of IV CYC every 15 days for 3 months, followed by oral azathioprine (AZA) for 2 years. The effectiveness was similar in both groups in the short and long-term follow-up (41 and 73 months).

New renal flares are frequent, even in those patients who had had a complete response to CYC, although they don’t necessarily result in loss of renal function if they are treated again with immunosuppressive drugs. Black race, male sex, young age, low socioeconomic level, high renal activity and chronicity indexes, low levels of complement, high titers of anti-dsDNA antibodies, high creatinine serum levels, nephrotic range proteinuria, severe anemia, hypertension, and a partial response to immunosuppressive therapy compared to a complete response, are predictors of new renal flares. It is more difficult to reach remission in patients with subsequent renal flares that in those treated the first time. CYC has, therefore, been a significant advance in the treatment of LN. In the 50’s, patients with LN class IV rarely lived more than 5 years, while presently more than 80% survive maintaining renal function 10 years after diagnosis. However, CYC’s toxicity profile and the lack of response in some patients, make it necessary to look for new treatment alternatives for LN. A systematic review concluded that the main secondary effect of the treatment with CYC was premature ovarian failure, affecting 47% of the women treated with CYC and CS, followed by infections in 20%. Furthermore it was observed that the therapy with CYC and CS was not entirely effective, since 24% doubled serum creatinine, 16% developed ESRD and 21% died.

**Role of Other Immunosuppressants in the Induction of Remission**

**Mycophenolate Mofetil**

Mycophenolate mofetil (MMF) is a powerful immunosuppressant that exerts a reversible inhibition 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. Initially, its use in LN was reserved for patients who had not responded to CS and CYC, or had presented an unacceptable toxicity. Although several uncontrolled studies had suggested the safety and efficacy of MMF.
in lupus nephritis,\textsuperscript{25-31} only recently has solid evidence on the role of MMF as induction therapy in comparison with CYC been published.\textsuperscript{32-36}

Chan et al\textsuperscript{32} 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 azathioprine (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 2 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 2 groups, occurring in 19% of the patients in the MMF group and in 33% of those in the CYC group (\textit{P}=.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 9 months, when the patients were receiving maintenance therapy. Later, the same authors published an extended long-term study\textsuperscript{33} 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 similarly in the 2 groups. 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\textsuperscript{34} 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\textsuperscript{35} 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/m\textsuperscript{2} 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 (\textit{P}=.70). Complete remission was achieved in three patients (12%) in the CYC group and 5 patients (26%) in the MMF group (\textit{P}=.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 (\textit{P}=.18) in the rate of adverse events between groups.

In the largest to date induction study in proliferative lupus nephritis, Ginzler et al\textsuperscript{36} compared oral MMF (initial dose, 1000 mg/d, increased to 3000 mg/d) with monthly IV CYC (0.5 g/m\textsuperscript{2} of body-surface area, increased to 1 g/m\textsuperscript{2}) 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% (\textit{P}=.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; \textit{P}=.51) and, on follow-up, there were no significant differences in the rates of renal relapse, end-stage renal failure or death. 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.

A recent meta-analysis\textsuperscript{37} including randomized studies of MMF in LN and cohort studies of SLE and LN patients concluded that treatment with daily oral MMF is more effective than oral or IV CYC. Treatment with MMF induced more remissions (complete and partial)
having a smaller mortality, less hospitalizations and less severe secondary effects, as the infections. Moreover, neither cases of amenorrhea nor alopecia were noted with MMF. This metaanalysis, however, doesn’t provide information on which subgroup of patients will respond better to MMF or other immunosuppressants, since the most severe patients were excluded from studies and the distribution by race and WHO class of LN was not homogeneous. Conclusions on the maintenance treatment can not be reached either because there is little information regarding long-term follow-up. Currently in progress is the Aspreva Lupus Management Study (ALMS),\textsuperscript{15} a randomized, multicentre prospective, phase III, controlled trial evaluating the effectiveness and safety of MMF as induction and maintenance therapy in more than 350 patients. In the induction phase patients have been randomized to receive oral MMF or IV CYC in addition to CS for 24 weeks in an open-label protocol. In a second phase, patients who have achieved partial or complete remission have been re-randomized to receive MMF or AZA as maintenance therapy in a double-blind protocol. The results of this study may allow a better understanding of which patients are more likely to achieve a favourable treatment response with MMF.

**Azathioprine**

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. Flanc et al\textsuperscript{25} published in 2004 a metaanalysis including randomized and controlled trials in LN. In their analysis they found that AZA reduced the global mortality in patients with LN although it didn’t reduce the risk of ESRD. This finding is probably due to the fact that only 3 trials\textsuperscript{39-41} with 78 patients comparing AZA with CS were included. Moreover, these trials were carried out in the 70’s, when the mortality of LN was much higher that at the present time. Later studies have not been able to demonstrate a difference in mortality, probably because the survival of patients with LN has improved due to dialysis and transplant.\textsuperscript{11} The analysis didn’t find an association of AZA with an increased frequency of infections including herpes zoster. More recently, Grootscholten et al\textsuperscript{42} 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/m\textdegree, 13 pulses in 2 years) as an induction regimen in 87 patients with proliferative lupus nephritis. During the first 2 years, the frequency of remission was not different, but infections, especially herpes zoster virus infections were more frequent in the AZA group. Ovarian failure rate was not different between groups. 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% CI, 1.5-31.8). Furthermore, renal biopsies obtained after 2 years of treatment showed that CYC delayed the progression of chronic lesions more effectively than AZA.\textsuperscript{43}

**Maintenance of Remission**

Once remission is reached, the main objective is to maintain it, avoiding relapses and the development of ESRD. Currently, it is thought that immunosuppressive therapy is necessary to maintain remission in LN, since the rate of relapses after CYC withdrawal is between 10% and 66%.\textsuperscript{12,20,44,45} According to the studies of the NIH, the accumulated probability of not developing ESRD after 72 months after having received a long regimen of IV CYC is 75%-100%,\textsuperscript{10,12,14} Keeping in mind the toxicity of CYC, mainly the premature ovarian failure,\textsuperscript{46} the NIH group compared the effectiveness and security of a short regimen of IV CYC of 6 monthly pulses with the same regimen followed by approximately 12 more quarterly pulses as maintenance therapy. Although the incidence of amenorrhea in the low CYC dose group was smaller ($P<0.03$) the accumulated probability of not developing new renal flares was also smaller in the patients who had only received maintenance therapy with CS (40% vs 87%; $P<.01$). In the last decade, it has been demonstrated that it is possible to maintain remission with other immunosuppressants, after administering a short initial course of IV CYC. Recently, Chan et al\textsuperscript{47} have demonstrated that the induction treatment with oral CYC and CS followed by low dose prednisone and AZA as maintenance therapy is also associated with a high incidence of complete remission (82% of the 66 patients included in the study) and maintenance of normal renal function in his Chinese population. In the ELNT,\textsuperscript{17,18} mainly comprised of a Caucasian population, 2 induction regimens with IV CYC were compared (see above) followed by AZA (2 mg/kg/d) and CS (prednisolone, 5-7.5 mg/d) as maintenance therapy for at least 30 months. In the 73-months follow-up renal function was preserved in 79% of the patients (80% in those that had received the ELNT regimen of CYC and 77% in those that had received the NIH regimen). MMF is also an useful drug for maintenance therapy in severe LN after an induction regimen with IV CYC. Contreras et al\textsuperscript{48,49} 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 monthly IV CYC.

\textsuperscript{10,12,14}
(0.5-1 g/m²) plus corticosteroids. Subsequently, patients were randomly assigned to one of 3 maintenance therapies: quarterly intravenous injections of CYC (0.5-1 g/m²), oral AZA (1-3 mg/kg/day), or oral MMF (500-3000 mg/day) for 1-3 years. During the follow-up, 4 patients died in the CYC group and 1 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<.05 and P<.009, respectively). Furthermore, the rate of relapse-free survival also was significantly higher in the MMF group than in the CYC group (P=.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, maintenance therapy with MMF or AZA appears to be more efficacious and safer than long-term therapy with IV CYC.

Calcineurin Inhibitors

Cyclosporine A (CsA) and tacrolimus block the transcription of interleukin 2, which inhibits T-lymphocyte activation. Theses drugs were developed for immunosuppression in transplanted organs. The experience in LN is still very limited, and its role is still to be defined. Generally, CsA is reserved for resistant cases or for those patients that have developed severe toxicity. It seems to be an effective drug in the treatment of membranous LN, improving proteinuria and serum albumin. In an open-label study including 11 patients with LN classes III-V, 8 of them without response to CYC or AZA, improvement in proteinuria and in anti-dsDNA titers was observed after a year of treatment. Tam et al treated 17 patients with class IV LN with CsA during a mean of 43.2 months. Seven of them had not responded to CYC and 2 to AZA. They observed a reduction of proteinuria and a significant elevation of serum albumin after the first month of treatment. After 12 months, repeated renal biopsies showed histologic improvement, with WHO type II changes and a reduction of the activity indexes in the 17 patients. More recently, Moroni et al published the results of a randomized trial comparing CsA with AZA as maintenance therapy in 75 patients with proliferative LN. The patients received CS and oral CYC as induction therapy and subsequently they were randomized to receive CsA or AZA for 2 years. During the follow-up to 4 years, there were 7 new flares in CsA group and 8 in the AZA group. No deaths or ESRD occurred. In both groups proteinuria decreased and, in the renal biopsies, there was a reduction in activity index and an increase in chronicity. The authors concluded that both AZA and CsA are useful as maintenance therapy for LN.

The possible adverse effects of CsA include hypertension, transitory worsening of renal function, hirsutism, gingival hyperplasia, tremors, and paresthesias; however, it appears better tolerated than CYC and approximately the same as MMF.

Tacrolimus is another inhibitor of calcineurin that has demonstrated a power from 10-100 times superior to CsA. Mok et al published in 2005 an open study on the use of tacrolimus in 9 patients with diffuse proliferative LN. After 6 months of treatment, 6 reached complete (67%) remission and 2 partial (22%) remission. A significant improvement was observed in proteinuria, haemoglobin, serum albumin, and C3 levels in comparison with the baseline values, starting from the second month of therapy. Severe adverse effects were not recorded. Tacrolimus has also been used in patients with membranous LN with promising preliminary results.

Leflunomide

Leflunomide is an inhibitor of de novo pyrimidine synthesis that is approved for the treatment of rheumatoid arthritis and psoriatic arthritis. It also inhibits the production of proinflammatory cytokines such as TNFα and interleukin 1β. Several small series have reported beneficial results in patients with SLE. In a prospective controlled trial including 47 patients with previously diagnosed SLE and biopsy confirmed proliferative LN, the effectiveness of oral leflunomide was compared with IV CYC in a 6 months follow-up. No patient had received immunosuppressive therapy previously. Statistically significant differences between both groups in the rate of complete (40% in the leflunomide group and 25% in the IV CYC group) and partial (80% and 75% respectively) remission were not seen. A more recent open study has demonstrated that treatment with leflunomide for 1 year reduced proteinuria in 17 patients with different classes of LN who had not responded to treatment with CYC, CsA, or AZA. Despite these results, it should be kept in mind that leflunomide has been reported to induce SLE or precipitate subacute cutaneous lupus.

Biological Therapy

Abetimus (LJP 394)

LJP 394 was designed to prevent the recurrence of renal flares in patients with established LN, by selectively reducing antibodies to dsDNA via antigen-specific
tolerance. It is a synthetic agent composed of four deoxyribonucleotide sequences bound to a triethylene glycol backbone. The first study of effectiveness, LJP-90-05, was designed to evaluate the ability of abetimus sodium to prolong the time to renal flare in a population of lupus patients at increased risk of renal flares. It included 230 patients with anti-dsDNA antibodies and prior history of LN who had experienced renal flares in the 4 years preceding the study entry. Patients were randomized to receive 100 mg of the drug or placebo weekly in a proportion of 1:1 during an induction phase of 16 weeks. This phase was followed by an 8-week drug holiday after which patients received 50 mg of drug or placebo for 12 weeks. The study continued for 18 months, with 8-week holidays after each of the 12-week maintenance phases. The time to renal flare and the number of renal flares were not significantly different in the 2 treatment groups, and the trial was discontinued prematurely. Anti-dsDNA antibodies titers were found to decrease significantly more in the abetimus group, with concomitant increase in C3 levels. A subgroup analysis in patients who had high affinity antibodies against abetimus showed a longer time to renal flare, with fewer flares and a decreased requirement for subsequent treatment with IV CYC in the abetimus group compared with the placebo group. Side effects were similar in both groups. Subsequently, a similar trial with the following exceptions was designed: drug holidays were eliminated, a dose of 100 mg was maintained throughout the study, and patients continued in the study until month 22 or until the study end point was reached, whichever occurred first. Analysis of intent-to-treat population showed that the estimated median time to renal flare was 123 months in the abetimus treatment group compared with 89 months in the placebo group (not statistically significant) and 25% fewer renal flares occurred in the abetimus high-affinity group (17/145, 12%) compared with the placebo group (24/153, 16%) (not statistically significant). Reductions in dsDNA antibodies occurred in the treatment group, whereas no change occurred in the placebo group (P<0.01). This reduction in dsDNA antibodies correlated with increases in C3 (P<0.001). The incidence of adverse events was similar in both groups. These data suggest that SLE patients who have reductions in dsDNA antibody levels are likely to have fewer renal flares than are patients who have stable or increasing dsDNA antibody levels. In addition, the data demonstrated that sustained reductions were approximately 2–4 fold more likely to occur in the treatment group than the placebo group. Based on patient self-reports, health-quality of life was significantly improved in the treated versus the placebo group. Currently, a new clinical trial with abetimus is in progress (LJP 90-014). A 300 mg-dosing arm has been added. Positive results of this study may lead to approval of abetimus for the treatment of LN.

Infliximab

Levels of TNFα correlate with disease activity in SLE. TNFα is expressed in the renal tissues of patients with LN. An open study of 6 SLE patients, 4 of whom had glomerulonephritis that did not respond adequately to CYC, AZA, or CsA, showed that infliximab (four 300 mg doses) was effective in ameliorating proteinuria in these patients. However, the post-treatment increase in the titers of anti-dsDNA and anticardiolipin antibodies may be a concern. Despite this observation, no increase in disease activity or adverse effects was observed. The same group has started a randomized, controlled, double-blind trial with infliximab and azathioprine in patients with membranous LN. There is no experience with other anti-TNFα agents in LN. A randomized, phase II, placebo-controlled trial study has been designed to evaluate the security and tolerability of etanercept in patients with LN.

Rituximab

Rituximab is a chimeric monoclonal antibody directed against the CD20 molecule on the surface of pre-B-cells and mature B-cells. Open-label trials and case reports have reported that rituximab is effective in various refractory SLE manifestations. In a pilot open study of 5 patients with refractory SLE, 3 of whom had nephritis, a combination of rituximab and CYC with high-dose corticosteroid was well tolerated and led to improvement of renal parameters in 2 patients. Using a similar protocol with higher doses of rituximab, the same group of investigators recently reported results in 24 SLE patients who were refractory to conventional therapies. Of these, 16 patients had diffuse proliferative nephritis that had been refractory to CYC and MMF. Improvement in SLE activity, serological markers such as anti-dsDNA titers, C3 levels, and protein-to-creatinine ratio was noted, although the latter change was not statistically significant. Another open study of 10 patients with active proliferative nephritis (not refractory) reported a renal response in 8 patients after therapy with a combination regimen of rituximab infusion and high-dose corticosteroids. Vigna-Pérez et al published an open study with 22 patients with refractory LN (mainly classes III and IV). They received rituximab (0.5–1 g in the days 1 and 15) added to the previous immunosuppressive therapy. They found a significant reduction in disease activity of SLE (P<0.05) and proteinuria (P<0.05) after 60 and 90 days from first infusion. There were no significant differences in complement levels neither in anti-dsDNA titers. One patient died of invasive histoplasmosis at day 70. They did not register any other severe adverse effects. More recently, Gunnarsson et al have published the results...
of treating 7 patients with CYC-resistant proliferative LN with a combination of rituximab and CYC. A clinically significant improvement was seen in the 6-month follow-up, with a reduction in SLEDAI score and in anti-dsDNA and anti-C1q titers. Repeated biopsies showed histological improvement and a reduction of the activity index in most of the patients. In December of 2006, the Food and Drug Administration (FDA) communicated the death of 2 SLE patients treated with rituximab due to progressive multifocal leucoencephalopathy, an infection caused by JC virus, which has no treatment. Keeping in mind the available data, further controlled trials are necessary to define the exact role of rituximab in patients with lupus. Currently, 2 randomized placebo-controlled clinical trials, the EXPLORER and LUNAR studies, are in progress. They will evaluate the efficacy and safety of rituximab, the former in SLE, and the second one in proliferative LN. Another small phase II Chinese study is designed to include 20 patients with SLE to compare three arms of treatment: rituximab alone, rituximab + CYC, and CYC alone.

Anti-B-lymphocyte Stimulator

B-lymphocyte stimulator (BLyS) is a member of the TNF cytokine family, which is present on B cells. LymphoStat-B is a fully human monoclonal antibody to BLyS. Recently, a phase II multicentre double-blind trial comparing different dosages of belimumab (1, 4, or 10 mg/kg) with placebo in 449 patients has been completed. Preliminary results show that belimumab treatment resulted in sustained improvement in SLE disease activity through 2.5 years independent of the baseline antibodies status. Belimumab normalized IgG, reduced autoantibodies and Ig isotypes while increasing complement without increasing adverse effects. All belimumab doses produced an improvement in the quality of life in seropositive patients. Currently, 2 new phase II, double-blind, placebo-controlled, randomized clinical trials are in progress, with a follow-up of 52 and 76 weeks respectively. They will evaluate the effectiveness and safety of belimumab in SLE patients.

High-dose Intravenous Immunoglobulins

IV immunoglobulins (Ig) therapy immunomodulates autoimmune diseases by interacting with various Fcγ receptors in such a way that it downregulates activating FcRIIA and FcRIIC and/or upregulates inhibitory FcRIIB. However, in SLE, additional mechanisms include inhibition of complement-mediated damage, modulation of production of cytokines and cytokine antagonists, modulation of T- and B-lymphocyte function, induction of apoptosis in lymphocytes and monocytes, downregulation of autoantibody production, manipulation of the idiotypic network, and neutralization of pathogenic autoantibodies. Some case reports and case series support a beneficial role of IVIg in SLE. In a metaanalysis, Zandman-Goddard et al concluded that the efficacy of IVIg in controlling disease activity and ameliorating classical disease manifestations range from 33% to 100%. A spectrum of SLE manifestations responds to IVIg therapy, including autoimmune hemolytic anemia, acquired von Willebrand disease, pure red cell aplasia, thrombocytopenia, pancytopenia, myelofibrosis, pneumonitis, pleural effusions, pericarditis, myocarditis, cardiogenic shock, nephritis, ESRD, encephalitis, neuropsychiatric lupus, psychosis, neuropathies, and vasculitis. The most extent experience is in LN. In small randomized trial with 14 LN patients, IVIg was shown to be as effective as intravenous pulse CYC as maintenance therapy. Uncontrolled studies have shown that IVIg was effective in membranous and proliferative lupus nephritis that was resistant to conventional regimens, improving proteinuria and creatinine levels. The role of IgIV in the treatment of LN, as well as the dose and duration of treatment are still to be established.

Plasmapheresis

Plasmapheresis in association with conventional therapy has not been shown to improve proliferative LN. In a randomized controlled trial 86 patients with severe LN were included. Forty-six patients received standard treatment with CYC and corticosteroids. Another 40 patients received standard therapy plus plasmapheresis. Although the patients treated with plasmapheresis had a faster reduction in the anti-dsDNA and cryoglobulin titers in the 2 year follow-up, there were no differences between groups with respect to proteinuria, renal failure and death. Other recent trials have not showed superiority of the combination of plasmapheresis-CYC over CYC alone, although the combination regimen led to a more rapid remission.

Additional Measures

Patients with LN have a higher prevalence of hypertension, hyperlipidemia, and antiphospholipid antibodies; hence, stopping smoking, strict control of arterial pressure and hyperlipidemia, and the reduction in protein intake are also an important objective in the treatment of LN, since they can slow the deterioration of renal function. Proteinuria and hypertension have been demonstrated to be independent risk factors for progressive renal damage.
in patients with LN.\(^9\) The angiotensin-converting enzyme inhibitors reduce blood pressure and improve proteinuria in patients with apparently quiescent LN.\(^9\) An aggressive control of blood pressure to below 120/80 mm Hg should be considered.\(^9\) Patients with progressive LN have elevated triglycerides and LDL-cholesterol with a reduction in HDL.\(^9\) Hyperlipidemia should also be treated to offer protection against accelerated vascular disease in SLE, especially in those with the membranous type of LN. Statins, besides their capacity to lower serum lipid levels, may also exhibit immunomodulatory properties that may be helpful in alleviating disease activity of SLE.\(^55,93,94\) Antiaggregation and the anticoagulation should also be considered, given the increased prevalence of arterial thrombosis.\(^55\) Although there is not solid evidence, treatment with low dose aspirin should be recommended in those patients with antiphospholipid antibodies or evidence of antiphospholipid syndrome nephropathy to prevent thromboembolism of the renal artery. Patients with persistent nephrotic syndrome that is refractory to treatment should be anticoagulated, especially when antiphospholipid antibodies are present.\(^55,93,96\)

### Conclusions

Currently, severe nephritis, either proliferative or membranous, is a frequent cause of significant morbidity and mortality in patients with SLE. Until few years ago, the standard treatment of severe LN consisted on the administration of intravenous CYC for 2 years. This therapy is effective in a significant percentage of patients but it is not exempt of frequent relapses of renal disease and sometimes serious adverse events. In the last years a considerable number of controlled clinical trials have been published in patient with LN; these studies have contributed valuable information on therapeutic alternatives to intravenous monthly CYC. Currently, the induction of remission in severe LN can be achieved with MMF to the same extent than with the use of CYC, with the standard dosing of NIH or with the ELNT administration (Table 1). The election of the optimal induction therapy should be based on a careful evaluation of the clinical and pathological features of the patient (Table 2). After reaching the remission, this can be maintained in an effective and safe way with the use of AZA or MMF for

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**TABLE 1. Most Relevant Randomized Clinical Trials in the Treatment of Proliferative Lupus Nephritis**

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<th>Author, y</th>
<th>Number of Patients</th>
<th>WHO Class</th>
<th>Follow-up</th>
<th>Regimen</th>
<th>Drug Doses</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al,(^19) 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,(^19) 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/d 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>Houssiau et al,(^17,18) (ELNT 2002 and extension 2004)</td>
<td>90</td>
<td>III, IV, Vc, Vd</td>
<td>41 and 73 months</td>
<td>Induction of remission</td>
<td>IV CYC 0.5-1 g/m² monthly followed by oral AZA 2 g/d/month for 3 months, both regimes followed by AZA 2 mg/kg/d</td>
<td>Equal</td>
<td>ELNT regimen less toxic</td>
</tr>
<tr>
<td>Hu et al,(^34) 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,(^35) 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,(^36) 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,(^48) 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>
<tr>
<td>Grootscholten et al,(^42) 2006</td>
<td>87</td>
<td>III, IV, Vc, Vd</td>
<td>5.7 years</td>
<td>Induction of remission</td>
<td>IV CYC 0.75 g/m² monthly vs AZA oral 2 mg/kg/d</td>
<td>CYC more effective</td>
<td>Equal</td>
</tr>
<tr>
<td>Moroni et al,(^54) 2006</td>
<td>75</td>
<td>IV, Vc, Vd</td>
<td>4 years</td>
<td>Maintenance of remission</td>
<td>CsA 2.5-3 mg/kg/d vs AZA 1.5-2 mg/kg/d</td>
<td>Equal</td>
<td>Equal</td>
</tr>
</tbody>
</table>

Abbreviations: AZA, azathioprine; CYC, cyclophosphamide; CsA, cyclosporine A; ELNT, EuroLupus Nephritis Trial; MMF, mycophenolate mofetil.
2 years (Table 1). Several agents, as the calcineurine inhibitors, leflunomide, the high-dose intravenous immunoglobulin, or anti-B cell or anti-TNF monoclonal antibodies could be useful in selected patients, refractory to agents like CYC, AZA, or MMF. The role of these new therapies in the therapeutic armamentarium of LN will be elucidated with further controlled trials. Several essentials questions still remain without answer, like which is the optimal induction and maintenance therapy, how long the different immunosuppressants should be maintained, the role of repeated kidney biopsies in the individualized design of the maintenance therapies, the role of the different biological agents that have vigorously emerged into the scene of the therapy of SLE, or the role of the genotypic and phenotypic stratification of the patients and their therapeutic and prognostic implications.

References


