Renal involvement is frequent in patients with systemic lupus erythematosus (SLE) and may strongly influence their expectancy and quality of life. Until recently, the treatment of lupus nephritis mainly rested on three drugs: corticosteroids, cyclophosphamide, and azathioprine. However, newer agents have been introduced in the last few years. In this paper, the available treatments for lupus nephritis are reviewed, with special emphasis on diffuse proliferative glomerulonephritis, which represents the most severe form of renal involvement in SLE.

The Conventional Therapies

After the seminal paper of Pollak et al. (1), who showed the better efficacy of high-dose prednisone over small doses, the treatment of diffuse proliferative SLE nephritis has been based for some years on high doses of corticosteroids. Such an approach, however, was often unable to control the progression of nephritis and was complicated by severe morbidity and elevated mortality. Therefore, a number of clinicians decided to add either cyclophosphamide or azathioprine to corticosteroids both to reduce the doses and side effects of corticosteroids and to slow the progression of renal disease. A meta-analysis of the available trials showed that the risk of renal insufficiency and dialysis was lowered by the addition of immunosuppressive drugs but mortality rate was not (2). In 1986, the group of the National Institutes of Health (NIH) reported the long-term results of a randomized trial, in which 107 patients with SLE nephritis were assigned to receive prednisone alone or moderate doses of prednisone in combination with intravenous (IV) pulses of cyclophosphamide, oral cyclophosphamide, azathioprine, or a combination of oral cyclophosphamide and azathioprine (3). The administration of IV pulses of cyclophosphamide was associated with a 10-yr renal survival significantly better than that observed with prednisone. However, there was not any significant difference in renal survival between IV cyclophosphamide and the other three immunosuppressive regimens.

After this report, most centers around the world used IV pulses of cyclophosphamide in association with moderate doses of prednisone in lupus nephritis. In two further trials, the NIH group confirmed the validity of this treatment and showed that its efficacy could be improved by the association with high-dose methylprednisolone pulses (4,5). On the other hand, the same group of investigators pointed out the risk of side effects caused by these regimens, such as ovarian failure, infection, avascular necrosis, etc. (5). As an alternative approach, other centers preferred to adopt a more flexible strategy based on induction with high-dose methylprednisolone pulses and oral cyclophosphamide for a few weeks, followed by maintenance with low-dose prednisone and azathioprine. The results with this approach were excellent both in the short term and in the long term (6,7). A recent meta-analysis concluded that cyclophosphamide in association with corticosteroids significantly reduced the risk of doubling serum creatinine compared with corticosteroids alone but had no impact on mortality. Conversely, azathioprine plus corticosteroids significantly reduced the risk of all-cause mortality compared with corticosteroids alone but did not alter renal outcome (8). Thus, azathioprine still has an important role in the treatment of lupus nephritis. At any rate, in spite of the burden of side effects, prolonged courses of IV cyclophosphamide pulses remained the standard treatment for lupus nephritis. More recently, a multicenter European trial was done with the goal of reducing toxicity by shortening the course and reducing the doses of IV cyclophosphamide. In this trial, 90 SLE patients were randomly assigned to receive six pulses of IV cyclophosphamide at a fixed dose of 0.5 g every two weeks followed by azathioprine, or a standard treatment with 1 g of IV cyclophosphamide every month for 6 months plus two quarterly pulses of 0.5 g/m² body surface area. No significant difference in efficacy or safety was found either in the short term (9) or in the long term (10) between the conventional doses of IV cyclophosphamide and a shorter course with lower doses, although there was a tendency toward fewer infections with the latter strategy.

Cyclosporine

Good results with this calcineurin inhibitor in association with steroids, cyclophosphamide, and methotrexate have been reported by Miescher et al. in patients with lupus nephritis refractory to previous treatment (11). Other papers reported that cyclosporine induced remission in most patients with SLE membranous nephropathy, but relapse of proteinuria was frequent when the drug was withdrawn (12,13). Clinical and histologic improvement with cyclosporine has been reported also in proliferative lupus nephritis both when the drug was given in patients resistant to IV cyclophosphamide (14) or when given for maintenance (15). In a randomized, controlled trial of proliferative lupus nephritis, Moroni et al. showed equivalence.
between cyclosporine and azathioprine for maintenance therapy up to four years (16).

**Mycophenolate Mofetil**

Mycophenolic acid, the active moiety of mycophenolate mofetil (MMF), may suppress the proliferation of T and B lymphocytes by inhibiting purine nucleotide synthesis and depleting the cells of guanosine triphosphate. Some pilot studies showed the efficacy of MMF in SLE patients who did not respond to other immunosuppressive therapies (17,18). The efficacy of MMF was confirmed by a randomized trial in which 42 patients with diffuse proliferative lupus nephritis were randomized to oral cyclophosphamide and prednisolone for 6 mo followed by 6 mo of azathioprine and prednisolone or to prednisolone and MMF at a dose of 2 g/d for 12 mo. The number of remissions was similar in the two arms of the study, but the cumulative number of side effects was significantly lower in the MMF arm (19). The authors enrolled a few other patients and reported the 5-yr follow-up more recently (20). Again they found no difference in disease activity, but the incidence in infection was significantly lower in the MMF group.

Contreras et al. (21) treated 59 patients with focal or diffuse proliferative SLE nephritis with an induction therapy consisting of a maximum of seven monthly boluses of IV cyclophosphamide (0.5 to 1.0 g/m² of body surface area) plus corticosteroids. Subsequently, the patients were randomly assigned to one of three maintenance therapies: quarterly IV injections of cyclophosphamide, oral azathioprine (1 to 3 mg/kg body weight per day), or oral MMF (0.5 to 3.0 g/d) for one to three years. After randomization, four patients in the cyclophosphamide group and one in the MMF group died. Chronic renal failure developed in three patients in the cyclophosphamide group and one each in the azathioprine and in MMF groups. The 72-mo event-free survival rate for the composite end point of death or chronic renal failure was significantly higher in the MMF and azathioprine groups than in the cyclophosphamide group. The rate of relapse-free survival was higher in the MMF group than in the cyclophosphamide group. The incidence of hospitalization, amenorrhea, infections, nausea, and vomiting was significantly lower in the MMF and azathioprine groups than in the cyclophosphamide group. A weak point of this study was the small number of patients followed in the long-term. Only 27 patients were followed for at least 3 yr, and only 5 patients were followed for 72 mo.

Ginzler et al. (22) conducted a 6-mo randomized trial comparing MMF at an initial dose of 1 g/d gradually increased to 3 g/d with monthly IV cyclophosphamide, 0.5 g/m² gradually increased to 1 g/m². Of 140 SLE patients recruited, 39 had membranous nephritis, 22 had focal proliferative nephritis, and the remaining patients had diffuse proliferative nephritis. There were significantly more complete remissions in the MMF group than in the cyclophosphamide group (22.5% and 5.8%, respectively). Partial remissions were observed in 29.6% of MMF-treated patients and in 24.6% of cyclophosphamide-treated patients. There were fewer severe infections but more diarrhea in the MMF group. Considering that these patients had normal renal function at randomization (serum creatinine 1.06 ± 0.52 and 1.08 ± 0.49 mg/dl, respectively), the rate of remissions at 6 mo appears to be small. One may also wonder why, for an induction therapy, the authors chose to start with small doses of either drug rather than initiate with an aggressive treatment followed by gradual tapering.

Pulling together the results with MMF, some questions still remain:

1. **Should MMF be preferred over other treatments for induction therapy?** The study of Ginzler et al. (22) showed that MMF gave more complete remission than IV cyclophosphamide. However, the selected patients had preserved renal function at presentation. Such a typology of patients does not require an aggressive therapy for induction. The role of MMF for induction should be tested in patients with hectic clinical and histologic activity associated with renal dysfunction.

2. **Is MMF superior to azathioprine for maintenance?** In spite of the low doses of azathioprine used (mean 1 mg/kg per day) the efficacy of azathioprine was comparable to that of MMF in the trial of Contreras et al. (21). In the study of Chan et al. (19), MMF, at a mean dose of 1 g/d, was replaced after one year by azathioprine at a dose of 1 mg/kg per day, apparently without any problem.

3. **What are the optimal doses of MMF for induction and maintenance therapy?** The dose for the induction is not clear. Ginzler et al. reported that of 71 patients assigned to receive MMF for induction, 15 discontinued the drug, mainly because of the lack of response (22). This means that the strategy of starting with low doses of MMF does not guarantee good results even in patients with mild to moderate lupus nephritis. On the other hand, only 63% of patients tolerated the dose of 3 g/d. There is now evidence that, in renal transplant recipients, the pharmacokinetics of mycophenolic acid is heavily influenced by renal function, albumin level, and hemoglobin level (23). As lupus patients requiring a true induction therapy have usually renal dysfunction, low serum albumin levels, and anemia, we need pharmacokinetic studies in this area to find the ideal dosage of MMF for induction. Also unclear is the optimal dosage of MMF for maintenance. Contreras et al. used doses ranging from 0.5 to 3.0 g/d, too a large range for drawing any conclusions (21). Other investigators administered MMF at doses between 0.5 and 2 g/d (17,24,25). MMF may be responsible for gastrointestinal side effects, which are dose-dependent. Not all the patients may tolerate high doses of the drug. On the other hand, if SLE activity may be controlled by low doses of MMF, it is likely that the drug may be safely replaced by the cheaper azathioprine, with few exceptions.

4. **Is it possible to minimize or even stop steroids under MMF?** Corticosteroids are responsible of many disabling and even life-threatening complications in SLE patients. Moreover, an indefinite number of patients do not adhere to medical prescriptions mainly because of the esthetic side effects of corticosteroids. It would be of great importance to know whether MMF may allow a reduction of the doses of
corticosteroids and related side effects in comparison with azathioprine or other treatments. Unfortunately, we do not have such information from the available trials.

Rituximab

Rituximab is a chimeric antibody directed against CD20, a phosphoprotein expressed on almost all B cells but not on plasma cells. Therefore, through the elimination of B cells rituximab may prevent the generation and expansion of antibody-secreting autoreactive cells (26).

A number of anecdotal cases of severe SLE successfully treated with rituximab have been reported. Thatayatikom and White (27) recently reviewed the published experience with rituximab in SLE. The doses used were different, but the most frequently used was 375 mg/m² weekly for 2 to 4 doses. Most patients demonstrated complete B cell depletion within 1 to 3 mo of treatment; these patients also had clinical response with improvement of arthralgias, serositis, cutaneous vasculitis, mucositis, and neurologic symptoms. The few patients without cell B depletion did not show clinical response. B cell depletion lasted 3 to 12 mo, but clinical benefits lasted longer. Less clear were the benefits on renal disease. Of 45 patients with nephritis (most of them class III or IV), 33 responded to rituximab. However, in many cases the response was evaluated by scores of lupus activity such as British Isles Lupus Assessment Group (BILAG), Systemic Lupus Activity Measure (SLAM), or Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). When the response was assessed by serum creatinine and proteinuria, out of 20 cases 6 entered complete remission, 8 had partial remission, and 6 failed to respond. These results are interesting, but because of clinical heterogeneity, different doses, and concomitant aggressive treatment with steroids and other immunosuppressive drugs a proper evaluation of the clinical efficacy of rituximab in lupus nephritis is difficult. Some investigators found that not all responders showed improvement in anti-dsDNA antibodies and serum complement levels (28,29). Others found that the decrease in anti-dsDNA antibodies was often independent of the clinical response (30).

In summary, rituximab appears to be a very effective drug that may control most symptoms of SLE. Using rituximab to deplete B cells may have the advantage of being generally well tolerated, and to spare T cells and plasma cells, which are CD20-negative (31). However, double-blind controlled trials are advocated to confirm its role in lupus nephritis and to find whether rituximab alone may be effective or should be associated with other drugs, and, in the latter case, what is the combination that offers the best therapeutic index. Until these data are available, the use of rituximab should be confined to cases resistant to standard induction therapy or to patients with contraindications to corticosteroids and immunosuppressive agents.

IV Immunoglobulins

IV immunoglobulins (IVIg) exert a variety of immunomodulating activities and are, therefore, being increasingly used for the treatment of immune-mediated diseases. However, the mechanism of action is still unknown. Acceleration of the rate of IgG catabolism is the most plausible unifying explanation for the beneficial action of high doses of IVIg. Such a process would eliminate individual IgG molecules in direct proportion to their relative concentration in plasma (32).

IVIg have been used successfully to treat clinical manifestations of SLE, including refractory thrombocytopenia, pancytopenia, central nervous system involvement, secondary antiphospholipid syndrome, and nephritis. The beneficial effects of IVIg on overall disease activity are usually prompt, with marked improvement within a few days, but they are often of limited duration (33). Orbach et al. reviewed the literature on the use of IVIg in autoimmune diseases and found 106 patients with lupus nephritis who had been treated with IVIg (34). In most reports, proteinuria, nephrotic syndrome, and values of creatinine clearance were improved. However, 32 papers reported that 78 patients treated with IVIg for different indications developed renal toxicity, particularly with the use of sucrose-containing IVIg products. Hemodialysis was required in 31% of patients and mortality occurred in 10% of patients with renal toxicity. Renal histology done in a minority of the cases demonstrated vacuolization and swelling of the proximal tubules consistent with osmotic injury. Thus, IVIg may obtain good results in some patients with lupus nephritis resistant to conventional therapy, but the exact success rate and clinical indications remain undetermined. On the other hand, nephrotoxicity can be a serious although rare complication of IVIg therapy. Patients with lupus nephritis should receive IVIg under close monitoring and after adequate hydration to correct volume depletion, which together with preexisting renal disease represents a risk factor for nephrotoxicity (34).

Agents under Evaluation

LJP394 is a complex of four oligonucleotides with strong avidity to anti-dsDNA antibodies. In a double-blind, placebo-controlled study, 230 SLE patients were randomized to receive 16 weekly doses of 100 mg of LJP 394 or placebo, followed by alternating 8-wk drug withdrawal and 12 weekly doses of 50 mg of LJP 394 or placebo. In the intent-to-treat population, the time to renal flare was not significantly different between treatment groups, but in patients with high-affinity antibodies to its DNA epitope, LJP 394 prolonged the time to renal flare, decreased the number of renal flares, and required fewer high-dose corticosteroid and/or cyclophosphamide treatments compared with placebo (35).

The co-stimulation signaling pathway plays a significant role in the production of autoantibodies and tissue injury in SLE. A trial with a humanized anti-CD40L antibody, BC9588, in patients with proliferative lupus nephritis showed significant reduction of anti-dsDNA antibodies, increase in C3 concentrations and decrease in hematia, but the study was terminated prematurely because of thromboembolic events (36). In a randomized study, 85 SLE patients were randomized to receive 6 infusions of another anti-CD40L monoclonal antibody, IDEC-131, or placebo over 16 wk. IDEC-131 was safe and well tolerated, but efficacy of the drug compared with placebo was not demonstrated (37).
Conclusion
Thanks to earlier diagnosis, better supportive treatments, and progress in specific therapy, the prognosis of lupus nephritis is improving. The efforts of clinicians should now be addressed not only to further ameliorate the long-term renal survival but also to reduce the side effects of treatment and to improve the quality of life of SLE patients. While the use of IV cyclophosphamide is an important component of therapy that allowed nephrologists to revolutionize the poor prognosis of SLE nephritis, there is now evidence that it is possible to obtain excellent results with fewer side effects and even avoiding its use in the long term (Figure 1). An aggressive therapy with corticosteroids and cyclophosphamide should, therefore, be confined to cases with rapid renal function impairment and/or severe proteinuria. Whenever possible, the dose of corticosteroids should be reduced and cyclophosphamide should be replaced by a nucleotide synthesis inhibitor or by low-dose cyclosporine. In the few cases where patients do not respond, rituximab or IVIg may be considered as a rescue treatment. The two main goals for maintenance therapy should be avoiding cyclophosphamide and minimizing the dosage of corticosteroids. The clinician may choose between MMF or azathioprine. Perhaps MMF might be preferred in the early postinduction period and azathioprine in a less active phase. In patients with severe proteinuria and/or bone marrow inhibition, cyclosporine at low doses may also be useful. The possibility of alternating these agents may help in preventing drug-related side effects and in improving compliance. The main strategy in treating lupus nephritis rests on (1) reinforcement of treatment should a renal or extrarenal flare occur and (2) not reducing too abruptly the doses of corticosteroids and immunosuppressive agents in quiescent phases of the disease. We should also be aware that in some patients with stable long-term remission a cautious attempt to gradually taper corticosteroids and/or immunosuppressive drugs until full discontinuation may be successfully tried (38).

References
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Figure 1. Proposed therapeutic options in patients with lupus nephritis and severe renal involvement at presentation or at renal flares. In patients with normal renal function the treatment of induction or flares may also consist of mycophenolate mofetil and oral prednisone. MP, methylprednisone; IVIg, intravenous immunoglobulins; MMF, mycophenolate mofetil.