Treatment of Lupus Nephritis

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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.

Tratamiento de la nefritis lúpica

La nefritis lúpica es una causa importante de morbilidad y mortalidad en los pacientes con lupus eritematoso sistémico. El tratamiento convencional de inducción de remisión en la nefritis lúpica grave se basa en la utilización de ciclofosfamida intravenosa mensual. Datos recientes han puesto de manifiesto que el mantenimiento de remisión de la nefritis lúpica se consigue con un menor número de efectos secundarios utilizando azatioprina o micofenolato, frente a la administración trimestral de ciclofosfamida intravenosa. En los últimos años se han publicado ensayos clínicos controlados y aleatorizados que plantean nuevas modalidades terapéuticas en la inducción de remisión en la nefritis lúpica, como son la utilización de pautas menos agresivas de ciclofosfamida intravenosa o el uso de micofenolato mofetilo. Se necesitan más estudios para establecer el tratamiento óptimo de los pacientes con nefritis lúpica grave.

Palabras clave: Nefritis lúpica. Micofenolato mofetilo. Ciclofosfamida. Lupus eritematoso sistémico.

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

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minority of patients with LN class III (focal and segmental proliferative glomerulonephritis), renal function worsens and progresses to class IV.[9]
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/m^2 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[10-14] 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.[11] In another study[15] 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[11] 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[16] 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)[17] 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[17] and long-term[18] follow-up (41 and 73 months).
New renal flares are frequent, even in those patients who had had a complete response to CYC,[7,19,20] 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.[19-21] It is more difficult to reach remission in patients with subsequent renal flares that in those treated the first time.[20] 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.[22] 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[23] 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.[24] 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,[25-31] only recently has solid evidence on the role of MMF as induction therapy in comparison with CYC been published.[32-36]

Chan et al[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 (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[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[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[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^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 (P=.70). Complete remission was achieved in three patients (12%) in the CYC group and 5 patients (26%) in the MMF group (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 (P=.18) in the rate of adverse events between groups.

In the largest to date induction study in proliferative lupus nephritis, Ginzler et al[36] compared oral MMF (initial dose, 1000 mg/d, increased to 3000 mg/d) with monthly IV CYC (0.5 g/m^2 of body-surface area, increased to 1 g/m^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% (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; 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[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 amenorrhoea 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 immunosuppresants, 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),[38] a randomized, multicentre prospective, phase III, controlled trial evaluating the effectiveness and security 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[23] 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[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.[11] The analysis didn´t find an association of AZA with an increase in the frequency of severe infections including herpes zoster. More recently, Grootscholten et al[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^2, 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.[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%.[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%.[10-12,14] Keeping in mind the toxicity of CYC, mainly the premature ovarian failure,[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=.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[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,[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[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

(0.5-1 g/m^2) plus corticosteroids. Subsequently, patients were randomly assigned to one of 3 maintenance therapies: quarterly intravenous injections of CYC (0.5-1 g/m^2), 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.[50,51] It seems to be an effective drug in the treatment of membranous LN, improving proteinuria and serum albumin.[52] 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.[50] Tam et al[53] 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[54] 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[52]; however, it appears better tolerated than CYC and approximately the same as MMF.[54]

Tacrolimus is another inhibitor of calcineurin that has demonstrated a power from 10-100 times superior to CsA.[55] Mok et al[56] 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.[57]

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 1b[58]. Several small series have reported beneficial results in patients with SLE.[59,60] In a prospective controlled trial including 47 patients with recently 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.[61] 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.[62] Despite these results, it should be kept in mind that leflunomide has been reported to induce SLE or precipitate subacute cutaneous lupus.[55]

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.[63,64] 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[65]. 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 deceased 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.[66] 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 ($P<.01$). This reduction in dsDNA antibodies correlated with increases in C3 ($P<.001$). 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.[67] Based on patient self-reports, health-quality of life was significantly improved in the treated versus the placebo group.[68]
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.[55] 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.[69] 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.[70] Using a similar protocol with higher doses of ritixumab, the same group of investigators recently reported results in 24 SLE patients who were refractory to conventional therapies.[71] 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[72]. Vigna-Pérez et al[73] 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 ($P<.05$) and proteinuria ($P<.05$) 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[74] 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.[75-78] 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 Immunoglubulins

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.[79] Some case reports and case series support a beneficial role of IVIg in SLE. In a metaanalysis, Zandman-Goddard et al[80] 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 autoinmune 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.[79-81] In a small randomized trial with 14 LN patients, IVIg was shown to be as effective as intravenous pulse CYC as maintenance therapy.[82] 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.[83-85] 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.[86] 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.[87,88]

Additional Measures

Patients with LN have a higher prevalence of hypertension, hyperlipidemia, and antiphospholipid antibodies[89]; 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.[55] Proteinuria and hypertension have been demonstrated to be independent risk factors for progressive renal damage

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

Author, y	Number of Patients	WHO Class	Follow-up	Regimen	Drug Doses	Efficacy	Safety
Chan et al,[32] 2000	42	III, IV, Vb	12 months	Induction of remission	Oral CYC 2-3 mg/kg/d vs oral MMF up to 3 g/d	Equal	MMF less toxic
Chan et al,[33] 2005 (extended study)	64	IV	63 months	Induction of remission	Oral CYC 2.5 mg/kg/d 6 months followed by oral AZA 1.5-2 mg/kg vs oral MMF 2 g/d	Equal	MMF less toxic
Houssiau et al,[17,18] (ELNT 2002 and extension 2004)	90	III, IV, Vc, Vd	41 and 73 months	Induction of remission	IV CYC 0.5-1 g/m^2 monthly for 6 months followed by 2 quarterly doses vs IV CYC 500 mg fortnightly for 3 months, both regimes followed by AZA 2 mg/kg/d	Equal	ELNT regimen less toxic
Hu et al,[34] 2002	46	IV	6 months	Induction of remission	IV CYC 0.75-1 g/m^2 monthly vs oral MMF 0.5-1,5 g/d	MMF more effective	MMF less toxic
Ong et al,[35] 2005	44	III, IV	6 months	Induction of remission	IV CYC 0.75-1 g/m^2 monthly vs oral MMF 2 g/d	Equal	Equal
Ginzler et al,[36] 2005	140	III, IV, V	6 months	Induction of remission	IV CYC 0.5-1 g/m^2 monthly vs oral MMF up to 3 g/d	MMF more effective	MMF less toxic
Contreras et al,[48] 2004	59	III, IV, Vb	1-3 years	Maintenance of remission	IV CYC 0.5-1 g/m^2 quarterly; oral AZA 1-3 mg/kg/d; or oral MMF up to 3 g/d	MMF and AZA more effective	MMF and AZA less toxic
Grootscholten et al,[42] 2006	87	III, IV, Vc, Vd	5.7 years	Induction of remission	IV CYC 0.75 g/m^2 monthly vs AZA oral 2 mg/kg/d	CYC more effective	Equal
Moroni et al,[54] 2006	75	IV, Vc, Vd	4 years	Maintenance of remission	CsA 2,5-3 mg/kg/d vs AZA 1.5-2 mg/kg/d	Equal	Equal

Abbreviations: AZA, azathioprine; CYC, cyclophosphamide; CsA, cyclosporine A; ELNT, EuroLupus Nephritis Trial; MMF, mycophenolate mofetil.

in patients with LN.[90] The angiotensin-converting enzyme inhibitors reduce blood pressure and improve proteinuria in patients with apparently quiescent LN.[91] An aggressive control of blood pressure to below 120/80 mm Hg should be considered.[90] Patients with progressive LN have elevated triglycerides and LDL-cholesterol with a reduction in HDL[92]. 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.[95] 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 morbility 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

TABLE 2. Suggested Treatment for Lupus Neprhitis Depending on Clinical and Pathologic Characteristics

	Induction	Maintenance	Additional Measures
Minimal changes	Prednisone 0.5 mg/kg/d for 4 weeks	Progressive reduction of CS	Strict control of arterial pressure and LDL-cholesterol
Mesangial	Prednisone 1 mg/kg/d for 4 weeks	Progressive reduction of CS	Strict control of arterial pressure and LDL-cholesterol
Focal proliferative	Prednisone 1 mg/kg/d for 4 weeks + NIH CYC or ELNT CYC or MMF	MMF or AZA	Strict control of arterial pressure and LDL-cholesterol
Diffuse proliferative	Prednisone 1 mg/kg/d for 4 weeks + NIH CYC or ELNT CYC or MMF	MMF or AZA	Strict control of arterial pressure and LDL-cholesterol
Focal or diffuse proliferative with poor prognosis features[a]	Prednisone 1 mg/kg/d for 4 weeks + NIH CYC	MMF or AZA	Strict control of arterial pressure and LDL-cholesterol
Membranous	Prednisone 1 mg/kg/d for 4-6 weeks	Progressive reduction of CS. In case of resistance or CS-dependence, try CYC, MMF or CsA	Strict control of arterial pressure and LDL-cholesterol
Sclerosis	Unnecessary	Unnecessary	Strict control of arterial pressure and LDL-cholesterol

Abbreviations: CYC, cycophosphamide; CsA; cyclosporine A; ELNT, EuroLupus Nephritis Trial; CS, corticosteroids; MMF, mycophenolate mofetil; NIH, National Institutes of Health.
[a]Renal insufficiency or nephrotic proteinuria or black race or poor-controlled arterial hypertension.

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

1. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoinmune diseases in the United States. Clin Immunol Immunopathol. 1997;84:223-43.
2. Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. Arthritis Rheum. 1995;38:551-8.
3. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1000 patients. Medicine (Baltimore). 1993;72: 113-24.
4. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1000 patients. Medicine (Baltimore). 2003;82:299-308.
5. Golbus J, McCune WJ. Lupus nephritis. Classification, prognosis, immunopathogenesis and treatment. Rheum Dis Clin North Am. 1994;20:213-42.
6. Howie AJ, Turhan N, Adu D. Powerful morphometric indicator of prognosis in lupus nephritis. QMJ. 2003;96:411-20.
7. Mok CC, Ying KY, Tang S, Leung CY, Lee KW, Ng WL, et al. Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. Arthritis Rheum. 2004;50: 2559-68.
8. Churg J, Sobin LH. Renal Disease: Classification and Atlas of Glomerular Disease. Tokyo: Igaku-Shoin; 1982.
9. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney International. 2004;65:521–30.
10. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. Arthritis Rheum 1991;34:945-950.
11. Austin HA 3rd, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med. 1986;314:614-9.

12. Boumpas DT, Austin HA 3rd, Vaughan EM, Klippel JH, Steinberg AD, Yarboro CH et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet. 1992;340:741-5.

13. Illei GG, Austin HA, Crane M, Collins L, Gourley MF, Yarboro CH, et al. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxiciy in patients with lupus nephritis. Ann Intern Med. 2001;135:248-57.

14. Gourley MF, Austin HA 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med. 1996;125:549-57.

15. Mok CC, Ho CT, Siu YP, Chan KW, Kwan TH, Lau CS, et al. Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. Am J Kidney Dis. 2001;38: 256-64.

16. Yee CS, Gordon C, Dostal C, Petera P, Dadoniene J, Griffiths B, et al. EULAR randomised controlled trial of pulse cyclophosphamide and methylprednisolone versus continous cyclophosphamide and prednisolone followed by azathioprine and prednisolone in lupus nephritis. Ann Rheum Dis. 2004;63:525-9.

17. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido E, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis. The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide. Arthritis Rheum. 2002;46:2121-31.

18. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido E, Danieli MG, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis. Arthritis Rheum. 2004;50:3934-40.

19. Illei GG, Takada K, Parkin D, Austin HA, Crane M, Yarboro CH, et al. Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of a cohort of 145 patients participating in randomized controlled studies. Arthritis Rheum. 2002;46:995-1002.

20. Ioannidis JPA, Boki KA, Katsorida ME, Drosos AA, Skopouli FN, Boletis JN, et al. Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide. Kidney Int. 2000;57:258-64.

21. Berden JHM. Lupus nephritis. Kidney Int. 1997;52:538-58.

22. Cameron JS. Lupus nephritis. J Am Soc Nephrol. 1999;10:413-24.

23. Flanc RS, Roberts MA, Strippoli GF, Chadban SJ, Kerr PG, Atkins RC. Treatment of diffuse proliferative lupus nephritis: a metaanalysis of randomized controlled trials. Am J Kidney Dis. 2004;43:197-208.

24. Allison AC. Preferential suppression of lymphocyte proliferation by mycophenolic acid and predicted long-term effects of mycophenolate mofetil in transplantation. Transplant Proc. 1994;26:3205-10.

25. Dooley MA, Cosio FG, Nachman PH, Fankelhaim ME, Hogan SL, Falk RJ, et al. Mycophenolate mofetil therapy in lupus nephritis: clinical observations. J Am Soc Nephrol. 1999;10:833-9.

26. Gaubitz M, Schorat A, Schotte H, Kern P, Domschke W. Mycophenolate mofetil for the treatment of systemic lupus erythematosus: an open pilot trial. Lupus. 1999;8:731-6.

27. Kingdon EJ, McLean Ag, Psimenous E, Davenport A, Powis SH, Sweny P et al. The safety and efficacy of MMF in lupus nephritis: a pilot study. Lupus. 2001;10:606-11.

28. Karim MY, Alba P, Cuadrado MJ, Abbs IC, D'Cruz DP, Khamashta MA, et al. Mycophenolate mofetil for systemic lupus erythematosus refactory to other immunosuppressive agents. Rheumatology (Oxford). 2002;41:876-82.

29. Kapitsinou PP, Boletis JN, Skopouli FN, Boki KA, Moutsopoulos HM. Lupus nephritis: treatment with mycophenolate mofetil. Rheumatology (Oxford). 2004;43:377-80.

30. Pisoni CN, Sanchez FJ, Karim Y, Cuadrado MJ, D'Cruz DP, Abbs IC, et al. Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. J Rheumatol. 2005;32:1047-52.

31. Karim MY, Pisoni CN, Ferro L, Tungekar MF, Abbs IC, D'Cruz DP, et al. Reduction of proteinuria with mycophenolate mofetil in predominantly membranous lupus nephropathy. Rheumatology (Oxford). 2005;44: 1317-21.

32. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med. 2000;343:1156-62.

33. Chan TM, Tse KC, Tang CS, Mok MY, Li FK; Hong Kong Nephrology Study Group. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol. 2005;16:1076-84.

34. Hu W, Liu Z, Chen H, Tang Z, Wang Q, Shen K, et al. Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. Chin Med J (Engl). 2002;115:705-9.

35. Ong LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, et al. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrology. 2005;10:504-10.

36. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, Petri M, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005;353:2219-28.

37. Moore RA, Derry S. Systematic review and meta-analysis of randomised trails and cohort studies of mycophenolate mofetil in lupus nephritis. Arthritis Res Ther. 2006;8:R182.

38. Sinclair A, Appel G, Dooley MA, Ginzler E, Isenberg D, Jayne D, et al. Mycophenolate mofetil as induction and maintenance therapy for lupus nephritis: rationale and protocol for the randomized, controlled Aspreva Lupus Management Study (ALMS). Lupus. 2007;16:972-80.

39. Cade R, Spooner G, Schlein E, Pickering M, DeQuesada A, Holcomb A, et al. Comparison of azathioprine, prednisone and heparin, alone or combined in treating lupus nephritis. Nephron. 1973;10:37-56.

40. Donadio JV, Holley KE, Wagoner RD, Ferguson RH, McDuffie FC. Further observations on the treatment of lupus nephritis with prednisone and combined prednisone and azathioprine. Arthritis Rheum. 1974;17:573-81.

41. Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus. Ann Intern Med. 1975;83:597-605.

42. Grootscholten C, Ligtenberg G, Hagen EC, van den Wall Bake AW, de Glas-Vos JW, Bijl M, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney Int. 2006;70:732-42.

43. Grootscholten C, Bajema IM, Florquin S, Steenbergen EJ, Peutz-Kootstra CJ, Goldschmeding R, et al. Treatment with cyclophosphamide delays the progression of chronic lesions more effectively than does treatment with azathioprine plus methylprednisolone in patients with proliferative lupus nephritis. Arthritis Rheum. 2007;56:924-37.

44. Ciruelo E, de la Cruz J, López I, Gómez-Reino JJ. Cumulative rate of relapse of lupus nephritis after successful treatment with cyclophosphamide. Arthritis Rheum. 1996;39:2028-34.

45. Mok CC, Wong RWS, Lai KN. Treatment of severe proliferative lupus nephritis: the current state. Ann Rheum Dis. 2003;62:799-804.

46. Boumpas DT, Austin HA, Vaughan EM, Yarboro CH, Klippel JH, Balow JE. Risk of sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. Ann Intern Med. 1993;119:366-9.

47. Chan TM, Tse KC, Tang CSO, Lai KN, Li FK. Long-term outcome of patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide followed by azathioprine. Lupus. 2005;14:265-72.

48. Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004;350:971-80.

49. Contreras G, Tozman E, Nahar N, Metz D. Maintenance therapies for proliferative lupus nephritis: mycophenolate mofetil, azathioprine and intravenous cyclophosphamide. Lupus. 2005;14:s33-8.

50. Dostál C, Tesar V Rychlík I, Zabka J, Vencovsk? J, Bartûnkova J, et al. Effect of 1 year cyclosporine A treatment on the activity and renal involvement of systemic lupus erythematosus: a pilot study. Lupus. 1998;7:29-36.

51. Caccavo D, Lagana B, Mitterhofer AP, Ferri GM, Afeltra A, Amoroso A, et al. Long-term treatment of systemic lupus erythematosus with Cyclosporin A. Arthritis Rheum. 1997;40:27-35.

52. Hallegua D, Wallace DJ, Metzger Al, Rinaldi RZ, Klinenberg JR. Cyclosporine for lupus membranous nephritis: experience with ten patients and review of the literature. Lupus. 2000;9:241-51.

53. Tam LS, Li EK, Leung CB, Wong KC, Lai FMM, Wang A, et al. Long-term treatment of lupus nephritis with cyclosporin A. Q J Med. 1998;91: 573-80.

54. Moroni G, Doria A, Mosca M, Alberighi OD, Ferraccioli G, Todesco S, et al. A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. Clin J Am Soc Nephrol. 2006;1:925-32.

55. Mok CC. Therapeutic options for resistant lupus nephritis. Semin Arthritis Rheum. 2006;36:71-81.

56. Mok CC, Tong KH, To CH, Siu YP, Au TC. Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: An open-labeled pilot study. Kidney Int. 2005;68:813-7.

57. Tse KC, Lam MF, Tang SCW, Tang CSO, Chan TM. A pilot study on tacrolimus treatment in membranous or quiescent lupus nephritis with proteinuria resistant to angiotensin inhibition or blockade. Lupus. 2007;16: 46-51.

58. Buhaescu I, Covic A, Deray G. Treament of proliferative lupus nephritis – A critical approach. Semin Arthritis Rheum. 2007;36:224-37.

59. Remer CF, Weisman MH, Wallace Dj. Benefits of leflunomide in systemic lupus erythematosus: a pilot observational study. Lupus. 2001;10:480-3.

60. Tam LS, Li EK, Wong CK, Lam CW, Szeto CC. Double-blind, randomized, placebo-controlled pilot study of leflunomide in systemic lupus erythematosus. Lupus. 2004;13:601-4.

61. Cui TG, Hou FF, Ni ZH, Chen XM, Zhang FS, Zhu TY, et al. Treatment of proliferative lupus nephritis with leflunomide and steroid: a prospective multicenter controlled clinical trial. Zhonghua Nei Ke Za Zhi. 2005;44: 672-6.

62. Tam LS, Li EK, Wong CK, Lam CW, Li WC, Szeto CC. Satety and efficacy of leflunomide in the treatment of lupus nephritis refractory or intolerant to traditional immunosuppressive therapy: an open trial. Ann Rheum Dis. 2006;65:417-8.

63. Ginzler EM, Dvorkina O. Newer therapeutic approaches for systemic lupus erythematosus. Rheum Dis Clin N Am. 2005;31:315-28.

64. Furie R. Abetimus sodium (Riquent) for the prevention of nephritis flares in patients with systemic lupus erythematosus. Rheum Dis Clin N Am. 2006;32:149-56.

65. Alarcón-Segovia D, Tumlin JA, Furie RA, McKay JD, Cardiel MH, Strand V, et al. LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus. Arthritis Rheum. 2003;48:442-54.

66. Cardiel MH. Abetimus sodium: a new therapy for delaying the time to, and reducing the incidence of, renal flare and/or major systemic lupus erythematosus flares in patients with systemic lupus erythematosus who have a history of renal disease. Expert Opin Investig Drugs. 2005;14:77-88.

67. Wallace DJ, Tumlin JA. LJP 394 (abetimus sodium, Riquent) in the management of systemic lupus erythematosus. Lupus. 2004;13:323-7.

68. Strand V, Aranow C, Cardiel MH, Alarcón-Segovia D, Furie R, Sherrer Y, et al for the LJP 394 Investigator Consortium. Improvement in health-related quality of life in SLE patients enrolled in a randomized clinical trial comparing LJP 394 treatment with placebo. Lupus. 2003;12:677-86.

69. Aringer M, Graninger WB, Steiner G, Smolen JS. Safety and efficacy of tumor necrosis factor a blockade in systemic lupus erythematosus: an open-label study. Arthritis Rheum. 2004;50:3161-9.

70. Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthritis Rheum. 2002;46:2673-7.

71. Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. Rheumatology. 2005;44:1542-5.

72. Sfikakis PP, Boletis JN, Lionaki S, Vigklis V, Fragiadaki KG, Iniotaki A, et al. Remission of proliferative lupus nephritis following B cell depletion therapy is preceded by down-regulation of the T cell costimulatory molecule CD40 ligand. Arthritis Rheum. 2005;52:501-13.

73. Vigna-Pérez M, Hernández-Castro B, Paredes-Saharopulos O, Portales-Pérez D, Baranda L, Abud-Mendoza C, et al. Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. Arthritis Res Ther. 2006;8:R83.

74. Gunnarsson I, Sundelin B, Jónsdóttir T, Jacobson SH, Henriksson EW, van Vollenhoven RF. Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. Arthritis Rheum. 2007;56:1263-72.

75. Stohl W, Chatham W, McKay J, Weisman MH, Merrill JT, Petri M, et al for the LBSL02/99 Study Group. Progressive Normalization of Autoantibody, Immunoglobulin, and Complement Levels Over 2.5 Years of Belimumab (Fully Human Monoclonal Antibody to BLyS) Therapy in Systemic Lupus Erythematosus (SLE) Patients. Arthritis Rheum. 2007;56 Suppl 9:S210.

76. Merrill JT, Wallace DJ, Stohl W, Furie R, Ginzler E, Stern S et al for the LBSL02/99 Study Group. Safety Profile of Belimumab (Fully Human Monoclonal Antibody to BLyS) in patients with systemic lupus erythematosus (SLE) treated during a placebo-controlled trial and in a long-term continuation study. Arthritis Rheum. 2007;56 Suppl 9:S210.

77. Petri M, Furie R, Ginzler E, Wallace DJ, Stohl W, Strand V, et al for the LBSL02/99 Study Group. Novel combined response endpoint and systemic lupus erythematosus (SLE) flare Index (SFI) demonstrate belimumab (Fully Human Monoclonal Antibody to BLyS) improves or stabilizes SLE disease activity and reduces flare rate over 2.5 years of therapy. Arthritis Rheum. 2007;56 Suppl 9:S527.

78. Strand V, Crawford B, Petri M, Ramsey-Goldman R, Weisman M, Lim S et al for the LBSL02 Study Group. Patients with ative systemic lupus erythematosus (SLE) treated with belimumab improve health-related quality of life (HRQOL) in a randomized controlled trial (RCT). Arthritis Rheum. 2006; 54 Suppl:S277.

79. Toubi E, Kessel A, Shoenfeld Y. High-dose intravenous immunoglobulins: an option in the treatment of systemic lupus erythematosus. Hum Immunol. 2005;66:395-402.

80. Zandman-Goddard G, Levy Y, Shoenfeld Y. Intravenous immunoglobulin therapy and systemic lupus erythematosus. Clin Rev Allergy Immunol. 2005;29:219-28.

81. Sherer Y, Shoenfeld Y. Intravenous immnunoglobulin for immunomodulation of systemic lupus erythematosus. Autoimmunity Reviews. 2006;5: 153-5.

82. Boletis JL, Ioannidis JP, Boki KA, Moutsopulos HM. Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis. Lancet. 1999;354:569-70.

83. Orbach H, Tishler M, Shoenfeld Y. Intravenous immunoglobulin and the kidney - a two-edged sword. Semin Arthritis Rheum. 2004;34:593-601.

84. Winder A, Molad Y, Ostfeld I, Kenet G, Pinkhas J, Sidi Y. treatment of systemic lupus erythematosus by prolonged administration of high dose intravenous immunoglobulin: report of 2 cases. J Rheumatol. 1993;20: 495-8.

85. Levy Y, Sherer Y, George J, Rovensky J, Lukac J, Rauova L, et al. Intravenous immunoglobulin treatment of lupus nephritis. Semin Arthritis Rheum. 2000;29:321-7.

86. Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. N Engl J Med. 1992;326:1373-9.

87. Wallace DJ, Goldfinger D, Pepkowitz SH, Fichman M, Metzger AL, Schroeder JO, et al. Randomized controlled trial of pulse/synchronization cyclophosphamide/apheresis for proliferative lupus nephritis. J Clin Apher. 1998;13:163-6.

88. Danieli MG, Palmieri C, Salvi A, Refe MC, Strusi AS, Danieli G. Synchronized therapy and high-dose cyclophosphamide in proliferative lupus nephritis. J Clin Apher. 2002;17:72-7.

89. Font J, Ramos-Casals M, Cervera R, García-Carrasco M, Torras A, Sisó A, et al. Cardiovascular risk factors and the long-term outcome of lupus nephritis. Q J Med. 2001;94:19-26.

90. Clark WF, Moist LM. Management of chronic renal insufficiency in lupus nephritis: role of proteinuria, hypertension and dyslipidemia in the progression of renal disease. Lupus. 1998;7:649-53.

91. Tse KC, Li FK, Tang S, Tang CS, Lai KN, Chan TM. Angiotensin inhibition or blockade for the treatment of patients with quiescent lupus nephritis and persistent proteinuria. Lupus. 2005;14:947-52.

92. Ettinger WH, Goldberg AP, Applebaum-Bowden D, Hazard WR. Dyslipoproteinemia in systemic lupus erythematosus. Am J Med. 1987;83:503-8.

93. Haubitz M. Exploring new territory: the move towards individualised treatment. Lupus. 2007;16:227-31.

94. Wierzbicki AS. Lipids, cardiovascular disease and atherosclerosis in systemic lupus erythematosus. Lupus. 2000;9:194-201.

95. Mok CC, Toug KH, To CH, Siu YP, Ho LY, Au TC. Risk and predictors of arterial thrombosis in lupus and non-lupus primary glomerulonephritis: a comparative study. Medicine (Baltimore). 2007;86:203-9.

96. Schneider M. Exploring new territory: considering the future. Lupus. 2007;16:221-6.