Update on the treatment of lupus nephritis

M Waldman[1] and GB Appel[2]

[1]Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, Maryland, USA and [2]Department of Medicine, Division of Nephrology, Columbia University College of Physicians and Surgeons, New York, New York, USA

Lupus nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus. Although the use of aggressive immunosuppression has improved both patient and renal survival over the past several decades, the optimal treatment of LN remains challenging. Improved outcomes have come at the expense of significant adverse effects owing to therapy. Moreover with long-term survival, the chronic adverse effects of effective therapies including risk of malignancy, atherosclerosis, infertility, and bone disease all become more important. Finally, some patients fail to achieve remission with standard cytotoxic therapy and others relapse when therapy is reduced. For these reasons, recent clinical trials have attempted to define alternate treatment protocols that appear to be efficacious in achieving and maintaining remission, but with less toxicity than standard regimens. This paper discusses established and newer treatment options for patients with proliferative and membranous LN, with an emphasis on the results of these recent clinical trials. We also review the experimental and human data regarding some of the novel targeted forms of therapy that are under investigation and in different phases of clinical trials.

Kidney International (2006) **70,** 1403–1412. doi:10.1038/sj.ki.5001777; published online 23 August 2006

KEYWORDS: lupus nephritis; mycophenolate mofetil; membranous lupus; rituximab; cytotoxic agents

Correspondence: *M Waldman, National Institute of Health, NIDDK, Clinical Research Building, Rm 5-2551, 10 Center Drive, Bethesda, Maryland 20892. E-mail: waldmanm@niddk.nih.gov*

Received 24 April 2006; revised 16 May 2006; accepted 3 July 2006; published online 23 August 2006

Renal involvement is a frequent and serious complication of systemic lupus erythematosus (SLE). It contributes both directly to morbidity and mortality of the patients as well as indirectly through side effects of therapy directed at the renal lesions. Although survival has improved dramatically in patients with focal and diffuse proliferative lupus nephritis (LN), until recently 'standard' treatment for severe disease was associated with multiple potential adverse toxicities. Newer treatments for severe LN show promise of equivalent efficacy but less toxicity as well as the potential to treat resistant disease.

Patient and renal survival of SLE patients has improved considerably over the past few decades, in part, due to earlier recognition of renal disease, aggressive immunosuppression, and prevention of complications of therapies.[1–3] The optimal immunosuppressive regimen for proliferative LN remains the subject of research, clinical trials, and intense debate. Until recently, the majority of nephrologists and rheumatologists relied on one 'standard' approach to the treatment of severe LN based upon a series of trials at the National Institutes of Health.[4–7] Recent well-performed, randomized controlled National Institutes of Health trials proved the efficacy of a regimen consisting of six monthly pulses of intravenous (i.v.) cyclophosphamide (CYC) (0.5–1 g/m^2) followed by subsequent i.v. CYC pulses every 3 months for 2 years. This regimen was shown to have fewer flares and relapses and better renal survival than a shorter regimen of six monthly treatments without follow-up doses. Subsequent studies at the National Institutes of Health proved that concomitant i.v. methylprednisolone with monthly pulse i.v. CYC[5,6] was more effective in the short term than either therapy alone. In longer follow-up of the same population, the combination regimen had no greater toxicity than CYC alone, but far superior renal outcomes. Although clearly effective, this regimen is associated with both short-term and long-term adverse effects, including increased risk of severe infections, gonadal damage,[5,8,9] and malignancy.[10] A significant proportion of patients (up to 22%) fail to achieve remission with this regimen or relapse after treatment and some patients still progress to end-stage renal disease.[11]

In view of this, there has been increasing attention on developing alternate therapies that promptly and effectively induce remission, prevent relapse, and maximize patient and renal survival while incurring the least toxicity. Akin to oncologists, nephrologists are now focusing on the concept of

'induction treatment' with vigorous initial therapies, followed by 'maintenance treatment' with lower doses of less toxic regimens. Such strategies include minimizing the use of CYC with lower dosages, use of sequential therapies with different immunosuppressive agents, and eliminating exposure to CYC entirely with use of alternative agents. Mycophenolate mofetil (MMF), rituximab, and newer biologics are all being studied in controlled, randomized trials. However, at present no single regimen has become the new standard of care for treatment of LN. Many physicians are cautious about using newer therapies until solid, long-term evidence shows that the alternate treatment is superior and/or less toxic. Furthermore, it has been difficult for many clinicians to integrate the results of multiple prospective and retrospective studies recently performed in different populations into their general practice.

The aim of this review is to update the reader on the results of several pivotal clinical trials, which lend strong support to the use of alternative induction and maintenance treatment regimens for proliferative LN. It will emphasize the potential benefits as well as the short comings of these studies. Recent data on treatment of membranous lupus nephropathy will be discussed. A brief overview of the promising novel biologic therapies currently under investigation will be included.

INDUCTION TRIALS

The Euro-Lupus Nephritis Trial, a European-based multicenter prospective trial, was a head-to-head comparison of low-dose to 'conventional' high-dose i.v. CYC for severe active LN.[12] Ninety patients were randomized to either high-dose CYC (six monthly i.v. pulses of 0.5–1 g/m^2 followed by two quarterly pulses) or low-dose CYC (fixed i.v. pulses of 500 mg given every 2 weeks for a total of six doses). Following CYC, both groups received oral azathioprine (AZA) as maintenance therapy. The majority of patients was Whites and had class IV diffuse proliferative lupus nephritis (DPLN). At 41 months, there were no significant differences in the primary end point, cumulative probability of treatment failure, between the high- and low-dose treatment arms (20 vs 16%, respectively). There were also no differences in renal remissions (54 vs 71%, respectively) or renal flares (29 vs 27%, respectively). The shorter regimen had less toxicity with fewer and less severe infections.

This study provides good support for a shorter duration and lower total dose of CYC for induction therapy for proliferative LN. Limitations of the Euro-Lupus trial include a population with relatively milder renal disease than in some other studies (mean creatinine 1–1.3 mg/dl; mean proteinuria 2.5–3.5 g/day for both groups). Moreover, almost 85% of the patients were Caucasian. In virtually every clinical study, African-Americans fare worse than non-Blacks and this racial factor is a strong independent risk for progressive renal disease.[13–17] Nevertheless, the 'Euro-Lupus regimen' is an option for some patients with proliferative LN, in particular, Caucasians with less severe renal injury. In addition, the study confirms that the sequential use of CYC and AZA is a viable strategy to reduce toxicity without compromising overall efficacy.

Recently, MMF has emerged as a promising alternative therapy for both induction and maintenance treatment for LN. Extensively used in organ transplantation, MMF has also been used in a variety of immune- and non-immune-mediated renal diseases. Mycophenolic acid (MPA), the active metabolite of MMF, is an inhibitor of the crucial enzyme involved in the *de novo* synthesis of guanosine nucleotides.[18,19] As lymphocytes do not possess a salvage pathway for the generation of these nucleotides, MMF results in selective blockade of B- and T-cell proliferation. Unlike CYC, MPA has little impact on other tissues with high proliferative activity (i.e. neutrophils, skin, intestine, bone marrow), which possess a salvage pathway for nucleotide synthesis. This accounts for its more favorable toxicity profile. In addition, MMF appears to have a variety of anti-inflammatory actions that are independent of its effect on cell-mediated immunity: (1) MPA may limit glomerular injury, progressive renal scarring, and fibrosis by inhibiting proliferation of mesangial cells and myofibroblast differentiation;[20,21] (2) MPA may limit lymphocyte migration into renal tissue by inhibiting the glycosylation (and consequently the affinity) of adhesion molecules expressed by lymphocytes,[22,23] and (3) MPA appears to diminish renal cortical expression of the inducible isoform of nitric oxide synthase (iNOS),[24] which has been implicated in the pathogenesis of renal injury in LN. Moreover, there is evidence to suggest that mycophenolate helps to retard the development of atherosclerosis. These properties and the potential to suppress both upstream and downstream inflammatory events make this medication an attractive therapy for treating LN.

Murine studies,[25,26] numerous case reports, and small uncontrolled series all suggested potential therapeutic value of MMF in SLE.[27–29] Recently, a number of major controlled trials have compared the efficacy of MMF to CYC in induction treatment for proliferative LN.

The first of such trials by Chan *et al.*[30] randomized 42 patients with DPLN to 6 months of induction with MMF (2 g/day) or oral CYC (2.5 mg/kg/day), both with concurrent oral prednisolone. During the maintenance phase, those in the MMF arm continued the drug at a reduced dose (1 g/day) and those in the CYC arm switched to AZA (1.5 mg/kg/day) for 6 months. At 12 months, there were no differences in complete remissions (CR), partial remissions (PRs), or relapses. There were also no significant differences in other parameters, including serum creatinine (Scr), complement, albumin, and 24 h urine protein. Adverse events were more common in the CYC group, although the rate of infectious complications was not statistically different. The study was extended to a period of over 5 years with enrollment of an additional 22 patients.[31] After a median follow-up of 63 months, there was no difference in CR or PR. A total of 6.3% in the MMF group and 10.0% of CYC-AZA-treated patients showed doubling of baseline creatinine during follow-up

($P = 0.667$). Four patients in the CYC-AZA group but none in the MMF group reached the composite end point of end-stage renal disease or death ($P = 0.06$). At long-term follow-up, there was a similar rate of relapse and relapse-free survival in both groups. Significantly, fewer patients administered MMF developed infections requiring hospitalization. In addition, leukopenia was only observed with CYC, the only two deaths were in the CYC group, and amenorrhea was more frequent with cytotoxic therapy (36 vs 3.6%, respectively).

The authors concluded that induction treatment with MMF was as effective as oral CYC, but with fewer side effects. This trial also suffers from limitations. It included only Chinese patients and, clearly, no African-Americans. Patients with some poor prognostic indicators including newly diagnosed DPLN, high Scr, and substantial glomerular and tubulointerstitial disease were also excluded from the study. Nevertheless, the study was well performed, randomized, and had long-term follow-up data. Certainly in the population studied, a strong argument can be made for use of MMF as induction therapy for many International Society of Nephrology class IV patients.

In another trial from China, Hu *et al.*[32] compared the efficacy of 6 months of MMF to conventional i.v. CYC for induction therapy in 46 patients with DPLN. Patients randomized to MMF had greater reduction of proteinuria, lupus serologic activity, urinary sediment activity, and glomerular immune deposits on repeat biopsy while experiencing fewer side effects.

A more recent study by Ginzler *et al.*[33] addressed the issue of efficacy of MMF induction in a high risk, multi-racial, American population in which 56% of the patients were African-American. This study was designed as an equivalency study. In this multi-center, prospective trial, 140 patients (the majority with class IV LN) were randomized to standard six monthly pulses of i.v. CYC or MMF (target dose 3 g/day) in conjunction with a tapering dose of corticosteroids. The study allowed crossover at 3 months for treatment failure or toxicity. No maintenance regimen was specified after the induction. The primary end point was CR at 24 weeks defined as normal values of Scr, absence of proteinuria, and normal urine sediment. PR was defined as $>50\%$ improvement in all renal parameters. At the 6-month end point, in an intention-to-treat analysis, there were fewer treatment failures, and more complete and complete plus PRs with MMF (22 and 52%, respectively) compared to CYC (4 and 30%, respectively). Crossover to the alternate arm was more common with CYC than with MMF (20 vs 8%, respectively). MMF was also associated with a lower incidence of severe infections, and in general fewer, milder side effects. At 3-year follow-up, there were no significant differences in time to first renal flare, renal failure, or death. However, all tended to be lower in the MMF group.

The authors concluded that induction therapy with MMF was superior to i.v. CYC in inducing remissions of LN and was better tolerated. A major limitation of this study is the short duration of follow-up. Longer-term studies are needed to determine the relapse rate and long-term renal survival in this population. This study also did not compare MMF to CYC with steroid pulses, which many clinicians routinely use for severe LN. The early crossover design may have resulted in premature designation of treatment failures. In addition, patients with rapidly progressive renal failure, ARF, and Scr >3 mg/dl or CrCl <30 cc/m were excluded. Finally, although the groups were matched for WHO histologic class on biopsy, it is unknown whether patients with a greater percentage of crescents or interstitial fibrosis will respond equally to the two treatment regimens. Despite these caveats, this study adds significant proof of efficacy for MMF induction therapy in at least some high-risk patients, including African-Americans, with proliferative LN. A new, multi-center, international trial randomizes 350 patients with severe LN to either 6 months of MMF vs. i.v. CYC. Patients with a satisfactory response in both groups at 6 months will subsequently be randomized to either MMF or AZA maintenance therapy (Aspreva Lupus Management Study/ALMS)(Appel G *et al.*, *J Am Soc Nephrol* 2005: 16: 528A; abstract).

It should be noted that at the time of these trials and even currently, there remain major questions about the optimal regimen, duration, and dosage of MMF therapy in LN. Dosing was initially adapted from transplantation regimens of fixed doses in combination with at least one other immunosuppressive drug. Drug levels have not typically been measured in lupus trials, despite the fact that the pharmacokinetics of mycophenolate shows large individual variability. Thus, further investigations will be necessary to obtain optimal target treatment ranges that allow tailoring of therapy in individual patients.

MAINTENANCE TREATMENT

Despite successful induction of proliferative GN, relapses are common, ranging from 10 to 65%.[34,35] With each relapse, continued renal damage can adversely affect long-term renal survival[36] and the treatment of these relapses adds to the toxicity burden. The major challenge of maintenance therapy is avoiding relapses and smoldering disease while minimizing the attendant side effects of continued therapy. The optimal treatment and duration of maintenance therapy remains controversial.

A recent trial by Contreras *et al.*[37] sheds light on the relative efficacy of maintenance regimens using either MMF, AZA, or continued i.v. CYC in severe LN. The high-risk study population included 59 patients, predominantly African-Americans and Hispanics. The majority had diffuse proliferative disease with mean Scr 1.6 mg/dl and urine protein/creatinine ratio >5. After induction therapy with 4–7 monthly pulses of i.v. CYC, 83% of the patients achieved remission and were then randomized to one of three maintenance regimens: i.v. CYC pulses (every third month) or AZA (1–3 mg/kg/day) or MMF (0.5–3 gm/day) for approximately 2 years. Fewer patients treated with AZA

and MMF group reached the primary end points of death and CRF compared to the CYC group. Relapse-free survival was higher with MMF (78%) and AZA (58%) compared to i.v. CYC (43%). Mortality was increased with i.v. CYC compared to both oral agents. Complications of therapy including hospitalizations, amenorrhea, infections, and gastrointestinal problems were significantly lower with MMF and AZA.

The authors concluded that maintenance therapy with either MMF or AZA was superior to i.v. CYC. There are several limitations with this study. Some patients did not achieve remission at the end of the induction phase with i.v. CYC, which may be attributable to the large percentage of Hispanics and Blacks in the study. Patients with rapidly progressive and crescentic disease were excluded. Nevertheless, the favorable response to AZA and MMF compared to continued every third month i.v. CYC strongly suggests a role for the less toxic oral agents in maintenance therapy.

In light of these results and the Euro-Lupus trial, a randomized multi-center trial (MAINTAIN Nephritis Trial) conducted by The European Working Party on Systemic Lupus Erythematosus is currently underway to compare the efficacy and toxicity of MMF and AZA as remission-maintaining treatment for proliferative LN following induction with a short course of i.v. CYC.

BIOLOGICS/IMMUNOMODULATION

Over the last two decades, increasing understanding of the complex pathologic mechanisms underlying SLE in combination with accelerating advances in molecular and cellular immunology have paved the way for development of biologic therapies for LN. In contrast to the global effects of conventional immunosuppressants, these novel agents interfere with specific pathways responsible for the pathologic autoimmune responses.

Although the pathophysiology of SLE is complex, B-cell hyperactivity and autoantibody production have been a consistent feature.[38–40] In addition to the production of antibodies, B cells lead to the activation of the immune system through antigen presentation, activation of autoreactive T cells, dendritic cell regulation, and production of cytokine and chemokines. Thus, B cells represent a rational therapeutic target in SLE. More than one therapeutic approach to impair or delete B-lymphocytes has been explored including the use of LJP 394 and rituximab.

LJP 394 (riquent, abetimus sodium) was the first of such agents designed to selectively modulate autoantibody producing B cells and reduce pathologic antibodies directed against dsDNA.[41] This agent, consisting of four dsDNA helices conjugated to an inert polyethylene scaffold, is believed to reduce circulating autoantibodies by two mechanisms: (1) crosslinking anti-dsDNA surface immunoglobulin receptors on B cells leading to tolerance via anergy or apoptosis, and (2) binding to circulating antibodies, forming small soluble complexes that are subsequently cleared.[42] In a multi-center, placebo-controlled trial, 230 patients with LN (class III, IV, V) were randomized to either LJP 394 or placebo for 76 weeks. Although anti-dsDNA titers decreased and C3 levels increased with therapy, time to renal flare and the number of renal flares was not significantly different in the two groups. In a subset analysis, time to renal flare was prolonged in patients who had antibodies with high-affinity binding to the epitope of LJP 394.[43] However, a subsequent trial designed to confirm the efficacy of LJP 394 specifically in patients with these high-affinity antibodies failed to demonstrate a significant difference in renal flares between LJP and placebo. This was likely secondary to better background immunosuppression, thus reducing the overall flare rate and making it harder to show a significant benefit of a newer agent over placebo.

Rituximab is a chimeric monoclonal antibody (mAb) directed against CD20, a membrane-associated glycoprotein present on B-lymphocytes, but not on plasma cells. It consists of the variable region of a murine anti-human CD20 B-cell hybridoma fused to human IgG1κ constant region. Although the mechanisms whereby rituximab achieves its effects remain incompletely understood, it seems to involve a combination of complement-dependent cell lysis, FcRγ-dependent antibody-dependent cell-mediated cytotoxicity, and induction of apoptosis.[44] Since its approval as treatment for B-cell lymphomas, rituximab has been successfully exploited for the off-label treatment of a wide variety of autoimmune diseases,[45–52] transplant rejection,[53,54] and certain glomerular diseases.[55–60] With its extensive use in the clinical setting, rituximab has accumulated an excellent safety and tolerability profile.[61,62]

There is growing evidence to suggest that rituximab can also be effective therapy in LN. Numerous case reports and several open-label, uncontrolled trials describe the efficacy of rituximab in lupus patients with a variety of renal and extrarenal manifestations refractory to conventional immunosuppression.[62–68] The patients were highly heterogeneous with respect to disease severity, organ involvement, prior therapy, concomitant treatment, and the specific regimen of rituximab used, thus making it difficult to fully evaluate the role of B-cell depletion for LN.

A small open-label study by Sfikakas *et al.*[69] investigated the efficacy of rituximab exclusively in patients with LN. Ten patients with class III or IV LN received rituximab (four weekly infusions of 375 mg/m^2) with oral prednisolone (0.5 mg/kg/day for 10 weeks followed by a slow taper). Eight patients achieved PR within 1–4 months, and five of these patients subsequently achieved CR after a median of 4 months. B-cell depletion lasted a median of 5 months. Three patients relapsed but CR was sustained in four patients at 12 months despite B-cell repletion. This suggests that total B-cell levels may not accurately reflect the overall immunologic impact of therapy. Although reductions in levels of antinuclear antibody and anti-dsDNA autoantibodies were observed in all patients, serologic improvement did not correlate with clinical response. This suggests that remission of nephritis was not only related to a decrease in

autoantibody production. Although these results are encouraging, other investigators have reported more modest clinical benefits with rituximab. Furthermore, it appears that many of the patients, while 'nephritic', did not have highly active nephritis, and as such, the clinical improvement may be achievable with the long duration of steroids. Nevertheless, the results of this and previous trials suggest a promising role for rituximab in the treatment of SLE. A multi-center prospective randomized placebo-controlled trial (LUNAR by Genentech) is currently underway to evaluate the additive benefit of rituximab to MMF for induction therapy and maintenance in patients with proliferative LN.

Despite widespread use of rituximab, there is still much to learn about the effects of this medication, particularly in patients with lupus whose response to this medication may be different compared to patients with other diseases. Further studies are warranted to evaluate the mechanisms whereby B-cell depletion improves disease, the relative sensitivities of the B-cell subsets to depletion, the role of the unaffected B-cell subsets (i.e. plasma cells), the kinetics of repopulation, the quality of reconstituted B cells, as well as the relevance of FcR polymorphisms and complement deficiency to response to therapy. There is evidence to suggest that the clinical benefits of rituximab may be explained by mechanisms independent of B-cell count and autoantibody production.[62,69,70] Clearly, patients can maintain remissions for extended periods of time, despite recovery of CD19 and CD20 cells. Indeed, following B-cell depletion, marked changes in several aspects of the immune response have been observed in lupus patients including downregulation of CD40 and CD80 on B cells as well as alterations in the activation potential of T helper cells (decreased CD40L and CD69).[69,71] These findings need to be validated in larger studies. Correlating such changes in immunologic responses with rituximab-induced clinical benefits will facilitate development of optimal therapeutic regimens that incorporate rituximab and may also uncover pathways that can be targeted simultaneously or consecutively with other agents.

Another promising therapeutic strategy for the treatment of LN is blockade of the interactions between B and T cells and is based on the observation that T-cell activation requires two signals.[72,73] The first signal is provided when the antigen is presented to the T-cell receptor in the context of major histocompatibility complex class II molecules on antigen-presenting cells. The second signal is provided by the interaction of costimulatory molecules on T-lymphocytes and antigen-presenting cells.[74,75] Disruption of this second, nonspecific costimulatory signal results in the interruption of the (auto)immune response, leading to a state of immune unresponsiveness or anergy. There is much evidence to suggest that aberrant expression of costimulatory molecules, dysregulation of costimulatory receptor–ligand interactions, and resultant T-cell-dependent expansion of autoreactive B and T cells contribute to loss of self-tolerance and development of SLE.[76–81] The CD40:CD40L and CD28:B7 family of molecules are considered important costimulatory elements in this regard.[82–90] This has provided the rationale for the development of therapies that disrupt these costimulatory pathways.

Impressive results with anti-CD40L therapy in lupus-prone mice[91] led to clinical trials using two different humanized anti-CD40L mAbs (BG9588 and IDEC-131) in patients with SLE. However, the anti-CD40L mAb approach in human lupus has not yet been fruitful. An open-label trial of BG9588 (riplizumab) showed reduction of serologic lupus activity and improvement of renal function in patients,[92] but the high prevalence of life-threatening thromboembolic events led to the premature termination of trials with this agent. IDEC-131 also did not prove to be clinically effective in human SLE despite being safe and well tolerated.[93,94]

One of the most prominent and well-characterized T-cell costimulatory signals is mediated through the CD28-CD80/86 pathway, which regulates interleukin-2 production and expression of antiapoptotic molecules, augments T-cell proliferation, and upregulates the expression of other costimulatory molecules.[74,95–97] CD28, present on most T cells, binds to both CD80 (B7-1) and CD86 (B7-2), which are present on antigen-presenting cells. Cytotoxic T-lymphocyte antigen 4 (CTLA-4), a structural homolog of CD28, is also expressed on the surface of activated helper cells and plays a crucial regulatory role in T-cell response.[98,99] CTLA-4 competes with CD28 for the same B7 ligands on antigen-presenting cells, but has a higher avidity for them.[100–103] The capture of B7 by CTLA-4 antagonizes CD28-dependent costimulation. It also provides important inhibitory signals that permit long-term tolerance.[104–108] The regulatory effects of interrupting CD28:B7 interactions by CTLA-4 have been exploited with the development of CTLA4-Ig, a recombinant molecule that fuses the extracellular domain of human CTLA-4 with the constant region of the human IgG_1 heavy chain.[101,109] In humans, two preparations of CTLA4-Ig, abatacept and belatacept, have been used clinically.[110] Initial experience with these agents in both the autoimmune and transplant arenas has been encouraging. For example, abatacept has been shown to be efficacious and well tolerated in patients with active rheumatoid arthritis.[111–114] A recently completed phase II clinical trial found belatacept to be as effective as cyclosporine in preventing acute rejection of renal allografts.[115] There is animal data to support the efficacy of CTLA4-Ig in lupus.[109,116] However, this approach has not yet been applied in human LN. Clinical trials using these mAbs in lupus are anticipated.

The discovery of new costimulatory molecules and immune mediators will inevitably suggest new treatment strategies for LN in the future. Other potential therapeutic targets include chemokines, cytokines (i.e. interleukin-6, interleukin-10,[117] interleukin-18), B-lymphocyte stimulator,[118–120]tumor necrosis factor-α, interferons,[121–123] Toll-like receptor[124–127] adhesion molecules, and complement components. Given the complexity of lupus, these biologic agents will likely be used in combination with conventional therapy (and other biologic agents) to induce remission in early

disease and to maintain remission. One of the major challenges to developing treatment strategies employing biologics is understanding the interactions between these agents and conventional immunosuppressive drugs. This is important clinically, as immunosuppressants may abrogate, synergize with, or not affect the function of such agents. For example, previous studies in a rodent transplant model showed that cyclosporine abrogated the effect of combined blockade of CD28:B7 and CD40L:CD40 by CTLA-4Ig and anti-CD40L mAb, respectively.[128,129] Future studies will need to address these issues.

MEMBRANOUS LUPUS NEPHRITIS

Membranous lupus nephritis (MLN) represents about 20% of clinically significant renal disease in lupus. The course and prognosis of MLN is variable and very different renal survival rates have been reported for these patients in the past.[130–133] This is in part related to the older WHO classification system, which subcategorized patients with coexisting membranous and proliferative lesions as subsets of MLN , that is, Vc or Vd. Thus, most published series described heterogenous populations with MLN. Furthermore, the data are confounded by variable use of steroids and other immunosuppressive agents often given for extrarenal manifestations. Nevertheless, proliferative changes in the presence of MLN (Vc, Vd) confer a worse prognosis compared to pure membranous lupus (WHO Class Va) and those with only mild mesangial proliferation (WHO Class Vb). In one series, renal survival was 75% for patients with Va and Vb, 59% for Vc, and 18% for Vd patients at 5 years.[130] The new International Society of Nephrology/Renal Pathology Society classification of LN[134,135] more clearly defines histologic patterns of MLN and clarifies the course of disease by separating the proliferative lesions from the membranous lesions.

Optimal therapy of pure MLN is uncertain. Controlled clinical treatment trials are limited and most studies are small uncontrolled series or retrospective analyses.[136–145] Corticosteroids in combination with several immunosuppressive agents including cyclosporine, chlorambucil, CYC, AZA, and MMF have been evaluated. Table 1 summarizes the results of several recent retrospective and uncontrolled trials. One randomized controlled trial from the National Institutes of Health evaluated therapies for MLN (Austin H *et al. J Am Soc Nephrol* 2004; 15:54A; abstract). In this trial, 42 patients with WHO Class Va and Vb LN were randomized to either intermittent pulse CYC, cyclosporine, or oral prednisone for 12 months. Baseline mean proteinuria was 5.8 g/day, serum albumin was 2.7 g/dl, and inulin clearance of 85 ml/min. There were more CRs and PRs with CYC and cyclosporine treatment arms compared to prednisone. Cyclosporine led to more rapid remissions than CYC, but relapses were also more frequent after cyclosporine was discontinued. Ten patients

Table 1 | Retrospective and uncontrolled treatment trials for MLN

Author Year Type of study	Therapy	No. of patients	Mean follow-up (months)	Results/comments
Hu *et al.*[142] 2003 Retrospective	CsA+prednisone	24	16±8.4	CR: 52% PR: 43% Relapse: 33% after withdrawal CsA
Moroni *et al.*[141] 1998 Retrospective	Chlorambucil+methylprednisolone alternating every month for 6 months (*n*=11) vs. Methylprednisolone (*n*= 8)	19	83±59	Corticosteroids+chlorambucil: CR: 63% PR: 36% Relapse: 9% Corticosteroids alone: CR: 37% PR: 12% Relapse: 87%
Mok *et al.*[143] 2004 Open label	AZA+prednisone × 12 months; Indefinite maintenance: low-dose prednisone and AZA	38	90±59	CR: 67% PR: 22% Relapse: 19% after mean 90 months Renal function: 13% had decline of CrCl; none had doubling of Scr
Chan *et al.*[140] 1999 Uncontrolled	Sequential therapy: Induction: oral CYC × 6 months + prednisolone; Maintenance: AZA	20	73.5±48.9	CR: 55% PR: 35% Relapse: 40% after mean 47 months Renal function: remained stable
Spetie *et al.*[145] 2004 Uncontrolled	MMF (6 months)+prednisone + aggressive BP and lipid control with ACEI and/or ARB + statin	13	16±8	CR: 69% PR: 15%

(CsA: cyclosporine A; CYC: cyclophosphamide; AZA: azathioprine; MMF: mycophenolate mofetil; CR: complete remission; PR: partial remission; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker).

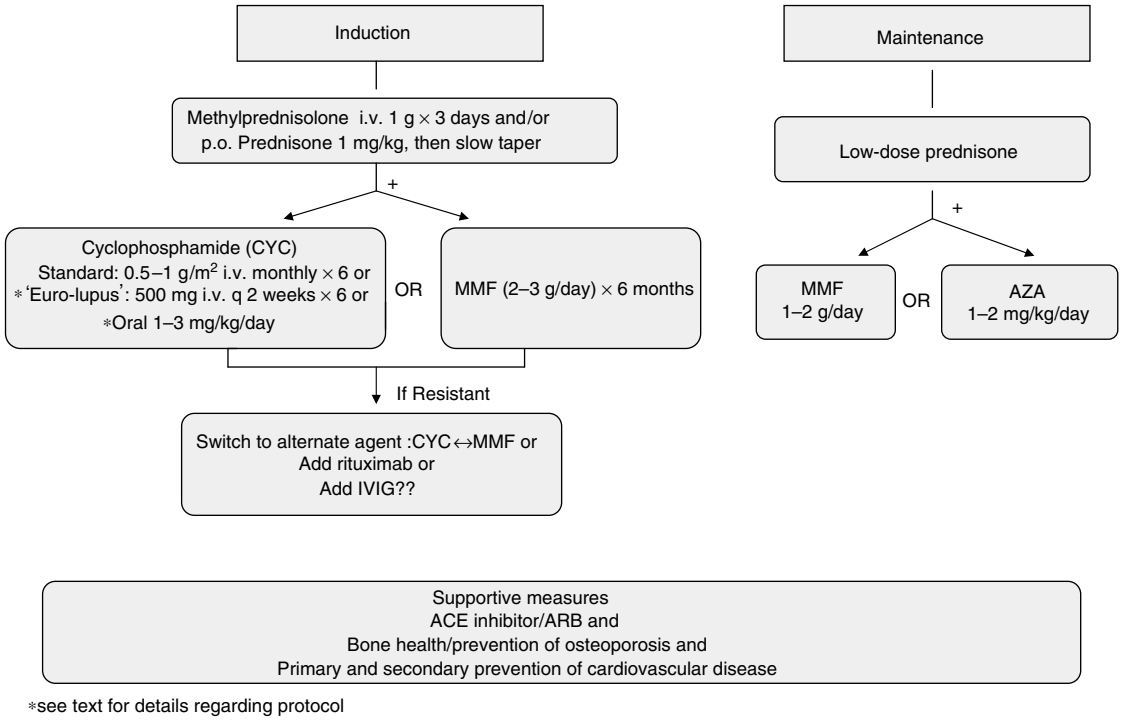

Figure 1 | Treatment options for severe proliferative LN.

who failed to respond to prednisone or cyclosporine or who relapsed after cyclosporine were subsequently treated with CYC and eight achieved remission (six PR, two CR). Thus, the authors concluded that i.v. CYC and cyclosporine are more effective than prednisone alone in inducing remission of proteinuria, but i.v. CYC leads to more sustained remissions.

The role of MMF in MLN is unclear. The response to MMF was poor in one series by Kapitsinou *et al.*[144] in which 18 patients with different classes of LN were treated with MMF. All four treatment failures were in those with a primarily membranous picture. Other investigators have reported more favorable results with MMF (Table 1).[139,145,146] In the previously described multi-center study by Ginzler *et al.*,[33] 27 of the 140 patients had pure membranous lupus. Subgroup analysis of 16 patients who completed 24 weeks of induction therapy revealed that response to MMF was similar to i.v. CYC with no difference in rates of PR or CR, changes in SCr, albumin, urinary protein, or serologies between the two groups at follow-up (Radhakrishnan J *et al. J Am Soc Nephrol* 2005;16:8A; abstract).

Treatment of MLN should be based on severity of disease. Patients with pure MLN with subnephrotic levels of proteinuria and preserved glomerular filtration rate have a good renal prognosis and consideration may be given to a short course of cyclosporine with low-dose corticosteroids along with inhibitors of the renin–angiotensin system and statins. For fully nephrotic patients and those at higher risk of progressive disease, based on the available evidence, options include cyclosporine, monthly i.v. pulses of CYC, MMF, or AZA plus corticosteroids. Patients with mixed membranous nephropathy and proliferative disease are treated in the same way as those with proliferative disease alone.

ADJUNCTIVE THERAPY

With the advent of more potent and safer immunosuppressive regimens, death from uncontrolled lupus activity is uncommon and patients live longer. Accelerated atherogenesis and coronary vascular disease are now a major cause of later mortality.[147] Possible risk factors for this include hypertension, hyperlipidemia, nephrotic syndrome, prolonged corticosteroid use, antiphospholipid antibody syndrome, and in some, the added vascular risks of CKD.[148,149] This underscores the importance of aggressive management of these modifiable risk factors. Although little data are available specifically for patients with LN, it appears prudent to apply the knowledge from the general population with CKD to this patient subset. Thus, tight blood pressure control ($<$130/80), the use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, and correction of dyslipidemia are recommended. In addition, measures to prevent glucocorticoid-induced osteoporosis should be taken, including use of calcium, vitamin D supplements, and bisphosphonates when necessary.

CONCLUSION

The past few years have been an exciting period of more rigorous investigation to find new therapeutic regimens for

LN. This review highlights the progress that has been made so far from recent randomized controlled trials. Figure 1 outlines an algorithm for the treatment of proliferative LN based upon the results of these trials. Clearly, treatment plans needs to be individualized according to clinical scenario, degree of activity and chronicity on biopsy, tolerability, willingness of the patients, and prior treatments. In addition, one needs to be aware of the limitations of the studies that lead to these recommendations in order to make appropriate decisions regarding therapy. Hopefully, future studies, some of which are already in progress, will help refine these recommendations as well as provide additional treatment options for patients suffering from this disease.

ACKNOWLEDGMENTS

This work was supported in part by the Glomerular Center at Columbia University and Zo's Fund for Life.

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