Treatment of Proliferative and Membranous Lupus Nephritis: Review of Key Clinical Trials

Hala Alshayeb, MD, Barry M. Wall, MD and Elvira O. Gosmanova, MD

Abstract: Lupus nephritis (LN) is a common complication of systemic lupus erythematosus (SLE), which is associated with significant morbidity and mortality. Renal involvement in SLE is heterogeneous; therefore, the treatment of LN is determined by the pathological type of LN and ranges from nonspecific measures such as maintenance of adequate blood pressure control and blockade of renin-angiotensin-aldosterone system to the use of immunosuppressive medications. Cyclophosphamide in combination with prednisone has been the standard of care for the treatment of proliferative forms of LN. However, the high rates of progression to end-stage renal disease coupled with adverse side effects from cyclophosphamide and prednisone administration have lead to an intensive search for more effective and less toxic therapies for LN. The authors review available treatment options for proliferative and membranous LN and summarize the results of recently published clinical trials that add new perspectives to the management of kidney disease in SLE.

Key Indexing Terms: Lupus nephritis; Treatment.

Up to 50% of patients with systemic lupus erythematosus (SLE) develop renal involvement during their disease course. Lupus nephritis (LN) is associated with increased mortality in patients with SLE. Accumulating evidence supports that induction of LN remission improves 5- and 10-year overall survival in patients with SLE and is associated with improved renal outcomes. However, LN relapses occur in approximately one third of treated patients and are associated with worsened kidney outcomes, such as doubling of serum creatinine (Scr) and a higher risk for the development of end-stage renal disease (ESRD). Overall patient outcomes in SLE have significantly improved over the past 40 years due to earlier recognition of the disease, aggressive treatment with immunosuppressive medications and prevention of complications. Nevertheless, the current treatments regimens remain suboptimal with up to 10% to 20% of patients with aggressive forms of LN still progressing to ESRD. Therefore, the optimal therapeutic regimen for LN is evolving and is a subject of debate and research. This article overviews treatment options for proliferative and membranous LN (MLN), including findings from recent clinical trials using novel therapies for LN.

INDUCTION TRIALS

Induction therapy refers to initial aggressive treatment aimed at resolution of disease activity, which in LN is typically defined as disappearance of active urinary sediment, improvement in Scr and decrease in urinary protein excretion to below 500 mg/d. Several drugs that have been tested for induction therapy of LN are discussed later.

Cyclophosphamide

The NIH Trials

A series of 3 NIH sponsored randomized controlled trials (RCTs) have provided the strongest evidence for the efficacy of intravenous (IV) cyclophosphamide (CYC) in the treatment of proliferative LN. In the first trial, IV CYC was found superior in lowering the probability of developing ESRD, when compared with oral glucocorticoids or azathioprine (AZA). The second NIH trial demonstrated that a regimen of 6 monthly pulse doses of IV CYC (0.5–1 g/m²) followed by subsequent quarterly pulse doses of IV CYC for 2 years was associated with a lower probability of doubling SCr, fewer flares of LN than a shorter 6 months regimen of IV CYC. In this trial, patients in both groups were also receiving low doses of oral glucocorticoids. In the third NIH trial, a regimen of combined IV methylprednisolone (MP) and IV CYC was shown to achieve higher remission rate of 85%, when compared with 62% with IV CYC alone, or 29% with IV MP alone. After 10 years of follow-up, none of the patients (n = 20) treated with combined therapy of IV MP and CYC had developed ESRD or doubling of SCr, and only 1 patient had 50% increase in SCr. There was no difference in the frequency of adverse events between the group that received combined therapy versus IV CYC alone; however, long-term use of CYC was associated with an increased risk of ovarian failure, severe infections and malignancies.

Euro-Lupus Nephritis Trial

Euro-Lupus Nephritis Trial (ELNT) was a multicenter European RCT involving 90 patients with proliferative LN, who were randomized to either high-dose IV CYC with 6 monthly pulses (0.5–1 g/m²) followed by 2 additional quarterly doses or low-dose IV CYC 500 mg every 2 weeks for 6 doses. Both groups received prednisone during induction and AZA as maintenance therapy. After a median follow-up of 41 months, there was no difference in the frequency of achieving renal remission, renal relapses between the 2 groups. More severe infections were observed with the prolonged CYC use, although the difference was not statistically significant. Extension of the follow-up to 73 months has led to similar results. An initial favorable response to therapy, defined as a reduction of 24-hour proteinuria, at 3 and 6 months of therapy was predictive of preservation of renal function at 6 years. Importantly, the majority of ELNT patients were whites (80%) with preserved renal function, such that results may not be generalizable to patients with SLE with different racial backgrounds or to those with impaired renal function.

Mycofenolate Mofetil

The suboptimal outcomes of CYC in African American patients and the associated drug toxicity with CYC coupled with the proven effectiveness of mycofenolate mofetil (MMF) in animal models of LN led to interest in studying treatment options for LN involving African American patients.
MMF as an alternative treatment option for LN. Mycophenolic acid, the active metabolite of MMF, inhibits the enzyme controlling the synthesis of guanosine nucleotides, which results in selective suppression of B and T-cell proliferation due to the absence of the salvage pathway necessary for DNA synthesis in these cells. Other cell lines with high proliferative activity such as neutrophils, dermal, and intestinal cells have alternative means of guanosine generation, which determines MMF selectivity and limits its side effects.17,18 MMF may have additional beneficial actions in kidney diseases including (1) inhibition of mesangial cell proliferation,19 (2) inhibition of expression of the adhesion molecules on endothelial cells, thus limiting the migration of lymphocytes into the renal tissue20 and (3) suppression of renal cortical expression of inducible nitric oxide synthetase, which has been shown to contribute to kidney injury.21

Chan et al22 randomized 42 patients with diffuse proliferative LN to either MMF 2 g/d for 6 months followed by 1 g daily or to oral CYC 2.5 mg/kg/d for 6 months followed by AZA 1.5 mg/kg/d. In addition, both groups received oral prednisone 0.8 mg/kg. After a median follow-up of 12 months, there was no difference between the 2 regimens in the complete remission, partial remission or relapse rates. More infections occurred in the CYC group: 33% versus 19% in the MMF group. Additional follow-up for 5 years demonstrated no difference in the number of patients who developed ESRD between the study groups.23 The limitations of the study were inclusion of only Asian patients (study was done in Hong Kong) and exclusion of patients with poor prognostic indicators such as rapidly progressive crescentic glomerulonephritis (RPGN), high SCr (>3.4 mg/dL) and substantial glomerular and tubulointerstitial disease.

In another multicenter MMF trial, Ginzler et al24 randomized 40 patients with active World Health Organization classes III to V LN to induction therapy with either a standard regimen of IV monthly CYC or MMF (target dose of 3 g/d); 55% of patients in the study were African Americans and had mean SCr of 1.07 mg/dL. After a median follow-up of 24 weeks, MMF was superior to IV CYC in inducing complete remissions (22% versus 5%) in proliferative LN. MMF was well tolerated and associated with fewer treatment withdrawals and less toxicity, when compared with CYC. These data supported MMF use as safe alternative to CYC for the induction therapy in proliferative LN. Limitations of this study had a short follow-up period of 6 months, and the early crossover design might have resulted in premature designation of treatment failure (20% in CYC group versus 8% in MMF, respectively). In addition, patients with RPGN, acute kidney injury and SCr >3 mg/dL or creatinine clearance <30 mL/min/min² were excluded.

The Aspreva Lupus Management Study (ALMS) reported by Appel et al25 was one of the largest and racially diverse RCTs for the treatment of LN. In this study, 370 patients with World Health Organization classes III, IV and V of LN were randomized to either oral MMF (target dose 3 g/d) or monthly IV CYC (0.5–1 g/m²) for 24 weeks. Both groups received a prednisone taper starting at 60 mg/d. The primary endpoint was a prespecified decrease in urine protein to creatinine ratio and stabilization or improvement of the SCr. Secondary endpoints were assessment of renal remission, systemic disease activity and safety. At 6 months of follow-up, there was no significant difference between the 2 groups in primary outcomes: 53% patients in the IV CYC reached primary endpoint versus 56% in the MMF group. Secondary outcomes, including rates of serious adverse events and infections were similar between the 2 groups. There were 9 deaths in the MMF group and 5 in the IV CYC; however, the difference was not statistically significant (P = 0.58). A subgroup analysis of the ALMS trial showed that patients of Hispanic and African American races had a significantly better response with MMF, when compared with IV CYC.26 Unlike the previous studies, which excluded patients with reduced kidney function, ALMS included 32 patients with glomerular filtration rate <30 mL/min/1.73 m². However, it is important to emphasize that these results are limited to 24 weeks of follow-up, and longer follow-up is warranted before conclusions about long-term efficacy and toxicity of MMF can be made.

MAINTENANCE TRIALS

The goal of maintenance therapy is to sustain the achieved renal remission, while avoiding renal relapses and minimizing drug toxicities.

Contreras et al27 randomized 59 patients with proliferative LN to a maintenance regimen consisting of MMF (MMF: 0.5–3 g/d), AZA (1–3 mg/kg/d) or long-term IV CYC (0.5–1 g/m² every 3 months) after a short course of monthly IV CYC of 4 to 7 does of 0.5 to 1 g/m² and prednisone for induction (80% of patients achieved remission after the induction). The majority of patients were at high risk of kidney disease progression: African Americans (46%) and Hispanics (49%), with mild renal impairment (mean SCr of 1.6 mg/dL) and nephrotic range proteinuria. Patients with crescents and RPGN were excluded. After a median follow-up of 2 years, fewer patients in the AZA and MMF groups reached the primary endpoint of death or chronic kidney disease, when compared with CYC group (20% in MMF versus 25% in AZA versus 55% in CYC group, respectively). Relapse-free survival was 87% in MMF group, 58% in AZA group versus 43% in the CYC group. Adverse events such as hospitalization, amenorrhea, infections and gastrointestinal complications were significantly lower with the MMF and AZA than with the CYC. These results suggest that in patients with proliferative LN, but without RPGN, that maintenance therapy with MMF or AZA is associated with better overall and renal survival, fewer relapses and fewer complications, when compared with long-term IV CYC.

The direct comparison between AZA and MMF for the maintenance therapy in LN could not be concluded from the above study and was subsequently addressed in the recently published MAINTAIN Nephritis Euro trial,28 involving 105 patients (80% whites), with proliferative LN (mean SCr: 1.02 mg/dL), and a 24-hour protein excretion ≥ 0.5 g, who received induction therapy with the ELNT regimen. Subsequently, patients were randomized to AZA (target dose: 2 mg/kg/d) or MMF (target dose: 2 g/d) as the maintenance therapy. After a median follow-up of 53 months, there was no difference between the 2 groups in rates of renal or severe systemic relapse, the times to renal remission or relapse or doubling of SCr. Although infectious complications were not different between the 2 groups, cytopenias were more common in the AZA group (P < 0.03). The trial design did not require patients to have a complete renal remission before starting the maintenance phase. This trial included a low risk, predominantly, white population. The results, therefore of the MAINTAIN Nephritis trial may not be applicable to patients with more severe disease or to other racial groups.

The preliminary results of the 36 months maintenance phase of the ALMS were recently reported in abstract form (Jayne et al, TH-FC111). In this study, 227 patients were
randomized to AZA (2 mg/kg/d) or MMF(2 g/d) for the maintenance therapy in classes III, IV and V LN, after achieving partial or complete response during the 6-month induction phase with steroids and either MMF or IV CYC. MMF was found to be superior to AZA in delaying the time to treatment failure, defined as a composite endpoint of death, serious renal damage or relapse of LN (16% in MMF versus 32% in AZA, \( P < 0.005 \)). Serious adverse events and withdrawals due to adverse events were more common in the AZA group. These preliminary data support MMF use as the first-line drug for maintenance therapy in active LN. The ALMS maintenance trial included a more diverse ethnic population than the MAINTAIN trial. Additionally, ALMS used slightly different primary outcome and included only patients who achieved renal remission at 6 months, when compared with the MAINTAIN, where the trial design did not require patients to have renal remission before starting maintenance treatment with AZA or MMF.

ADDITIONAL THERAPIES FOR LN

Rituximab and Other Biologicals and Immunosuppressors

B-cell hyperactivity and autoantibody production, along with activation of the immune system have been a consistent feature of LN. Therefore, B cells represent a rational therapeutic target in SLE.29 Rituximab is a chimeric monoclonal antibody directed against CD20, a membrane-associated glycoprotein that present on B lymphocytes. There has been growing evidence from case series and uncontrolled trials on the effectiveness of rituximab for the treatment of refractory and relapsing LN.30 Additionally, rituximab has been successfully used in observational studies for the induction of remission in LN.31 Catapano et al30 treated 31 patients with relapsing or refractory SLE, 11 of whom had relapsing/refractory LN with rituximab (either 375 mg/m2/week for 4 weeks or 1000 mg x 2 doses). After a follow-up of 30 months, 97% of patients had depleted peripheral B cells and 87% of patients achieved remission (17 complete and 10 partial). Renal response occurred in 10 of 11 patients with active glomerulonephritis. Clinical improvement was evident by a reduction of disease activity, proteinuria and daily prednisolone dose. Sixty-seven percent of the treated patients relapsed after a median of 11 months. In 50% of the relapsed patients, relapses occurred with the return of circulating B cells. Retreatment with rituximab was effective.

Despite the promising conclusions of uncontrolled series,30,31 preliminary results of the Lupus Nephritis Assessment with Rituximab trial did not support the benefit of rituximab addition to a standard therapy for LN. In this study, 144 patients with proliferative LN, mean Scr of 1.0 mg/dL and urinary protein excretion of >1 g/d were randomized to either rituximab (1000 mg) or placebo administered on days 1, 15, 168 and 182 in addition to therapy with corticosteroids and MMF. There was no statistically significant difference between the 2 treatment groups with respect to partial or complete remissions (57% in the rituximab group versus 46% in the placebo, \( P = 0.55 \)). However, there was a better serological response with a decrease in antinuclear antibodies and improvement in C3 titters in the rituximab group. Limitations of this study included the use of rituximab as add on therapy to a highly effective baseline immunosuppressive regimen, small study size and a short follow-up period.

Several other immunomodulators have been evaluated in the treatment of SLE with promising results. Belimumab binds soluble B-lymphocyte stimulator (BAFF), a cytokine essential for B-cell growth, differentiation and survival, and inhibits its biologic activity.32 In a study of belimumab in patients with SLE (BLISS-52 and BLISS-76), belimumab improved clinical symptoms and serologic profiles and markers of renal function, as well as prevented SLE flares.33 In addition, belimumab was found to be well tolerated. Epratuzumab, fully humanized form of an anti-CD 22 monoclonal antibody, in a small prospective study of 14 patients with moderately active SLE was found to be well tolerated and showed sustained clinical improvement even after the first infusion across most body systems.34 However, data on effectiveness of belimumab or epratuzumab for the treatment of LN are still lacking. Abatacept is a fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 linked to modified portion of human immunoglobulin G1 and targets CD28/B7 interactions, thus antagonizing CD28-dependent costimulation and autoimmune responses.35 It is currently being studied for the induction therapy in patients with LN (Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis).

Plasmapheresis

The role of plasmapheresis for the treatment of proliferative LN was studied by the LN collaborative study group.36 In this RTC, the addition of plasmapheresis to a standard regimen of steroids and CYC did not improve any clinical outcomes, including overall mortality or the number of patients progressing to kidney failure or attaining clinical remission, despite a more rapid reduction in circulating antibody in the plasmapheresis group. Therefore, there is insufficient evidence to recommend plasmapheresis for the treatment of proliferative LN.

MEMBRANOUS LN

MLN comprises approximately 20% cases of LN. MLN can coexist with proliferative LN and is associated with poor renal outcomes due to increased thrombotic complications due to hypercoagulability, hyperlipidemias and carries a substantial risk for ESRD development.37 The scarcity of RCT in MLN makes treatment challenging. Austin et al38 randomized 42 patients with high-risk MLN to either cyclosporine (CsA) for 11 months versus an alternate-month IV CYC regimen for 6 doses or alternate day oral steroids. At the beginning of treatment, the mean glomerular filtration rate was 83 ml/min/1.73 m2 BSA and with urinary protein excretion of 5.4 g/d. At 1 year, the cumulative probability of remission was 27% with prednisone, 60% with IV CYC and 83% with CsA. Relapse of nephrotic syndrome occurred more often after completion of CsA, when compared with IV CYC (\( P = 0.02 \)). Patients with impaired renal function were excluded from the study.

Pooled analysis of 2 RCT of induction therapy in patients with pure MLN,39 including 33 patients receiving MMF and 32 patients receiving IV CYC as induction therapy for 24 weeks, demonstrated that both MMF and IV CYC-based regimens seemed to have equivalent benefits for the induction of remission of MLN, including patients with nephrotic range proteinuria. However, longer follow-up is needed to establish benefits beyond the 6 months.

Mok et al40 in a small open-labeled study treated 38 patients with MLN with AZA and prednisone for 12 months, followed by indefinite maintenance therapy with low-dose prednisone and AZA. After a mean follow-up of 90 months, the complete remission, partial remission and cumulative relapse rates were reported as 67%, 22% and 19%, respectively. Additionally, none of the patients developed doubling of Scr. Several clinical trials on the treatment of MLN with MMF, tacrolimus, serolimus and infliximab are currently underway.
underway or listed as completed at www.clinicaltrials.gov. Therefore, additional information on the treatment of MLN may be forthcoming.

CONCLUSIONS

This review article summarizes the results of the recent clinical trials on the management of LN. Many nephrologists continue the use of CYC for the treatment of proliferative LN. However, accumulating evidence from several RTC supports mycophenolate as safe and effective alternative to CYC in the treatment of proliferative and membranous LN, especially in African Americans and Hispanics. Mycophenolate can be used both for the induction and the maintenance phases of proliferative LN. The findings from the Lupus Nephritis Assessment with Rituximab study do not support rituximab as add-on treatment for proliferative LN; therefore, its role for LN remains to be determined. B-cell depleting strategies using belimumab and epratuzumab seem promising in SLE; and their effectiveness for the treatment of LN requires further validation in clinical trials. These conclusions are in agreement with a recent review of treatment options for LN by Bomback and Appel.41

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REFERENCES


AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

1—Please spell out NIH, RTC, BSA and BAFF.

2—Please check whether the unit “mL/min/min²” is OK as given.

3—Please provide complete details of “Jayne et al” in the reference list.

4—Please provide department/division name (if any) for the second affiliation.