Immunosuppressive Agents for the Treatment of Lupus Nephritis

A recent meta-analysis of 25 articles on randomized controlled trials found that CYC in combination with steroids reduced the risk for doubling of serum creatinine compared with steroids alone (relative risk [RR] 0.59), but had no impact on overall mortality.11

In a prospective study from 1988 to 2000 of 38 biopsy-proven LN patients treated with pulse methylprednisolone (MP) and CYC, the mean time to remission was 10±15 months, with 47% patients going into complete remission (CR) or partial remission (PR) during the study. About one-quarter of the patients still had proteinuria >1g/24 hours with normal renal function after two years of treatment. Repeat renal biopsies showed an increase in features of chronicity, including marked glomerular sclerosis and tubulointerstitial fibrosis. About 85% of relapses occurred within the first five years of treatment, with 13% of patients progressing to ESRD.12 Although CYC remains the recommended treatment for patients with severe LN, according to the 2008 European League Against Rheumatism (EULAR) task force report it is far from the perfect medication for LN.13

Mycophenolate Mofetil

Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid, was approved for prevention of renal transplant rejection in 1995 and, one year later, for other solid-tumor transplants. Within two years, case reports were published regarding its successful use as rescue therapy for LN refractory to other immunosuppressive agents, including biologics.

Cyclophosphamide

In 1986, Austin et al. published the results of the five treatment arms of the NIH LN trial. They found that prednisone (PDN) alone increased the risk for renal flares compared with high-dose intravenous (IV) CYC. Oral CYC showed a marginal advantage in maintaining renal function and preventing end-stage renal disease (ESRD) over PDN alone.10 However, the use of CYC is limited by its side-effect profile, which includes hemorrhagic cystitis, bone marrow suppression, opportunistic infections, and premature gonadal failure.10

To address the issue of toxicity related to high cumulative doses of CYC, Houssiau et al. compared high-dose with low-dose CYC in the Euro-Lupus Nephritis trial. Ninety SLE patients were randomized to either the NIH regimen of 0.75–1g/m² body surface area (high-dose) or CYC IV 500mg every two weeks for six doses for induction followed by oral azathioprine (AZA) for maintenance treatment (low-dose). The cumulative probability of renal remission and treatment failure was comparable between the two groups. Even the risk for renal flares was similar between the two regimens, although the rate of infections was lower in the low-dose group. Of note, however, the patients in this trial had less severe LN than the patients in the NIH trials.8,10

Lupus nephritis (LN) is one of the most serious complications in patients with systemic lupus erythematosus (SLE). Initial clinical presentation with renal involvement is associated with more frequent exacerbations of lupus and lower survival.1 Although LN continues to be associated with high morbidity and mortality, even partial remission with treatment improves patient and renal survival significantly at 10 years.2,3

The first National Institutes of Health (NIH) trials for LN were initiated in the late 1970s; there are currently 30 ongoing clinical trials listed under clinicaltrials.gov. Although the NIH trials were instrumental in establishing cyclophosphamide (CYC) as the standard-of-care immunosuppressive agent for LN, the cumulative rate of relapse in an observational study was 25% at five years and 46% at 10 years in patients treated with this agent.4

With recent insights into the pathogenesis of SLE and with the design of biologic agents, the search for a safer and more effective ‘gold standard’ in LN treatment has led to several clinical trials in the last decade, some with promising and some with disappointing results. In this article we will present an overview of the treatment options currently available for patients with LN and provide a brief glimpse into what the future holds with respect to other immunosuppressive agents, including biologics.

Archana R Vasudevan, MD, is a Clinical Assistant Professor in the Division of Rheumatology at the State University of New York (SUNY). She earned her MD from Lady Hardinge Medical College, India, and completed her internship and residency in internal medicine at Kettering Medical Center, Ohio. E: archana.vasudevan@downstate.edu

Ellen M Ginzler, MD, is a Professor of Medicine at the State University of New York (SUNY), where she has served as Chief of Rheumatology since 1991. She is a Fellow of the American College of Physicians, serves on the Board of Governors of the New York Chapter of the Arthritis Foundation, and was named a Kirkland Scholar of the Mary Kirkland Center for Lupus Research in 2005. Professor Ginzler earned her MD from Case Western Reserve University School of Medicine and her Masters in Public Health from the Yale University School of Epidemiology and Public Health. She completed her internship and residency in internal medicine at King’s County Hospital and Bellevue Hospital in New York, followed by fellowship training in rheumatology at SUNY Downstate Medical Center and in epidemiology at Yale. E: ellen.ginzler@downstate.edu
patients treated with MMF after failing treatment with CYC. A significant decrease in proteinuria as measured by urine protein-to-creatinine ratio, as well as an improvement in the baseline serum creatinine, was noted. The first randomized controlled trial comparing MMF with oral CYC was reported by Chan et al. Forty-two LN patients were treated with MMF in combination with prednisone for 12 months, and the CR and PR rates were compared with those of CYC plus prednisone for six months followed by azathioprine. Although there were no differences in remission rates between the two groups, the very high remission rates published in this study—81% in the MMF-treated group and 76% in the patients treated with CYC—have not been reproducible in subsequent trials.15

In another randomized controlled trial comparing MMF with IV CYC in 46 patients, Hu et al. demonstrated that there was more effective inhibition of autoantibody formation and fewer chronicity changes on repeat renal biopsies in the MMF group.14 Twenty patients with renal biopsy changes associated with poor prognosis—such as non-inflammatory necrotizing vasculopathy, thrombotic microangiopathy, and vasculitis—had a CR rate of 44.4% in MMF patients compared with 0% in the CYC arm of the study (p=0.026). Fifty-five percent of patients in the MMF group improved to the IV CYC group (p=0.05).17 Infections occurred in 30.4% of the patients in the CYC group versus only 17.4% of those in the MMF group.14 A 10-fold decrease in amenorrhea was also noted in women treated with MMF versus CYC.16

In the largest published study to date of MMF in LN, Ginzler et al. conducted a 24-week open-label, randomized, non-inferiority trial in 140 patients comparing MMF with monthly IV CYC as induction therapy. The primary end-point was complete remission and the secondary end-point was partial remission. At 24 weeks, 22.5% of patients on MMF had attained CR versus only 5.8% of those on IV CYC (p=0.005). Although there was no difference in the rates of PR, the overall remission rates were statistically significant, with 52.1% patients in MMF group having either CR or PR versus 30.4% in the IV CYC group (p=0.009).14 Further analyses of the data from the Aspreva Lupus Management Study (ALMS) to determine the response rates by ethnicity found that patients of Hispanic and ‘other’ ethnic backgrounds (which included African-American patients), who tend to have worse prognosis with LN, had better response rates with MMF than with CYC in the ‘other’ subgroup, 60.4% responded to MMF, whereas only 38.5% responded to IV CYC (p=0.033); in the Hispanic population subgroup, 60.9% responded to MMF and only 38.8% to IV CYC (p=0.011).20 The maintenance phase of the ALMS trial is ongoing. Patients who initially responded have been re-randomized to double-blind, placebo-controlled maintenance treatment with AZA or MMF with corticosteroids. The primary outcome measure is event-driven, defined as the number of renal flares up to three-year follow-up; a secondary end-point is time to treatment failure.21

In a meta-analysis of all controlled trials using MMF as an induction treatment, the RR of failure to induce remission was 0.68, favoring MMF over CYC (p=0.001). The pooled RR for the composite outcome of death or ESRD again favored MMF over CYC at 0.44 after extended study follow-up.22 In a three-arm trial comparing maintenance therapies using IV CYC quarterly, oral AZA, and oral MMF therapy after six months of induction treatment with IV CYC, Contreras et al. found that the 72-month event-free survival rate for the composite end-point of death or ESRD was significantly higher for the MMF (p=0.05) and AZA (p=0.009) arms than the CYC arm. Although the chronicity index favored the CYC arm in this trial (p=0.009), the rate of relapse-free survival was higher in the MMF group (p=0.02).23 An ongoing trial in Europe, MAINTAIN, is comparing MMF with AZA in the maintenance regimen to determine whether one of these agents is superior in preventing renal flares. Apart from its efficacy in treating LN, quality of life (QoL) assessment was noted to be superior in the MMF group in two studies. This was attributed to a higher response rate and a lower infection rate in the MMF group. One of these studies, however, was based on recall of remote events. The other study, which also looked at quality-adjusted life years (QALYs) for induction treatment for LN, found that MMF was less expensive than IV CYC, as it did not require admission for drug administration and hydration.24 25

Azathioprine
Azathioprine has been used since the 1970s as a steroid-sparing agent and for the maintenance phase of LN treatment. A meta-analysis of all randomized controlled trials for the treatment of proliferative LN suggested that AZA in combination with steroids as an induction regimen reduced all-cause mortality compared with steroids alone.26 However, when the AZA and MP combination was compared with IV CYC in an open-label trial by the Dutch Working Party on Systemic Lupus Erythematosus, relapses and infections were both more frequent in the AZA arm than the CYC arm of the study, with no differences in either proteinuria or serum creatinine between the groups.26 Furthermore, CYC is also more effective than AZA in halting progression of chronic changes in LN.27

Hydroxychloroquine
Hydroxychloroquine (HCQ) is known for its beneficial effects on patients with SLE, especially with regard to prevention of flares, prevention of thrombotic events, and overall survival. The study by Kasitanon et al. also shows that patients with LN have better outcomes when treated with HCQ compared with controls. Of the patients who experienced CR, 64% received HCQ compared with 22% of those who did not.28

Apart from its efficacy in treating lupus nephritis, quality of life assessment was noted to be superior in the mycophenolate mofetil group in two studies.
Myeloablation and Autologous Stem Cell Transplant
There have been two large published case series—one from the US and the other from the European Bone Marrow Transplant Group (EBMT)/EULAR registry. The US series was a non-randomized, open-label, non-myeloablative autologous hematopoietic stem cell transplantation (HSCT) study of 50 patients with organ-threatening or life-threatening SLE that was refractory to standard therapies. The conditioning regimen included CYC, antithymocyte globulin, and methylprednisolone. There were a total of eight deaths in this study. The probability of five-year survival was 84% and the probability of disease-free survival was 50% at five years.31 The European study of autologous HSCT for refractory severe SLE was carried out at 23 centers. Conditioning regimens were not uniform but were non-myeloablative. There were 12 deaths in this study. After a follow-up period of 26 months, disease remission occurred in 33 cases (66%), of which 32% later relapsed.32

Biologics
The landscape changes almost monthly with the current investigational trials—some for induction and maintenance therapy, others only for prevention of flares. As we gain more in-depth knowledge of the pathophysiology of SLE, treatments are being tailored to target the abnormal function of cells or molecules in lupus patients. B-cell depletion therapies such as rituximab, an anti-CD 20 monoclonal antibody (mab), have been used as induction agents when patients have been resistant to treatment with all conventional immunosuppressive agents.31–35 Inhibition of T-lymphocyte co-stimulation with abatacept, CTLA-4 Ig, is currently being studied for patients with active LN.36 Monoclonal antibodies that block cytokines affecting B cells, such as atacicept, are in phase III and phase III/IV trials.31,32

The translational effects of these agents have not always worked as well for lupus patients as they have in animal models. One such agent, abetimus sodium, leads to phagophorosis of anti-double-stranded DNA (ds-DNA) antibodies by cross-linking anti-ds-DNA surface immunoglobulin receptors on B cells. This triggers signal transduction pathways, causing B-cell anergy and apoptosis, thereby reducing titers of anti-ds-DNA antibodies. There was no difference in time to renal flares between the treatment arms, and the benefits of this agent to date have not been very impressive in comparison with placebo.31,32,33 A re-designed phase III trial is ongoing. A trial of a monoclonal antibody to CD40 ligand resulted in improvement in anti-ds-DNA titers and a 50% reduction in proteinuria, but this study had to be terminated early due to an increased incidence of thromboembolic events in the treatment arm.31,32,33 Another company’s trial of anti-CD40 ligand was carried to completion, but failed to show a difference in response between the treatment and placebo arms.31,32

Trials for generalized lupus, also in progress, include belimumab (anti-BLyS monoclonal antibody), MEDI-545 (for blocking interferon-α), and tocilizumab (anti-IL-6 receptor antibody).31,32 The results of these investigations may be extended to consideration for LN therapy.

Non-biologics
There have been case reports regarding the successful use of tacrolimus, leflunomide, cyclosorpine A, fludarabine, mizoribine, and other immunomodulatory agents in the treatment of LN, but randomized controlled trials are still ongoing.31,32

Summary and Recommendations
Fifty years after the discovery of steroids and 30 years after the first use of CYC for the treatment of LN, LN still continues to be a predictor for poor prognosis among lupus patients. Patients with LN require close monitoring with optimal blood pressure control and treatment of comorbidities such as diabetes and dyslipidemia. Angiotensin-converting enzymes inhibitors/angiotensin receptor blockers (ACEIs/ARBs) have also been found to reduce proteinuria and increase serum albumin in patients with proteinuria >1g/24 hours after resolution of active LN.45 Among patients who progress to ESRD and undergo renal transplant, no difference has been found in the actuarial 10-year patient survival rates and the death-censored graft survival rates. However, intravascular thrombotic events were higher in patients with SLE (17.4% versus 5% in other patients; p<0.01).46

Editor’s Recommendation

Immunosuppressive Therapy in Lupus Nephritis: The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-dose versus High-dose Intravenous Cyclophosphamide
Houssiau FA, et al.

Glomerulonephritis is a severe manifestation of systemic lupus erythematosus (SLE) that is usually treated with an extended course of intravenous (IV) cyclophosphamide (CYC). Given the side effects of this regimen, we evaluated the efficacy and the toxicity of a course of low-dose IV CYC prescribed as a remission-inducing treatment, followed by azathioprine (AZA) as a remission-maintaining treatment. In this multicenter, prospective clinical trial (the Euro-Lupus Nephritis Trial [ELNT]), we randomly assigned 90 SLE patients with proliferative glomerulonephritis to a high-dose IV CYC regimen (six monthly pulses and two quarterly pulses; doses increased according to the white blood cell count nadir) or a low-dose IV CYC regimen (six fortnightly pulses at a fixed dose of 500mg), each of which was followed by AZA. Intent-to-treat analyses were performed. Follow-up continued for a median of 41.3 months in the low-dose group and for 41 months in the high-dose group. Sixteen percent of those in the low-dose group and 20% of those in the high-dose group experienced treatment failure (not statistically significant by Kaplan-Meier analysis). Levels of serum creatinine, albumin, C3, and 24-hour urinary protein and disease activity scores significantly improved in both groups during the first year of follow-up. Renal remission was achieved in 71% of the low-dose group and in 54% of the high-dose group (not statistically significant). Renal flares were noted in 27% of the low-dose group and 29% of the high-dose group. Although episodes of severe infection were more than twice as frequent in the high-dose group, the difference was not statistically significant. The data from the ELNT indicate that in European SLE patients with proliferative lupus nephritis, a remission-inducing regimen of low-dose IV CYC (cumulative dose 3gm) followed by AZA achieves clinical results comparable to those obtained with a high-dose regimen.
Autoimmune Disease  Systemic Lupus Erythematosus

Direct healthcare costs related to hospitalizations and dialysis are higher in lupus patients than patients without renal involvement. Developments in the last 15 years have offered some hope, with the introduction of MMF for the treatment of LN and newer biologics, but we are still far despite from a gold standard in terms of remission rates or side-effect profile. Despite the lack of published long-term data regarding MMF, its use in combination with corticosteroids for induction therapy is well recognized as the standard of care. Questions remain concerning the optimal dose of MMF for induction versus maintenance therapy, the rapidity of a tapering regimen, and the benefit of the addition of biologics to MMF without sacrificing safety. CYC should be considered in selected patients with rapidly progressing renal insufficiency or features of vasculitis. Given the high rate of infectious complications, cost of therapy, and significant relapse rate, autologous stem cell transplantation is unlikely to have a major positive impact on lupus outcomes. Consideration should be given to the patient's ethnic and racial background and the likelihood of differential response to therapeutic agents. HCO and ACEi/ARBs need to be part of every SLE patient's regimen to help reduce proteinuria and attain remission.

With many new medications in various stages of clinical trials and more pharmacogenomic investigations being performed, researchers and clinicians may be able to provide individualized therapeutic regimens that would be highly efficacious while minimizing toxicity.