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Treatment options for severe lupus nephritis

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Summary

Renal involvement in systemic lupus erythematosus is a common complication that significantly worsens morbidity and mortality. Landmark trials conducted by the National Institutes of Health established cyclophosphamide as the mainstay of therapy. Since then, the prognosis of patients with lupus nephritis has markedly improved, and 10-year survival rates now surpass 75%. These superior outcomes have come at the expense of adverse events such as serious infections and gonadal failure in a significant number of patients, and the relapsing nature of the disease continues to pose a problem. For these reasons, new treatment protocols, such as mycophenolate mofetil induction or sequential therapies using azathioprine or mycophenolate mofetil in the maintenance phase, have been developed in recent years with the goal to maintain remission and reduce adverse events. In addition, ongoing research into the pathogenesis of lupus nephritis has confirmed the importance of B and T cell activation, leading to the identification of potential new therapeutic targets. This article discusses established and novel treatment options for patients with severe lupus nephritis corresponding to WHO classes III, IV, and V with III or V with IV.

Key words: lupus erythematosus • systemic • lupus nephritis • drug therapy

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INTRODUCTION

Systemic lupus erythematosus (SLE) is the prototype of autoimmune diseases and mainly affects young women. The incidence and prevalence are 6 and 50 cases per 100,000 people, respectively, in the United States, and in population-based studies, Asians, Hispanics and African Americans are more frequently affected than Caucasians^{69, 89, 95, 120, 126}. Diagnostic criteria have been set forth by the American Rheumatism Association⁷⁰, lupus nephritis is present in approximately 25–50% of patients at the time of diagnosis and eventually develops in up to 60% of adults and 80% of children²⁴. Renal involvement, which may manifest itself as proteinuria, active urine sediment with hematuria and cellular casts, hypertension, and renal failure, adds significantly to the morbidity and mortality of SLE. Young patients with SLE may die from active disease or from associated infections, and studies have found a strong association between renal involvement and excess SLE deaths. This is particularly true among non-Caucasians, although some of this association may be explained by socio-economic status^{1, 2, 16}.

Lupus nephritis is an immune-complex-mediated glomerular disease; however, concomitant tubulointerstitial involvement with or without immune deposits is almost always seen. Involvement of the renal vasculature is also common, ranging from indolent vascular immune deposits to fibrinoid necrosis and thrombotic microangiopathy. In 1964, Pollak et al.¹¹¹ careful histologic observations established semi-quantitative criteria for assessing lupus nephritis that formed the basis of the currently used classifications. The most commonly used classification system for lupus nephritis is the one published by the World Health Organization formulated in 1974⁹⁶, which underwent subsequent modifications^{10, 103, 111} and has recently been revised by the International Society of Nephropathology and the Renal Pathology Society¹³². Almost all observational and experimental studies have shown that the long-term follow-up of patients with WHO class II or mesangial glomerulonephritis is associated with a good prognosis and that patients with this lesion do not require specific therapy unless transformation to WHO classes III or IV occurs^{7, 10, 111}. Some controversy exists regarding the optimal therapy of WHO class V or membranous glomerulonephritis due to the uncertain natural history of this disease, variable outcomes after treatment, and the combination of membranous glomerulonephritis with proliferative glomerulonephritis in some trials^{8, 11, 90, 109, 111, 113}. The worst outcomes are associated with proliferative forms of lupus nephritis. For WHO class III or focal proliferative glomeru-

lonephritis, the 5-year kidney and patient survival are 85 and 72%, respectively, and for WHO class IV or diffuse proliferative glomerulonephritis, the 5-year renal survival is 86% and patient survival is 67%⁷.

The low incidence of lupus nephritis makes recruitment of a large number of patients into clinical trials difficult, and the long course of the disease, with periods of remission and relapse, adds an additional challenge. For these reasons, only a limited number of immunosuppressive regimens have been studied in prospective clinical trials. Here we discuss selected agents that have been compared with corticosteroids in controlled clinical trials for patients with proliferative lupus nephritis. We will also discuss the results of studies investigating sequential immunosuppressive therapies, as well as adjunct and experimental modalities.

CORTICOSTEROIDS

Corticosteroids are very effective in treating extrarenal manifestations of SLE, such as fever, rash, and arthralgias. A review of the experience at the Massachusetts General Hospital between 1922 and 1966 that was published in 1979 bolstered the rationale to use corticosteroids in patients with lupus nephritis⁴. The interpretation of this analysis was limited by an unclear definition of “high risk” in these early publications, and the possibility that improvements in outcome could reflect an improvement in overall healthcare. A number of uncontrolled clinical trials performed between 1976 and 1982 suggested improvement of renal function with corticosteroids alone^{26, 48, 112}. However, subsequent randomized clinical trials performed at the National Institutes of Health (NIH) clearly demonstrated that corticosteroids alone were inferior to cyclophosphamide in the treatment of proliferative lupus nephritis^{9, 121}. Follow-up studies demonstrated that the combination of pulse methylprednisolone and cyclophosphamide conveyed an additional benefit, and this regimen has become the standard of care in many centers^{65, 74}.

CYCLOPHOSPHAMIDE

Cyclophosphamide is an alkylating agent that results in impaired DNA replication and transcription. Dose and duration of therapy determine the degree of inhibition of immune function. Cyclophosphamide has been used as a therapy for lupus nephritis since the 1960s, and a retrospective analysis published in 1984 suggested a benefit in regards to progression towards end-stage renal disease and the incidence of death⁵⁶. Two prospective, randomized clinical trials by the

NIH established the superiority of intermittent pulse cyclophosphamide combined with pulse methylprednisolone for approximately 36 months over methylprednisolone alone^{9, 18}. Intravenous cyclophosphamide conveyed better preservation of renal function and a lower chance of relapse. By survival analysis, the 72-month cumulative probability of remaining free of chronic renal failure ranged 75–100% with cyclophosphamide therapy. The relapse-free cumulative probability was approximately 87%. These results were confirmed by meta-analyses, demonstrating that the combination of intravenous cyclophosphamide and oral corticosteroids reduces the risk for both end-stage renal disease (ESRD) and death compared with corticosteroids alone¹⁵. Interestingly, a more recent meta-analysis concluded that there was no significant reduction in mortality with cyclophosphamide, and cyclophosphamide prevented doubling of serum creatinine, but not the development of ESRD⁵⁷. However, the two meta-analyses use different methodologies, and the patient populations included differ markedly in their risk for death and chronic renal failure. The beneficial effect of long-term cyclophosphamide must be weighed against its significant toxicity. The incidence of amenorrhea was significantly increased, ranging 45–71% in the groups receiving cyclophosphamide compared with the groups receiving corticosteroids alone ($p < 0.05$). Also, the incidence of herpes zoster infection was significantly increased, ranging 25–33% in the groups receiving cyclophosphamide compared with the groups receiving corticosteroids alone ($p < 0.05$). Hemorrhagic cystitis was seen only in the groups receiving oral cyclophosphamide, with an incidence ranging 14–17%. Infections were seen in approximately 35% of the patients in each group^{9, 18, 65}.

In one of the NIH trials, published in 1992¹⁸, the efficacy and safety of a short-term intravenous cyclophosphamide regimen with corticosteroids using 6 monthly pulses of cyclophosphamide with expected minimal toxicity was compared with the long-term cyclophosphamide regimen with the same 6-month induction course followed by approximately 12 more pulses of quarterly intravenous cyclophosphamide with oral corticosteroid maintenance. Although the incidence of sustained amenorrhea was significantly lower in the short-term cyclophosphamide group compared with the long-term cyclophosphamide group (17 vs. 64%, $p = 0.03$), the patients in the short-term cyclophosphamide group had a low cumulative probability of remaining relapse-free when they were not treated with immunosuppressive maintenance other than corticosteroids. The 60-month cumulative probability of remaining relapse-free was approximately 40 and

87% in the short-term and long-term cyclophosphamide groups, respectively ($p < 0.001$).

The incidence of ovarian failure is dose-related^{17, 101, 114, 131}. Regimens employing short courses of cyclophosphamide have reported a much lower incidence of toxicities than regimens using long-term cyclophosphamide^{30, 31, 99}. Recent data from clinical trials demonstrated that short courses of cyclophosphamide with cumulative dose ranging 3–8 g are efficacious and safe when followed by immunosuppressive agents such as azathioprine or mycophenolate mofetil maintenance^{30, 31, 37, 72}. There is still some debate in regards to the optimal route of administration of cyclophosphamide. It has been postulated that oral cyclophosphamide may be more efficacious than intravenous cyclophosphamide, given that a higher cumulative dose is more quickly reached. However, this has not been clearly shown to date^{9, 100}.

AZATHIOPRINE

Azathioprine inhibits purine synthesis in all replicating cells, which leads to a decreased number of circulating B and T lymphocytes as well as decreased antibody production and interleukin (IL)-2 expression. Three randomized clinical trials evaluated the role of azathioprine in the treatment of proliferative lupus nephritis^{9, 22, 66}. The most recent meta-analysis showed that azathioprine, but not cyclophosphamide, conferred a survival benefit. Although cyclophosphamide reduced the risk for a doubling of serum creatinine, neither azathioprine nor cyclophosphamide significantly reduced the risk for ESRD⁵⁷. There is no head-to-head comparison of cyclophosphamide and azathioprine with enough power to detect difference less than 15% in outcomes such as death, doubling of serum creatinine, and ESRD; however, the trial of Austin et al.⁹ includes patients treated with cyclophosphamide or azathioprine. In this trial, there was no significant difference in the risk for a doubling of serum creatinine when comparing azathioprine with cyclophosphamide; however, the incidence of amenorrhea was significantly lower in the azathioprine group compared with the cyclophosphamide groups (18% vs. 45–71%, $p < 0.05$). Also, the incidence of herpes zoster infection was significantly lower in the azathioprine group compared with the cyclophosphamide groups (11% vs. 25–33%, $p < 0.05$). A recent cohort study in patients treated with steroids and azathioprine suggested similar outcomes when compared with published data from patients treated with cyclophosphamide¹⁰⁷. Given the lower costs and lower incidence of ovarian failure with azathioprine therapy, a head-to-head comparison of azathioprine and

cyclophosphamide in a prospective, randomized clinical trial is under way to establish the role of azathioprine in the therapy of proliferative lupus nephritis¹²⁷. Currently, azathioprine is most commonly used in sequential regimens (see below) and in combination with corticosteroids to treat severe lupus nephritis during pregnancy.

COMBINATION THERAPIES INCLUDING CYCLOPHOSPHAMIDE

Several attempts have been made to either increase efficacy or reduce side effects by combining cyclophosphamide with various other agents. The best known is intravenous cyclophosphamide combined with pulse methylprednisolone, as mentioned above. Several investigators evaluated the combination of cyclophosphamide and azathioprine^{45, 61}, and azathioprine appeared to have a cyclophosphamide-sparing effect, resulting in fewer adverse events¹⁵. Despite positive early reports, the addition of plasmapheresis to cyclophosphamide therapy does not appear to convey an additional benefit^{91, 130, 133}.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF), like azathioprine, inhibits purine synthesis; however, its effect is selective for lymphocytes. MMF has been extensively studied in renal transplantation⁴⁶. In the transplant arena, MMF was superior to azathioprine^{6, 67}, and in mouse models of lupus nephritis MMF produced very encouraging results^{38, 78}. This has led to clinical trials of MMF in patients with proliferative lupus nephritis. Initial case reports showed a good response^{47, 63}. Chan et al.³⁰ initiated a randomized clinical trial comparing induction with oral cyclophosphamide for 6 months followed by azathioprine for 6 months to MMF for 12 months. The study concluded that both treatments were equivalent, with remission rates above 75% and similar infection rates at 12 months. However, there was only a short follow-up. After 12 months of MMF, the patients were switched to azathioprine maintenance and long-term follow-up data describing the incidences of renal failure, death, relapse rate, and infections have only been partially released³². Preliminary data from another induction study suggest that MMF is at least equally efficacious when compared with monthly intravenous cyclophosphamide induction in a high-risk population with 56% African-Americans⁶².

SEQUENTIAL THERAPIES INCLUDING CYCLOPHOSPHAMIDE, AZATHIOPRINE AND MMF

In the last decade, sequential immunosuppressive regimens for the treatment of proliferative lupus

nephritis have been used in uncontrolled and controlled clinical trials^{30, 31, 37, 72}. The goals of these studies were to achieve remission with a limited exposure to cyclophosphamide during the induction phase and to suppress renal flares during the maintenance phase. Both are important, since failure to achieve remission and frequent nephritic relapses have been associated with poor outcome and progression of renal disease^{7, 75, 87, 104}.

The sequential regimen most widely used is cyclophosphamide induction followed by azathioprine maintenance. More recently, MMF maintenance, and it is based on the following major clinical trials.

Houssiau et al.⁷² published a clinical trial that included a predominantly Caucasian population. In this trial, two sequential immunosuppressive regimens were compared⁷². One group of patients received induction therapy with low-dose intravenous cyclophosphamide (fixed dose of 0.5 g) every 2 weeks for 6 pulses. The other group of patients received induction therapy with high-dose intravenous cyclophosphamide consisting of 6 monthly pulses and 2 quarterly pulses at a dose of 0.5 g/m² adjusted to leukocyte count nadir. Each induction regimen included corticosteroids, and it was followed by azathioprine maintenance and corticosteroids. Both regimens were efficacious, with cumulative probabilities for remaining free of treatment failure (80–84%) and comparable rates of sustained amenorrhea (4%). The rates of severe infection were 15 and 25% in the low-dose cyclophosphamide and high-dose cyclophosphamide groups, respectively.

In an Asian population, Chan et al.³¹ demonstrated that patients with proliferative forms of lupus nephritis can be effectively treated with short-term oral cyclophosphamide and corticosteroids followed by oral azathioprine and corticosteroid maintenance without a significant risk for progression to chronic renal failure. The authors used oral cyclophosphamide induction for 6 months followed by azathioprine maintenance and achieved a remission rate of 76%. The incidence of permanent amenorrhea and infection were 8 and 33%, respectively, and none of the patients had an increase in serum creatinine level to double the baseline value.

Our prospective, randomized clinical trial comparing long-term intravenous cyclophosphamide with two sequential therapies of either azathioprine or MMF maintenance after short-term intravenous cyclophosphamide induction with corticosteroids showed that sequential therapies are superior to long-term cyclophosphamide in preventing a composite end-

-point of chronic renal failure or death (80–89% vs. 45%, $p < 0.005$), and sequential therapies were found to have significantly fewer adverse events, such as severe infections (2% vs. 25%, $p \leq 0.02$)³⁷. It is important to note that our study included predominantly a high risk population of Hispanics and African-Americans compared with the predominantly Caucasian population in the NIH trials^{1, 2, 47}.

When comparing the two sequential regimens, sequential short-term intravenous cyclophosphamide followed by MMF was associated with a trend for a reduction in relapse rates compared with sequential intravenous cyclophosphamide followed by azathioprine (3 of 20 patients vs. 6 of 19 patients, p not significant). However, our trial did not find a significant difference in the primary and secondary end-points between the two sequential regimens because the study was not powered to detect the observed differences of 10–20%. The outcomes of the MAINTAIN study may help resolve this issue⁷¹.

CYCLOSPORINE A AND TACROLIMUS

Calcineurin inhibitors block the transcription of IL-2 and thus inhibit the activation of T lymphocytes. Cyclosporine A is widely used to treat renal diseases characterized by the nephrotic syndrome^{27, 28, 97}, but there is little data on its effect on proliferative lupus nephritis. Two studies have shown that cyclosporine can significantly reduce proteinuria, overall disease activity, and improve renal function^{49, 123}. However, long-term data are not available, and a number of patients in these studies received additional immunosuppressive medications, such as azathioprine. Given the paucity of data, cyclosporine cannot be recommended as a first-line therapy at this time, and its use is reserved to patients failing traditional treatment approaches or who cannot tolerate other immunosuppressive treatments. In our practice we avoid cyclophosphamide in pregnant women who present with active lupus nephritis and we use cyclosporine with corticosteroids instead⁷³, although some case reports suggest that cyclophosphamide may be safe in this setting⁸². Tacrolimus had beneficial effects in lupus-prone mice⁵³, but only very little clinical data is available on patients with SLE. A report of 3 patients by Duddridge et al.⁵⁰ suggests that tacrolimus may be useful in patients who failed other regimens; however, therapy had to be discontinued in 1 of the 3 patients because of nephrotoxicity.

EXPERIMENTAL TREATMENTS

Most novel strategies target B and T cells, which play a crucial role in the pathogenesis of lupus nephritis²⁹,

^{39, 83}. Agents that are currently under investigation include anti-proliferative drugs, such as nucleoside analogues, antibodies directed against cytokines that may stimulate proliferation and auto-antibody production, and agents that interfere with cell-surface antigens to inhibit the interaction of B and T cells or deplete B cells altogether.

Nucleoside analogues, such as fludarabine and cladribine, are being investigated in an attempt to target proliferating B and T cells. Efficacy and safety have been shown in two pilot studies including patients with both idiopathic or lupus membranous nephropathy and proliferative lupus nephritis, and larger trials are needed to confirm these results^{19, 40}.

Several cytokines play an important role in the pathogenesis of lupus nephritis and are currently under investigation as new therapeutic targets. IL-6, IL-10, IL-12, interferon (IFN)- γ , and tumor necrosis factor (TNF)- α have received particular attention^{1, 23, 25, 77, 86, 92, 98, 135}. Anti-IL-6 has beneficial effects in lupus-prone mice⁸⁵, but no data in patients with lupus nephritis are available as yet. Anti-IL-10 has shown a good response in addition to corticosteroid-sparing effects in patients with corticosteroid-resistant SLE⁹³; however, it has not yet been investigated in patients with lupus nephritis. IL-12 and IFN- γ have been implicated in both murine models and patients with lupus nephritis; however, no clinical treatment data are available at this time^{23, 25, 86, 98}. Patients with rheumatoid arthritis are successfully treated with anti-TNF- α antibodies⁵⁵, and elevated TNF- α concentrations have been demonstrated in the serum of patients with SLE. However, a lupus-like picture was observed in several anti-TNF- α -treated patients with rheumatoid arthritis³³, which dims the prospects of this agent in the context of lupus nephritis. IL-2 is a powerful stimulator of T cell proliferation, and sirolimus inhibits the signal transduction after the binding of IL-2 to its receptor. The efficacy of sirolimus in the treatment of lupus nephritis will be tested in an NIH-sponsored clinical trial that is currently enrolling patients with idiopathic and lupus membranous glomerulonephritis¹⁰⁶.

Inhibition of T cells, which may play an important role in autoimmunity by initiating immune responses against small antigens presented by MHC class II molecules, has been explored. Clinical trials are ongoing in patients with rheumatoid arthritis using anti-CD4 monoclonal antibodies^{35, 76, 124} and CTLA-4Ig¹⁰³; however, there is only little data about patients with lupus nephritis to date⁶⁸. Suppression of the production of antibodies directed against dsDNA was hypothesized to ameliorate lupus nephritis¹¹⁷.

Antibody production is stimulated by the interaction of CD40 on the B cell surface and CD40 ligand expressed by T cells. Excess soluble CD40 ligand may interfere with this process. However, clinical trials failed to reproduce the encouraging results with this strategy in animal models^{41, 51}. Early clinical trials with LJP-394, an agent designed to induce tolerance that likely enhances clearance of anti-dsDNA antibodies, showed encouraging results in pilot studies^{2, 60, 122}. The CD20 antigen is present on all mature B cells, and administration of an anti-CD20 antibody may deplete B cells and thus reduce auto-antibody production. Preliminary data suggest a possible role for this agent in the treatment of lupus nephritis^{52, 58, 110}.

Based on the experience derived from animals, two additional avenues have been pursued. Dehydroepiandrosterone, an adrenal steroid with limited androgenic activity, ameliorates lupus nephritis in mice⁹⁴; however, initial pilot studies could not consistently show a beneficial effect on proteinuria although overall disease activity was improved^{128, 129}. Activation of the complement cascade is a typical feature of patients with active SLE^{88, 118}, and anti-C5 monoclonal antibodies inhibiting both the classical and alternative pathways are currently being investigated in various settings, including rheumatoid arthritis and lupus nephritis^{14, 43, 81, 119}.

Taken together, many avenues are actively pursued to identify new treatment regimens for lupus nephritis. However, most of the novel strategies are in very early stages of development at this time.

NON-SPECIFIC THERAPIES

The goal of non-specific therapies is to slow the progression of renal disease and avert co-morbidities such as cardiovascular disease, thromboembolic complications, and bone loss. Little data is available specifically for patients with lupus nephritis, but it appears prudent to apply the knowledge from the general population with chronic kidney disease to this patient subset. All patients require tight blood pressure control¹³, the use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor block-

ers^{20, 21, 115, 125}, correction of dyslipidemia¹², smoking cessation¹⁰⁸, and anticoagulation to an INR of 3–4 if symptomatic antiphospholipid syndrome is present^{8, 36, 54, 59, 84, 116}. Patients requiring prolonged corticosteroid therapy have a high risk to develop osteopenia and osteoporosis and should receive preventive treatment for bone loss, including calcium, vitamin D, and anti-resorptive agents^{42, 80}. Despite optimal therapy, 10–30% of patients with proliferative lupus nephritis will develop end-stage renal failure⁷. Patients with symptomatic antiphospholipid syndrome who develop ESRD may pose a particular challenge due to repeated clotting episodes leading to vascular access problems or allograft loss after renal transplantation⁷⁹. Otherwise, patient survival is similar to the general hemodialysis or peritoneal dialysis population³⁴. Despite morphological recurrence of lupus nephritis after transplantation in about 10–40%, graft loss is rare^{44, 64, 105}, and for this reason transplantation should be actively pursued¹³⁴.

CONCLUSIONS

Based on currently published clinical trials, induction therapy with cyclophosphamide combined with pulse corticosteroids is the best treatment option to achieve remission. Currently there is not enough data to suggest that either oral or intravenous cyclophosphamide induction is more efficacious, and risk-to-benefit ratio, patient preference and adherence, feasibility, and cost all have to be taken into account. The smallest effective dose and the shortest duration of cyclophosphamide treatment should be chosen to avoid adverse events, in particular gonadal failure and infections, which can be achieved by using sequential therapy with either azathioprine or mycophenolate mofetil in the maintenance phase. In pregnant women, both cyclosporine A and azathioprine in combination with corticosteroids have been successfully used to treat severe lupus nephritis. Mycophenolate mofetil is a promising new agent that may replace cyclophosphamide in the induction phase; however, it remains to be seen whether the encouraging short-term results will translate into improved long-term outcomes.

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