Published in final edited form as:

Rheum Dis Clin North Am. 2014 August ; 40(3): 519–535. doi:10.1016/j.rdc.2014.05.001.

RECENT CLINICAL TRIALS IN LUPUS NEPHRITIS

Michael M. Ward

SYNOPSIS

Recent clinical trials have provided evidence for the efficacy of low-dose intravenous cyclophosphamide and mycophenolate mofetil as induction treatment for patients with proliferative lupus nephritis in comparative trials with standard-dose intravenous cyclophosphamide. Trials of maintenance treatments have had more variable results, but suggest that mycophenolate mofetil may be similar to quarterly standard-dose intravenous cyclophosphamide and somewhat more efficacious than azathioprine. Differential responses to mycophenolate mofetil based on ethnicity suggest that it may be more effective in black and Hispanic patients. Rituximab was not efficacious as an adjunct to induction treatment with mycophenolate mofetil.

Keywords

lupus nephritis; randomized controlled trial; cyclophosphamide; mycophenolate mofetil; azathioprine; cyclosporine; rituximab

INTRODUCTION

Lupus nephritis (LN) is an autoimmune-mediated glomerulonephritis and tubulointerstitial disease that is among the most common and serious manifestations of systemic lupus erythematosus (SLE). LN develops in 30% to 60% of patients with SLE, most often occurring early in the course of SLE [1–3]. Common accompaniments include anemia, hypertension, hypocomplementemia, and autoantibodies to double-stranded DNA and the extractable nuclear antigens ribonucleoprotein and Sm [3–5]. Rarely, LN may be the presenting manifestation of SLE in an otherwise asymptomatic patient. Persons of black African or Hispanic ancestry are two- to three-times more likely to develop LN, and tend to have more severe disease, than whites [3,6,7]. While improvements in treatment have transformed severe LN from a near universally fatal condition to a manageable chronic disease, patients with LN are at more than twice the risk of death than patients without LN, and those with chronic kidney disease have more than three times the risk of death [8,9].

Correspondence: Michael M. Ward, MD, Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Building 10CRC, Room 4-1339, 10 Center Drive, Bethesda MD 20892. wardm1@mail.nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures: None

Both the high prevalence of LN and the intensity of clinical care required by patients with LN make it the most costly manifestation of SLE [10].

Course of Lupus Nephritis

LN is largely an asymptomatic condition, and requires active screening to be detected. Clinical and laboratory features reflect the type of renal histological lesions present in a given patient. Proteinuria, microscopic hematuria, urinary casts, and hypertension, occasionally severe, are common in patients with proliferative LN, and renal insufficiency may develop. Nephrotic syndrome with peripheral edema, serous effusions, wasting, and hypercoagulability can occur in patients with membranous or proliferative LN. LN can present with acute renal failure, or can be rapidly progressive due to severe glomerular inflammation, cellular crescents, and fibrinoid necrosis, but these presentations are rare [11]. In most patients, LN is a subacute or chronic condition, with treatment-induced remissions and spontaneous relapses being fairly common.

Prognosis

Prognosis of LN is closely related to the renal histologic class and the degree of active inflammation and chronic damage incurred [12–14]. Patients with mesangial LN have only mild laboratory abnormalities and very low risk of chronic kidney disease. Patients with membranous LN often have morbidity related to nephrosis but over 90% achieve remission, and excluding transitions to a proliferative subtype, fewer than 10% of patients progress to end-stage renal disease after 15 years [15, 16]. In patients with proliferative LN, prognosis is poorer in those with diffuse compared to those with focal glomerular involvement, and in those with crescents and extensive chronic damage [14]. End-stage renal disease develops in 25% to 40% of patients with proliferative LN after 15 years, predominantly among those with diffuse involvement [5,17,18]. Advanced sclerosing glomerulonephritis represents an end-stage inactive lesion with more than 90% of glomeruli showing global sclerosis, with a high risk of endstage renal disease.

Additional poor prognostic factors include delayed initiation of immunosuppressive treatment, incomplete response to induction therapy, occurrence of nephritic relapses, and poor control of hypertension [19].

Goals of Treatment

The goals of treatment of LN are to prevent end-stage renal disease and to decrease the risk of chronic kidney disease and its atherosclerotic and metabolic consequences. Treatment can also facilitate blood pressure control and help avoid the vascular complications of hypertension. In addition, treatment of nephrotic syndrome can lessen the morbidity associated with fluid overload, hypoalbuminemia, and risk of thrombosis.

It is important to recognize that, apart from proteinuria, these goals are not typically measured as outcomes in controlled clinical trials in LN. Chronic kidney disease and end-stage renal disease are often late manifestations, and impractical to measure in short-term clinical trials. Even five years of follow-up may not be sufficient to see differences in risks of these outcomes. The large functional reserve of kidneys makes measures of renal function

insensitive to even moderate degrees of dysfunction. Doubling of the serum creatinine level has questionable validity for predicting long-term renal outcomes in patients with good renal function at baseline [20]. Recent clinical trials have used improvement or normalization of proteinuria, improvement in urine sediment, and stabilization or improvement in serum creatinine levels as endpoints. Although the rationale that reductions in signs of active inflammation should translate into lower risks of kidney damage and dysfunction in the future is sound, the definitions of response in clinical trials have not been validated as good surrogate markers of late renal outcomes.

Traditional Treatment Approach

A shift from using glucocorticoids alone to using cytotoxic drugs together with glucocorticoids to treat serious LN occurred in the 1970's and 1980's with evidence from clinical trials of improved renal outcomes from combination therapy [21]. A central role for cyclophosphamide was solidified on the basis of trials conducted at the National Institutes of Health, which showed numerically better outcomes after 10 years among patients with active (mostly proliferative) LN treated with intravenous cyclophosphamide (CYC) compared to those treated with azathioprine or prednisone alone [22]. Trials showing that prolonged treatment with CYC resulted in fewer nephritic flares and lower risks of end-stage renal disease ushered in the notion of induction and maintenance phases of treatment of LN, and established the "NIH regimen" of monthly intravenous CYC for 6 months followed by quarterly infusions for 24 additional months as an accepted treatment for severe LN [23, 24]. However, treatment-related complications including infection, ovarian failure, hemorrhagic cystitis, bladder cancer, and treatment-related mortality emerged as concerns [25].

The need for treatments with less toxicity and equal or better efficacy has motivated studies of new medications, and new methods of administering CYC. Here we review recent clinical trials of new medications or treatment strategies in LN. We limited this review to medications that are currently available in the clinic, because these can be used by clinicians today. We also limited the review to published full-length studies in adults with LN.

TRIALS OF ALTERNATIVE DOSING OF CYCLOPHOSPHAMIDE

Euro-Lupus Nephritis Trial

This randomized controlled trial compared a short-course regimen of low-dose intravenous CYC to a longer regimen of higher dose intravenous CYC as induction treatment of active proliferative LN [26]. The experimental group was given 500 milligrams (mg) of intravenous CYC every two week for six doses, while the control group was treated with 0.5 grams/meter² body surface area of intravenous CYC monthly for six doses, followed by two additional doses at 9 months and 12 months. In the control group, the dose of CYC was sequentially increased, based on nadir peripheral blood leukocyte counts, to a maximum of 1500 mg. Both groups received pulse methylprednisolone at the start of treatment, followed by tapering doses of prednisone, and received azathioprine 2 mg/kg daily for maintenance treatment at the end of the CYC course.

The primary endpoint was treatment failure, defined as either persistent renal insufficiency or nephrotic syndrome, glucocorticoid-resistant flare, or doubling of the serum creatinine

level. Endpoints were assessed in a time to event analysis with a median follow-up of 41 months. The occurrence of the primary endpoint did not differ between treatment groups (Table 1). The probability of renal remission (71% versus 54%) and renal flare (27% versus 29%) over time also did not differ between the low dose and high dose groups. Two patients in the low dose group died and 1 progressed to end-stage renal disease, while 2 patients in the high dose group progressed to end-stage renal disease. Severe infections were more common in the high dose group, while the frequencies of non-serious infections, leukopenia, and ovarian failure were similar in the two treatment groups.

The authors concluded that the low-dose CYC regimen was comparable in efficacy to a higher dose regimen in patients with proliferative LN, and that a high dose regimen was not required as treatment for all patients with proliferative LN. However, the authors noted that although most patients had diffuse proliferative LN, the majority did not have severe disease, with 22% having an elevated serum creatinine and 28% with nephrotic syndrome at study entry. The trial included few ethnic minorities. The results may not be generalizable to patients with more severe LN. Although the low-dose regimen was anticipated to have less toxicity, and was associated with fewer serious infections, other adverse events were similar between treatment groups.

Several points are worth noting. Although presented as a superiority trial, an a priori power calculation was not apparent, and consequently the interpretation of statistical differences is difficult. A larger sample would be needed to demonstrate non-inferiority between the treatments convincingly. The primary endpoint consisted of an absence of worsening for most patients, rather than demonstration of improvement. Therefore the possibility of persistent LN activity among “responders” also raises questions about how the results should be interpreted. Renal outcomes in both groups were excellent at 10 years, suggesting that residual activity did not affect long-term outcomes, although most patients still required immunosuppressive treatment [27]. The high-dose CYC regimen was shorter than the typical NIH regimen, which somewhat complicates comparisons among studies. However, the results of this trial suggest that the intensity of immunosuppression can be tailored to the severity of disease among patients with proliferative LN.

Myeloablative Regimen

This randomized trial compared the efficacy of a myeloablative regimen of intravenous CYC with that of monthly intravenous CYC followed by quarterly infusions for 3 years, following the NIH regimen [28]. The rationale for testing myeloablative treatment was to attempt to eliminate autoreactive lymphocytes and re-set the immune system. Patients with treatment-refractory SLE were eligible, and although the study was not limited to patients with LN, data on those with LN were reported separately. Complete response required a normal serum creatinine, normal creatinine clearance, normal urinary sediment, and proteinuria less than 500 mg/day. Complete responses were rare at 6 months, but were more common among those treated with the NIH regimen than with the myeloablative regimen at 30 months (Table 1).

Additional Trials

Sabry and colleagues replicated the Euro-Lupus Nephritis Trial in a 12-month randomized trial in 46 patients with proliferative LN [29]. No differences in outcomes were observed, but the power of the study was limited. Mitwalli and colleagues found no difference in patient and renal survival between patients randomized to short-term high dose intravenous CYC and a longer course of lower dose CYC [30].

TRIALS OF AZATHIOPRINE, CYCLOSPORINE, OR TACROLIMUS AS ALTERNATIVES TO CYCLOPHOSPHAMIDE AS INDUCTION TREATMENT

Dutch Working Party Trial

This randomized trial compared treatment with azathioprine 2 mg/kg daily along with three courses of pulse methylprednisolone to the NIH regimen of intravenous CYC in patients with proliferative LN [31]. At entry, 56% of patients had renal impairment and 53% had nephrotic-range proteinuria. Over a median follow-up of 5.7 years, four times as many patients in the azathioprine group as in the CYC group met the primary endpoint of doubling of serum creatinine (Table 2). Although the likelihood of complete remission was similar in the two treatment groups over the first 2 years of the study, relapses were higher in the azathioprine group (7.1 per 100 patient-years versus 1.1 per 100 patient-years). Infections, particularly herpes zoster, were more common in the azathioprine group. On extended follow-up to a median of 9.6 years, the azathioprine group had numerically higher frequency of doubling of serum creatinine (16% versus 8%), mortality (16% versus 10%), and renal relapses (38% versus 10%) [32]. Although the reports emphasized the lack of significant differences in endpoints other than relapses, the power of the study to detect differences in other outcomes was limited, and the weight of evidence suggests greater efficacy for intravenous CYC compared to azathioprine.

Trials of Calcineurin Inhibitors

Chen and colleagues compared outcomes at 6 months between patients with active LN (89% proliferative; 11% membranous) treated with either tacrolimus (.05 mg/kg daily, titrated to serum trough levels of 5 to 10 ng/ml) or intravenous CYC by the NIH regimen in a randomized non-inferiority trial (Table 2) [33]. Ten percent of patients had an elevated serum creatinine and 43% had nephrotic-range proteinuria at entry. Complete remission at 6 months was seen in 52% of tacrolimus-treated patients and 38% of CYC-treated patients, with most failures due to persistent proteinuria. The study enrolled only one-half of the projected sample size needed to test non-inferiority adequately. In a smaller trial of similar design, Li et al reported complete or partial remission in 75% of tacrolimus-treated patients and 60% of CYC-treated patients at 6 months [34]. Responses after 9 months of treatment were also similar in a small trial that compared cyclosporine with intravenous CYC [35]. Notable in these studies is the rapid improvement in proteinuria and generally good responses regardless of treatment arm, but their small sizes limit the strength of any comparisons.

TRIALS OF MYCOPHENOLATE MOFETIL AS INDUCTION TREATMENT

Seven trials have compared mycophenolate mofetil (MMF) to CYC as induction treatment for LN (Table 3) [34, 36–41]. Five trials included fewer than 50 patients, and four of these five trials reported similar treatment effects at 6 months. Bao, et al studied combined treatment with MMF and tacrolimus versus intravenous CYC in patients with mixed class V and IV LN, and found that combined treatment led to more complete remissions [39]. We review in more detail the two largest studies.

Non-inferiority study

Ginzler and colleagues tested the non-inferiority of MMF to intravenous CYC in a 6 month study of induction treatment in patients with active proliferative (81%) or membranous (19%) LN [40]. Patients were randomized to treatment with either open-label MMF at 1000 – 3000 mg daily or intravenous CYC by the NIH regimen. The primary endpoint was complete remission at 6 months, defined as normalization of the serum creatinine level, proteinuria, and urinary sediment. An early response to treatment at 12 weeks was required for patients to continue treatment through 24 weeks, and those without an early response were offered cross-over to the alternative treatment.

Seventy-six percent of patients were black or Hispanic. Patients had active nephritis with a mean serum creatinine of 1.07 mg/dL, and 44% had nephrotic-range proteinuria at study entry. Mean doses of MMF were greater than 2500 mg daily, while only 62% of those in the CYC group completed all infusions. Early responses were seen in 79% of the MMF group and 61% of the CYC group, and these patients completed 6 months of the assigned treatment. More patients in the CYC group withdrew from the trial before week 12 (10 versus 6 in the two treatment groups). Eight patients crossed to the alternative treatment.

In the intent-to-treat analysis, more patients in the MMF group than in the CYC group had complete remission at 6 months (22.5% versus 5.8%), a difference that exceeded the threshold for non-inferiority. Results were similar among patients who completed their assigned treatment. The frequency of partial remission was similar between the groups (29.6% versus 24.6%), as were improvements in serum creatinine levels, proteinuria, and urinary sediment. Severe infections were more common in the CYC group, and there were 2 deaths in this group. Diarrhea was more common in the MMF group. While the study found more frequent complete remissions in the MMF-treated patients, this finding turned on the rapidity of response due the design of the early escape at 12 weeks. The high number of withdrawals, particularly in the CYC group, complicates the interpretation.

ALMS

The Aspreva Lupus Management Study (ALMS) was designed to test if MMF was superior to intravenous CYC as induction treatment for active LN [41]. This large multi-national study enrolled patients with active, or active and chronic, proliferative or membranous LN. Those patients with class III or class V LN were required to have proteinuria of 2 grams per day or more. Patients were randomized to open-label MMF with a target dose of 3000 mg daily, or intravenous CYC by the NIH protocol. Patients who worsened over the first 12

weeks of the trial were withdrawn. The primary endpoint was renal response, defined as improvement in proteinuria and stabilization or improvement in the serum creatinine level. The study was planned to enroll enough patients so that a 15% difference in renal response between groups would be detected as statistically significant, should a difference of this magnitude be observed.

Mean serum creatinine level at entry was 0.8 mg/dL, and mean urine protein/creatinine ratio was 4.1. Sixteen percent of patients had membranous LN. The treatment groups were well balanced. Eighty-three percent of the 307 patients completed the 6 month study. Most patients in the MMF group took more than 2500 mg daily, and the median CYC dose was 0.75 mg/m², with a mean number of infusions per patient of 5.6. In contrast to the MMF non-inferiority study, withdrawals were not more frequent in the CYC group.

Renal response was seen in 56.2% of patients in the MMF group and 53% of patients in the CYC group in the intent-to-treat analysis. Renal responses were also similar when those who completed the trial were analyzed separately (63.7% versus 57.1%), as were frequencies of normalization of serum creatinine and proteinuria. Eight percent of patients in each group achieved complete remission at 6 months. Adverse events, including infections, were similar between groups, but severe gastrointestinal events were somewhat more frequent in the MMF group. There were 9 deaths in the MMF group and 5 deaths in the intravenous CYC group.

The authors concluded that the efficacy and tolerability of MMF and intravenous CYC over 6 months as induction treatment were similar. Given the low proportion of complete remissions, they speculated that longer induction periods may be needed to differentiate between treatments. In an interesting sub-analysis, renal responses were substantially more common with MMF treatment than with CYC treatment among the subgroup of black and Latin patients, while little difference was present among whites or Asians. This finding may explain the results favoring MMF in the study by Ginzler et al, which largely included black and Hispanic patients [40]

TRIALS OF ALTERNATIVES TO PROLONGED TREATMENT WITH CYCLOPHOSPHAMIDE AS MAINTENANCE TREATMENTS

Miami Study

Contreras and colleagues tested the efficacy of maintenance treatment with either azathioprine or MMF to that of intravenous CYC given every three months in a randomized trial of patients with proliferative LN who had completed a maximum of 7 monthly infusions with intravenous CYC as induction treatment (Table 4) [42]. The azathioprine group received 1 – 3 mg/kg daily (mean 1 mg/kg), the MMF group received 500 mg to 3000 mg daily (mean 1500 mg), and the CYC group received 0.5 – 1.0 grams/m² body surface area (mean 0.55 g/m²). Patients also were treated with prednisone up to 0.5 mg/kg daily. Maintenance treatments were continued long-term, with median durations of 30 months, 29 months, and 25 months in the azathioprine, MMF, and CYC groups, respectively.

Patients were predominantly black (45%) or Hispanic (49%) and had severe proliferative LN, with mean serum creatinine at entry of 1.6 mg/dL, hypertension (97%), and nephrotic syndrome (64%). Most patients responded to induction treatment, with no imbalances among maintenance treatment groups.

The primary endpoints were patient survival and renal survival, defined as either sustained doubling of serum creatinine or end-stage renal disease. At 60 months, patient survival was significantly lower in the CYC group (57%) than in the azathioprine group (100%) and in the MMF group (94%). Chronic renal disease developed in 15%, 5%, and 5% in the CYC, azathioprine, and MMF groups, respectively, with renal survival of 74%, 80%, and 95%. Relapse-free survival was higher in the MMF group. Infections, hospital days, and amenorrhea were more common in the CYC group.

The authors concluded that maintenance treatment with MMF or azathioprine following induction treatment with intravenous CYC was superior in both outcomes and tolerability to continued intravenous CYC as maintenance treatment. This study highlighted the potential for alternative treatments to avoid toxicities associated with prolonged CYC treatment, and raised the notion that patient ethnicity may influence responses to different treatments. However, the mechanisms underlying the poorer response to CYC than to azathioprine or MMF as maintenance treatment is unclear, given that patients had responded to induction treatment with CYC.

ALMS

Maintenance treatment options were compared in a follow-on study in patients who had acceptable clinical responses to either MMF or intravenous CYC in the ALMS induction study. After the 6 month induction trial, this trial re-randomized patients to treatment with either MMF 2000 mg daily or azathioprine 2 mg/kg daily for 36 months [43]. Randomization was stratified by the type of induction treatment patients had received (MMF or CYC), ethnicity, and renal histological class, to produce groups similar in these characteristics. Sixty-three percent of patients treated with MMF and 48% of patients treated with azathioprine completed 36 months of observation, with most withdrawals due to adverse events. The primary endpoint was treatment failure, defined as any of the following events: death, end-stage renal disease, sustained doubling of the serum creatinine level, renal flare, or need for additional immunosuppression to treat active LN.

MMF was superior to azathioprine in the proportion of patients meeting the primary endpoint, with fewer patients having treatment failure (16% versus 32%) and a lower risk of treatment failure in a time-to-event analysis (hazard ratio = 0.44). Renal flares and need for additional immunosuppression were also less common in the MMF group. End-stage renal disease occurred in 2.7% of azathioprine-treated patients but in no MMF-treated patients. Adverse events were similar in the two groups, with infections in 78% and serious infections in 10–12% of patients. The strengths of this study were its large size and blinding using a double-dummy method, wherein all patients took both active and placebo pills for the alternative medications. Consistency of results among many different endpoints also strengthens the evidence in favor of MMF. However, it is important to recognize that the majority of patients treated with azathioprine also did well.

MAINTAIN

This study tested maintenance treatment with either azathioprine or MMF in patients with proliferative LN after induction treatment with intravenous CYC using the Euro-Lupus protocol [44]. Patients entered with active LN (mean serum creatinine 1 mg/dL; 10% with renal insufficiency; 39% with nephrotic-range proteinuria) and all were treated with pulse methylprednisolone and six infusions of CYC before being randomized to either azathioprine 2 mg/kg daily or MMF 2000 mg daily, regardless of their response to CYC. The primary endpoint was renal flare, defined as either development of nephrotic syndrome, an increase in serum creatinine, or an increase in proteinuria accompanied by hematuria and depression of C3 levels.

Seventy-four percent of patients were taking the assigned medication at 3 years, with the mean azathioprine dose ranging from 100 mg to 125 mg daily, and the mean MMF dose ranging from 1600 to 2000 mg daily. During follow-up, renal flares were observed in 25% of patients treated with azathioprine and 19% of those treated with MMF. Times to severe flare and to renal remission were similar between groups. In a sub-analysis of patients who had a primary response to treatment, 14% of patients in both treatment groups developed a subsequent renal flare. One patient in each group developed end-stage renal disease, and two patients in the MMF group died. Cytopenias were more common in the azathioprine group, but infections were equally frequent.

The study was designed to test the superiority of MMF relative to azathioprine, and the authors concluded that there was insufficient evidence to support superiority. In contrast to the ALMS, treatments were open-label rather than blinded, and patients were not enrolled based on their response to induction treatment. The primary outcome was also more focused in MAINTAIN, which may have lessened the opportunity to detect differences between treatment groups, as would the smaller sample. The ethnic composition of the study group might have also affected assessment of the relative efficacy of these two medications, if MMF has particular benefit in ethnic minorities.

Cyclosporine versus Azathioprine

Moroni and colleagues compared cyclosporine 4 mg/kg daily to azathioprine 2 mg/kg daily as maintenance treatment for patients with proliferative LN after induction treatment with pulse methylprednisolone and oral CYC 1 – 2 mg/kg daily for 3 months [45]. Seven renal flares, either proteinuric or nephritic (with an increase in serum creatinine level), occurred in the cyclosporine group, for a rate of 10.6 flares per 100 patient-years of treatment, while eight renal flares occurred in the azathioprine group, for a rate of 13.4 flares per 100 patient-years. Improvements in serum creatinine levels and proteinuria were similar in the two groups, but comparisons were hampered by the small sample.

TRIAL OF RITUXIMAB

LUNAR

The Lupus Nephritis Assessment with Rituximab (LUNAR) study was a randomized placebo-controlled trial designed to test whether treatment with rituximab could boost

complete renal responses among patients with active LN when added to other immunosuppressive treatments [46]. This study was motivated by the suboptimal rates of complete responses to induction treatment seen with MMF or intravenous CYC in patients with active proliferative LN. In this trial all patients were started on induction treatment with MMF 3000 mg daily and pulse methylprednisolone. In addition, blinded treatment with rituximab (1 g) or placebo was given on days 1, 15, 168 and 182 of treatment, with 72 patients in each group. The primary outcome was complete renal response, defined as normalization or stabilization of the serum creatinine level, and normalization of the urinary sediment and proteinuria. Rituximab was effective in B cell depletion. At 52 weeks, 26.4% of patients in the rituximab group had complete renal response, compared to 30.6% in the placebo group. Partial responses were numerically higher in the rituximab group, and serological parameters improved more in this group, but other renal responses did not differ. Two deaths occurred in the rituximab group, while the risks of other adverse events, including serious infections, were not different between treatment groups.

Despite encouraging results from many observational studies and uncontrolled trials [47], this study demonstrated lack of benefit from rituximab when added to a regimen of MMF and corticosteroids for induction treatment. The study was not designed to test if rituximab could be an acceptable replacement for other induction medications, nor if the use of rituximab would permit more rapid tapering of corticosteroids or reduced doses of MMF without worsening control of LN [48]. Combining rituximab with MMF did not result in additional safety concerns.

TRIALS IN MEMBRANOUS LUPUS NEPHRITIS

Membranous LN has commonly been treated with alternate-day corticosteroids, although studies have also investigated the effectiveness of cyclosporine, tacrolimus, MMF, and CYC. Austin, et al performed an open-label randomized trial comparing cyclosporine 200 mg/m² daily and high-dose alternate-day prednisone, intravenous CYC 0.5 – 1.0 g/m² every other month for 6 infusions and high-dose alternate-day prednisone, and high-dose alternate-day prednisone alone in 42 patients with membranous LN and proteinuria of at least 2 g daily (median 5.4 g daily) [49]. At 12 months, remission was present in 83% of patients treated with cyclosporine, 60% treated with CYC, and 27% treated with prednisone alone. Patients in the cyclosporine group responded more rapidly, but were also more likely to relapse on discontinuation of treatment than those treated with CYC. However, either medication provided better short-term control of proteinuria than corticosteroids alone.

Radhakrishnan et al performed a sub-analysis of patients with membranous LN who were enrolled in two trials of induction treatment that compared intravenous CYC and MMF [50]. Among 24 patients in the non-inferiority study of Ginzler and colleagues and 60 patients in the ALMS, improvements in proteinuria and serum creatinine were similar between those treated with intravenous CYC or MMF in a completers analysis.

SYNTHESIS OF THE EVIDENCE

Cochrane Review

In a review of 50 randomized controlled trials, most of which investigated induction treatment, Henderson and colleagues concluded that MMF was as effective as intravenous cyclophosphamide for induction treatment while having lower risks of ovarian failure [25]. They also concluded that MMF was more effective than azathioprine as maintenance treatment, but there was insufficient data on other treatments to provide adequate comparisons.

American College of Rheumatology Treatment Recommendations

Using a systematic literature review and the RAND/UCLA Appropriateness method, researchers developed a series of recommendations for approaches to the treatment of patients with LN [51]. This panel recommended pulse methylprednisolone and either MMF or intravenous CYC for induction treatment in patients with proliferative LN, with varied preferences between treatments based on the ethnicity of the patient. Maintenance treatment was recommended with either MMF or azathioprine, with rituximab or calcineurin inhibitors as second-line agents. The panel recommended MMF as initial treatment for patients with membranous LN with nephrotic range proteinuria.

Despite these recommendations, there remains substantial controversy among rheumatologists and nephrologists on the most appropriate first-line treatment for patients with severe lupus nephritis [52].

CONCLUSIONS

These trials demonstrate the progress has been made in the past 15 years in the treatment of patients with LN, but also that current treatment is not curative. Direct comparisons among these studies are complicated by the use of different endpoints. While consensus is evolving on the most appropriate endpoints for studies of induction treatment, more work is needed on linking the outcomes measured in short-term trials to future end-stage renal disease, comorbidities, and mortality. The length of induction treatment may need reconsideration to produce more durable responses. Because most studies focus on short-term responses, it is not clear how the treatment changes tested in these trials will impact the frequency of important long-term outcomes, particularly end-stage renal disease. Some evidence suggests that long-term outcomes of LN have not improved in recent years, raising the question of whether currently available treatments can provide the results we want and patients need [53–55].

The introduction of low-dose regimens, and differences in responses based on patient ethnicity, suggest that the most important advance may have been a change in philosophy from use of a uniform protocol to more individualized or tailored treatment. Further testing of medications for equivalence or superiority will likely not yield important advances. Currently, the most important clinical question is, between two medications that are similarly effective on the group level, which patients will need the more toxic or expensive

medication, and which patients will do well, now and in the long-term, with the least toxic and least expensive treatment?

Acknowledgments

This work was supported by the Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health.

REFERENCES

1. Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunological patterns of disease expression in a cohort of 1000 patients. *Medicine*. 1993; 72:113–124. [PubMed: 8479324]
2. Pons-Estel BA, Catoggio LJ, Cardiel MH, et al. The GLADEL Multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus. Ethnic and disease heterogeneity among “Hispanics”. *Medicine*. 2004; 83:1–17. [PubMed: 14747764]
3. Bastian HM, Roseman JM, McGwin G Jr, et al. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus*. 2002; 11:152–160. [PubMed: 12004788]
4. Huong DL, Papo T, Beaufile H, et al. Renal involvement in systemic lupus erythematosus. A study of 180 patients from a single center. *Medicine*. 1999; 78:148–166. [PubMed: 10352647]
5. Neumann K, Wallace DJ, Azen C, et al. Lupus in the 1980s: III. Influence of clinical variables, biopsy, and treatment on the outcome of 150 patients with lupus nephritis seen at a single center. *Semin Arthritis Rheum*. 1995; 25:47–55. [PubMed: 8525390]
6. Cooper GS, Parks CG, Treadwell EL, et al. Differences by race, sex and age in the clinical and immunologic features of recently diagnosed systemic lupus erythematosus patients in the southeastern United States. *Lupus*. 2002; 11:161–167. [PubMed: 11999880]
7. Korbet SM, Schwartz MM, Evans J, et al. Severe lupus nephritis: racial differences in presentation and outcome. *J Am Soc Nephrol*. 2007; 18:244–254. [PubMed: 17167111]
8. Wallace DJ, Podell T, Weiner J, et al. Systemic lupus erythematosus survival patterns. Experience with 609 patients. *JAMA*. 1981; 245:934–938. [PubMed: 7463697]
9. Mok CC, Kwok RCL, Yip PSF. Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus. *Arthritis Rheum*. 2013; 65:2154–2160. [PubMed: 23754671]
10. Li T, Carls GS, Panopalis P, et al. Long-term medical costs and resource utilization in systemic lupus erythematosus and lupus nephritis: a five-year analysis of a large Medicaid population. *Arthritis Rheum*. 2009; 61:755–763. [PubMed: 19479688]
11. Balow JE. Clinical presentation and monitoring of lupus nephritis. *Lupus*. 2005; 14:25–30. [PubMed: 15732284]
12. Austin HA III, Muenz LR, Joyce KM, et al. Prognostic factors in lupus nephritis. Contribution of renal histologic data. *Am J Med*. 1983; 75:382–391. [PubMed: 6351607]
13. Weening JJ, D’Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol*. 2004; 15:241–250. [PubMed: 14747370]
14. Hiramatsu N, Kuroiwa T, Ikeuchi H, et al. Revised classification of lupus nephritis is valuable in predicting renal outcome with an indication of the proportion of glomeruli affected by lesions. *Rheumatology*. 2008; 47:702–707. [PubMed: 18390590]
15. Moroni G, Quaglini S, Gravellone L, et al. Membranous nephropathy in systemic lupus erythematosus: long-term outcomes and prognostic factors of 103 patients. *Semin Arthritis Rheum*. 2012; 41:642–651. [PubMed: 22285127]
16. Mercadel L, Montcel ST, Nochy D, et al. Factors affecting outcome and prognosis in membranous lupus nephropathy. *Nephrol Dial Transplant*. 2002; 17:1771–1778. [PubMed: 12270983]

17. Mok CC, Wong RWS, Lau CS. Lupus nephritis in southern Chinese patients: clinicopathologic findings and long-term outcome. *Am J Kidney Dis.* 1999; 34:315–323. [PubMed: 10430980]
18. Pasquali S, Banfi G, Zucchelli A, et al. Lupus membranous nephropathy: long term outcome. *Clin Nephrol.* 1993; 39:175–182. [PubMed: 8491046]
19. Chan TM. Preventing renal failure in patients with severe lupus nephritis. *Kidney International.* 2005; 67:S116–S119. [PubMed: 15752227]
20. Lambers Heerspink HJ, Perkovic V, de Zeeuw D. Is doubling of serum creatinine a valid clinical “hard” endpoint in clinical nephrology trials? *Nephron Clin Pract.* 2011; 119:c195–c199. [PubMed: 21832844]
21. Felson DT, Anderson J. Evidence for the superiority of immunosuppressive drugs and prednisone over prednisone alone in lupus nephritis. Results of a pooled analysis. *N Engl J Med.* 1984; 311:1528–1533. [PubMed: 6390198]
22. Austin HA III, Klippel JH, Balow JE, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med.* 1986; 314:614–619. [PubMed: 3511372]
23. Boumpas DT, Austin HA III, Vaughn EM, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet.* 1992; 340:741–745. [PubMed: 1356175]
24. Illei GG, Austin HA III, Crane M, et al. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. *Ann Intern Med.* 2001; 135:248–257. [PubMed: 11511139]
25. Henderson L, Masson P, Craig JC, et al. Treatment for lupus nephritis. *Cochrane Database Syst Rev.* 2012; 12:CD002922. [PubMed: 23235592]
26. Houssiau FA, Vasconcelos C, D’Cruz D, et al. Immunosuppressive therapy in lupus nephritis. The Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum.* 2002; 46:2121–2131. [PubMed: 12209517]
27. Houssiau FA, Vasconcelos C, D’Cruz D, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis.* 2010; 69:61–64. [PubMed: 19155235]
28. Petri M, Brodsky RA, Jones RJ, et al. High dose cyclophosphamide versus monthly intravenous cyclophosphamide for systemic lupus erythematosus: a prospective randomized trial. *Arthritis Rheum.* 2010; 62:1487–1493. [PubMed: 20131296]
29. Sabry A, Abo-Zenah H, Medhat T, et al. A comparative study of two intensified pulse cyclophosphamide remission-inducing regimens for diffuse proliferative lupus nephritis: an Egyptian experience. *Int Urol Nephrol.* 2009; 41:153–161. [PubMed: 18214709]
30. Mitwalli AH, Al Wakeel JS, Hurraib S, et al. Comparison of high and low dose of cyclophosphamide in lupus nephritis patients: a long-term randomized controlled trial. *Saudi J Kidney Dis Transpl.* 2011; 22:935–940. [PubMed: 21912022]
31. Grootsholten C, Ligtenberg G, Hagen EC, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. *Kidney Int.* 2006; 70:732–742. [PubMed: 16820790]
32. Arends S, Grootsholten C, Derksen RHWM, et al. Long-term follow-up of a randomised controlled trial of azathioprine/methylprednisolone versus cyclophosphamide in patients with proliferative lupus nephritis. *Ann Rheum Dis.* 2012; 71:966–973. [PubMed: 22128082]
33. Chen W, Tang X, Liu Q, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. *Am J Kidney Dis.* 2011; 57:235–244. [PubMed: 21177013]
34. Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. *Nephrol Dial Transplant.* 2012; 27:1467–1472. [PubMed: 21917733]
35. Zavada J, Pesickova SS, Rysava R, et al. Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study. *Lupus.* 2010; 19:1281–1289. [PubMed: 20605876]
36. Chan TM, Li FK, Tang CSO, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med.* 2000; 343:1156–1162. [PubMed: 11036121]

37. El-Shafey EM, Abdou SH, Shareef MM. Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferative lupus nephritis in Egyptian patients? *Clin Exp Nephrol*. 2010; 14:214–221. [PubMed: 20169461]
38. Ong LM, Hooi LS, Lim TO, et al. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrology*. 2005; 10:504–510. [PubMed: 16221103]
39. Bao H, Lui Z-H, Xie H-L, et al. Successful treatment of class V + IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol*. 2008; 19:2001–2008. [PubMed: 18596121]
40. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med*. 2005; 353:2219–2228. [PubMed: 16306519]
41. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol*. 2009; 20:1103–1112. [PubMed: 19369404]
42. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. *N Engl J Med*. 2004; 350:971–980. [PubMed: 14999109]
43. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med*. 2011; 365:1886–1895. [PubMed: 22087680]
44. Houssiau FA, D'Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN nephritis trial. *Ann Rheum Dis*. 2010; 69:2083–2089. [PubMed: 20833738]
45. Moroni G, Doria A, Mosca M, et al. A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. *Clin J Am Soc Nephrol*. 2006; 1:925–932. [PubMed: 17699309]
46. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis. The Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum*. 2012; 64:1215–1226. [PubMed: 22231479]
47. Gunnarsson I, Jonsdottir T. Rituximab treatment in lupus nephritis – where do we stand? *Lupus*. 2013; 22:381–389. [PubMed: 23553781]
48. Condon MB, Ashby D, Pepper RJ, et al. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but with no oral steroids. *Ann Rheum Dis*. 2013; 72:1280–1286. [PubMed: 23740227]
49. Austin HA III, Illei GG, Braun MJ, Balow JE. Randomized controlled trial of prednisone, cyclophosphamide, and cyclosporine in membranous lupus nephropathy. *J Am Soc Nephrol*. 2009; 20:901–911. [PubMed: 19297556]
50. Radhakrishnan J, Moutzouris D-A, Ginzler EM, et al. Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. *Kidney Int*. 2010; 77:152–160. [PubMed: 19890271]
51. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res*. 2012; 64:797–808.
52. Rovin BH. Lupus nephritis: Guidelines for lupus nephritis – more recommendations than data? *Nat Rev Nephrol*. 2012; 8:620–621. [PubMed: 23007619]
53. Croca SC, Rodrigues T, Isenberg D. Assessment of a lupus nephritis cohort over a 30-year period. *Rheumatology*. 2011; 50:1424–1430. [PubMed: 21415024]
54. Faurschou M, Dreyer L, Kamper A-L, Starklint H, Jacobsen S. Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. *Arthritis Care Res*. 2010; 62:873–880.
55. Fiehn C, Hajjar Y, Mueller K, Waldherr R, Ho AD, Andrassy K. Improved clinical outcome of lupus nephritis during the past decade: importance of early diagnosis and treatment. *Ann Rheum Dis*. 2003; 62:435–439. [PubMed: 12695156]

Key points

- Low-dose, short-course intravenous cyclophosphamide and mycophenolate mofetil have similar efficacy to standard high-dose intravenous cyclophosphamide for induction treatment of proliferative lupus nephritis, but these findings may depend on the ethnicity of the patients studied.
- Mycophenolate mofetil is likely more effective than azathioprine as maintenance treatment of proliferative lupus nephritis.
- Alternatives to high-dose intravenous cyclophosphamide have a lower risk of ovarian failure, but risks of other toxicities are not different.
- Lack of recent improvement in long-term renal outcomes suggests that new treatment approaches are needed.

Table 1

Controlled trials of alternative dosing of cyclophosphamide (CYC) as induction treatment.

Study	Design	Intervention		N		Primary endpoint*	Outcomes	
		Experimental	Control	Experimental	Control		Experimental	Control
Euro-Lupus [26]	Superiority	CYC 0.5 g every 2 weeks $\times$ 6	CYC 0.5 g/m ² monthly $\times$ 6, then quarterly $\times$ 2	44	46	Treatment failure	16%	20%
Myeloablative [28]	Superiority	CYC 50 mg/kg daily $\times$ 4	CYC 0.75 g/m ² monthly $\times$ 6, then quarterly for 2 years	10	12	Complete response	20%	64%
Sabry, et al [29]	Superiority	CYC 0.5 g every 2 weeks $\times$ 6	CYC 0.5 g/m ² monthly $\times$ 6, then quarterly $\times$ 2	20	26	Treatment failure	5%	3.4%
Mitwalli, et al [30]	Superiority	CYC 5 mg/kg monthly $\times$ 6, then every 2 months $\times$ 18	CYC 10 mg/kg monthly $\times$ 6, then every 2 months $\times$ 6	44	73	Patient and renal survival	100% at 6 months, no results for long-term	100% at 6 months, no results for long-term

* Defined in text.

Table 2

Comparative controlled trials of azathioprine, cyclosporin, or tacrolimus as induction treatment.

Study	Design	Intervention		N		Primary endpoint*	Outcomes	
		Experimental	Control	Experimental	Control		Experimental	Control
Dutch Working Party [31]	Superiority	Azathioprine 2 mg/kg daily and pulse methylprednisolone $\times$ 9	CYC 0.75 g/m ² monthly $\times$ 6, then quarterly for 21 months	37	50	Doubling of serum creatinine	16%	4%
Chen [33]	Non-inferiority	Tacrolimus .05 mg/kg daily, titrated to trough levels	CYC 0.75 g/m ² monthly $\times$ 6	42	39	Complete remission	52%	38%
Li, et al [34]	Superiority	Tacrolimus .08 – .1 mg/kg daily, titrated to trough levels	CYC 0.5 – 0.75 g/m ² monthly $\times$ 6	20	20	Complete or partial remission	75%	60%
Cyclofa-Lune [35]	Superiority	4–5 mg/kg daily $\times$ 9 months	CYC 10 mg/kg $\times$ 8 over 9 months	19	21	Complete remission	26%	24%

Table 3

Trials of mycophenolate mofetil (MMF) as induction treatment.

Study	Design	Intervention		N		Primary endpoint*	Outcomes	
		Experimental	Control	Experimental	Control		Experimental	Control
Li, et al [34]	Superiority	MMF 1500 – 2000 mg daily	CYC 0.5 – 0.75 g/m ² monthly × 6	20	20	Complete or partial remission	75%	60%
Chan, et al [36]	Superiority	MMF 2000 mg daily	Oral CYC 2.5 mg/kg daily × 6 months, then azathioprine 1.5 mg/kg daily	21	21	Complete remission	81%	76%
El-Shafey, et al [37]	Non-inferiority	MMF 2000 mg daily	CYC 0.5 – 1.0 g/m ² monthly × 6	24	23	Complete or partial remission	58%	52%
Ong, et al [38]	Superiority	MMF 2000 mg daily	CYC 0.75 – 1.0 g/m ² monthly × 6	19	25	Complete or partial remission	58%	52%
Bao, et al [39]	Superiority	MMF 2000 mg daily and tacrolimus 4 mg daily	CYC 0.75 g/m ² monthly × 9	20	20	Complete remission	65%	15%
Non-inferiority study [40]	Non-inferiority	MMF 1000 – 3000 mg daily	CYC 0.5 – 1.0 g/m ² monthly × 6	71	69	Complete remission	22.5%	5.8%
ALMS [41]	Superiority	MMF 1000 – 3000 mg daily	CYC 0.5 – 1.0 g/m ² monthly × 6	185	185	Renal response	56.2%	53%

Table 4

Comparative trials of alternative maintenance treatments.

Study	Design	Intervention		N		Primary endpoint*	Outcomes	
		Experimental	Control	Experimental	Control		Experimental	Control
Miami [42]	Superiority	Azathioprine 1–3 mg/kg daily or MMF 500 to 3000 mg daily	CYC 0.5 – 1.0 g/m ² quarterly	Azathioprine = 19; MMF = 20	20	Patient and renal survival	Azathioprine patient 100%; renal 80% MMF patient 94%; renal 95%	Patient 57%; renal 74%
ALMS [43]	Superiority	MMF 2000 mg daily	Azathioprine 2 mg/kg daily	116	111	Treatment failure	16%	32%
MAINTAIN [44]	Superiority	MMF 2000 mg daily	Azathioprine 2 mg/kg daily	53	52	Renal flare	19%	25%
Moroni, et al [45]	Superiority	Cyclosporine 4 mg/kg daily	Azathioprine 2 mg/kg daily	36	33	Renal flare	10.6 per 100 patient-years	13.4 per 100 patient-years