CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will review trials of newer regimens for lupus nephritis

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New and future therapies for lupus nephritis

ABSTRACT

Based on data from randomized controlled trials over the past decade, oral mycophenolate (CellCept) now rivals intravenous cyclophosphamide (Cytoxan) as a first-line therapy for lupus nephritis, offering similar efficacy but less toxicity. The roles of rituximab (Rituxan) and new immunomodulatory agents are being explored. Creativity in treating lupus nephritis is needed; one regimen does not fit all.

KEY POINTS

Mycophenolate is at least equivalent to intravenous cyclophosphamide for induction and maintenance treatment of severe lupus nephritis.

The role of rituximab is unclear, and for now it should only be used in relapsing patients or patients whose disease is resistant to standard therapy.

Using combination therapies for induction treatment and maintenance is becoming increasingly common.

Three-year maintenance therapy is now considered advisable in most patients.

Entirely new drugs under study include costimulatory blockers, inhibitors of human B lymphocyte stimulator, tolerance molecules, and cytokine blockers.

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Treatment for lupus nephritis has changed dramatically in recent years. Only 10 years ago, rheumatologists and nephrologists, whether specializing in adult or pediatric medicine, treated lupus nephritis with a similar regimen of monthly intravenous cyclophosphamide (Cytoxan) and glucocorticoids. Although the regimen is effective, side effects such as infection, hair loss, and infertility were extremely common.

Effective but very toxic therapy is common in autoimmune diseases. In the last decade, clinical trials have shown that less toxic drugs are as effective for treating lupus nephritis. This article will review new developments in therapy for lupus nephritis, which can be viewed as a prototype for other fields of medicine.

DEMOGRAPHICS ARE IMPORTANT

Although numerous factors have prognostic value in lupus nephritis (eg, serum creatinine, proteinuria, renal biopsy findings), the most important to consider when designing and interpreting studies are race and socioeconomic variables.

A retrospective study in Miami, FL,[1] evaluated 213 patients with lupus nephritis, of whom 47% were Hispanic, 44% African American, and 20% white. At baseline, African Americans had higher blood pressure, higher serum creatinine levels, and lower household income. After 6 years, African Americans fared the worst in terms of doubling of serum creatinine, developing end-stage renal disease, and death; whites had the best outcomes, and Hispanics were in between. Low income was found to be a significant risk factor, independent of racial background.

In a similar retrospective study in New York City in 128 patients (43% white, 40% Hispanic, and 17% African American) with proliferative lupus nephritis,[2] disease was much more

likely to progress to renal failure over 10 years in patients living in a poor neighborhood, even after adjustment for race.

We need to keep in mind that racial and socioeconomic factors correlate with disease severity when we design and interpret studies of lupus nephritis. Study groups must be carefully balanced with patients of similar racial and socioeconomic profiles. Study findings must be interpreted with caution; for example, whether results from a study from China are applicable to an African American with lupus nephritis in New York City is unclear.

OLDER STANDARD THERAPY: EFFECTIVE BUT TOXIC

The last large National Institutes of Health study that involved only cyclophosphamide and a glucocorticoid was published in 2001,[3] with 21 patients receiving cyclophosphamide alone and 20 patients receiving cyclophosphamide plus methylprednisolone. Although lupus nephritis improved, serious side effects occurred in one-third to one-half of patients in each group and included hypertension, hyperlipidemia, valvular heart disease, avascular necrosis, premature menopause, and major infections, including herpes zoster.

Less cyclophosphamide works just as well

The multicenter, prospective Euro-Lupus Nephritis Trial[4] randomized 90 patients with proliferative lupus nephritis to receive either standard high-dose intravenous (IV) cyclophosphamide therapy (six monthly pulses and two quarterly pulses, with doses increasing according to the white blood cell count) or low-dose IV cyclophosphamide therapy (six pulses every 2 weeks at a fixed dose of 500 mg). Both regimens were followed by azathioprine (Imuran).

At 4 years, the two treatment groups were not significantly different in terms of treatment failure, remission rates, serum creatinine levels, 24-hour proteinuria, and freedom from renal flares. However, the rates of side effects were significantly different, with more patients in the low-dosage group free of severe infection.

One problem with this study is whether it is applicable to an American lupus nephritis population, since 84% of the patients were white. Since this study, others indicate that this regimen is probably also safe and effective for different racial groups in the United States.

At 10-year follow-up,[5] both treatment groups still had identical excellent rates of freedom from end-stage renal disease. Serum creatinine and 24-hour proteinuria were also at excellent levels and identical in both groups. Nearly three quarters of patients still needed glucocorticoid therapy and more than half still needed immunosuppressive therapy, but the rates were not statistically significantly different between the treatment groups.

The cumulative dose of cyclophosphamide was 9.5 g in the standard-treatment group and 5.5 g in the low-dose group. This difference in exposure could make a tremendous difference to patients, not only for immediate side effects such as early menopause and infections, but for the risk of cancer in later decades.

This study showed clearly that low-dose cyclophosphamide is an option for induction therapy. Drawbacks of the study were that the population was mostly white and that patients had only moderately severe disease.

Low-dose cyclophosphamide has largely replaced the older National Institutes of Health regimen, although during the last decade drug therapy has undergone more changes.

MYCOPHENOLATE AND AZATHIOPRINE: ALTERNATIVES TO CYCLOPHOSPHAMIDE

In a Chinese study, mycophenolate was better than cyclophosphamide for induction

In a study in Hong Kong, Chan et al[6] randomized 42 patients with severe lupus nephritis to receive either mycophenolate mofetil (available in the United States as CellCept; 2 g/day for 6 months, then 1 g/day for 6 months) or oral cyclophosphamide (2.5 mg/kg per day for 6 months) followed by azathioprine (1.5–2.0 mg/kg per day) for 6 months. Both groups also received prednisolone during the year.

At the end of the first year, the two groups were not significantly different in their rates of complete remission, partial remission, and relapse. The rate of infection, although not significantly different, was higher in the cyclophosphamide group (33% vs 19%). Two patients (10%) died in the cyclophosphamide group, but the difference in mortality rates was not statistically significant.

In lupus nephritis, race and socioeconomic factors correlate with disease severity and prognosis

Nearly 5 years later,[7] rates of chronic renal failure and relapse were still statistically the same in the two groups. Infections were fewer in the mycophenolate group (13% vs 40%, $P = .013$). The rate of amenorrhea was 36% in the cyclophosphamide group and only 4% in the mycophenolate group ($P = .004$). Four patients in the cyclophosphamide group and none in the mycophenolate group reached the composite end point of end-stage renal failure or death ($P = .062$).

This study appeared to offer a new option with equal efficacy and fewer side effects than standard therapy. However, its applicability to non-Chinese populations remained to be shown.

In a US study, mycophenolate or azathioprine was better than cyclophosphamide as maintenance

In a study in Miami,[8] 59 patients with lupus nephritis were given standard induction therapy with IV cyclophosphamide plus glucocorticoids for 6 months, then randomly assigned to one of three maintenance therapies for 1 to 3 years: IV injections of cyclophosphamide every 3 months (standard therapy), oral azathioprine, or oral mycophenolate. The population was 93% female, their average age was 33 years, and nearly half were African American, with many of the others being Hispanic. Patients tended to have severe disease, with nearly two-thirds having nephrotic syndrome.

Low-dose IV cyclophosphamide has replaced the older IV regimen

After 6 years, there had been more deaths in the cyclophosphamide group than in the azathioprine group ($P = .02$) and in the mycophenolate group, although the latter difference was not statistically significant ($P = .11$). The combined rate of death and chronic renal failure was significantly higher with cyclophosphamide than with either of the oral agents. The cyclophosphamide group also had the highest relapse rate during the maintenance phase.

The differences in side effects were even more dramatic. Amenorrhea affected 32% of patients in the cyclophosphamide group, and only 7% and 6% in the azathioprine and mycophenolate groups, respectively. Rates of infections were 68% in the cyclophosphamide group and 28% and 21% in the azathioprine and mycophenolate groups, respectively. Patients given cyclophosphamide had 13 hospital days per patient per year, while the other groups each had only 1.

This study showed that maintenance therapy with oral azathioprine or mycophenolate was more effective and had fewer adverse effects than standard IV cyclophosphamide therapy. As a result of this study, oral agents for maintenance therapy became the new standard, but the question remained whether oral agents could safely be used for induction.

In a US study, mycophenolate was better than cyclophosphamide for induction

In a noninferiority study, Ginzler et al[9] randomized 140 patients with severe lupus nephritis to receive either monthly IV cyclophosphamide or oral mycophenolate as induction therapy for 6 months. Adjunctive care with glucocorticoids was given in both groups. The study population was from 18 US academic centers and was predominantly female, and more than half were African American.

After 24 weeks, 22.5% of the mycophenolate patients were in complete remission by very strict criteria vs only 4% of those given cyclophosphamide ($P = .005$). The trend for partial remissions was also in favor of mycophenolate, although the difference was not statistically significant. The rate of complete and partial remissions, a prespecified end point, was significantly higher in the mycophenolate group. Although the study was trying to evaluate equivalency, it actually showed superiority for mycophenolate induction therapy.

Serum creatinine levels declined in both groups, but more in the mycophenolate group by 24 weeks. Urinary protein levels fell the same amount in both groups. At 3 years, the groups were statistically equivalent in terms of renal flares, renal failures, and deaths. However, the study groups were small, and the mycophenolate group did have a better trend for both renal failure (N = 4 vs 7) and deaths (N = 4 vs 8).

Mycophenolate also had fewer side effects, including infection, although again the numbers were too small to show statistical significance. The exception was diarrhea (N = 15 in the mycophenolate group vs 2 in the cyclophosphamide group).

A drawback of the study is that it was designed as a crossover study: a patient for whom therapy was failing after 3 months could switch to the other group, introducing potential confounding. Other problems involved the small

population size and the question of whether results from patients in the United States were applicable to others worldwide.

In a worldwide study, mycophenolate was at least equivalent to cyclophosphamide for induction

The Aspreva Lupus Management Study (ALMS)[10] used a similar design with 370 patients worldwide (United States, China, South America, and Europe) in one of the largest trials ever conducted in lupus nephritis. Patients were randomized to 6 months of induction therapy with either IV cyclophosphamide or oral mycophenolate but could not cross over.

At 6 months, response rates were identical between the two groups, with response defined as a combination of specific improvement in proteinuria, serum creatinine, and hematuria (50%–55%). In terms of individual renal and nonrenal variables, both groups appeared identical.

However, the side effect profiles differed between the two groups. As expected for mycophenolate, diarrhea was the most common side effect (occurring in 28% vs 12% in the cyclophosphamide group). Nausea and vomiting were more common with cyclophosphamide (45% and 37% respectively vs 14% and 13% in the mycophenolate group). Cyclophosphamide also caused hair loss in 35%, vs 10% in the mycophenolate group.

There were 14 deaths overall, which is a very low number considering the patients' severity of illness, and it indicates the better results now achieved with therapy. The mortality rate was higher in the mycophenolate group (5% vs 3%), but the difference was not statistically significant. Six of the nine deaths with mycophenolate were from the same center in China, and none were from Europe or the United States. In summary, the study did not show that mycophenolate was superior to IV cyclophosphamide for induction therapy, but that they were equivalent in efficacy with different side effect profiles.

Membranous nephropathy: Mycophenolate vs cyclophosphamide

Less evidence is available about treatment for membranous disease, which is characterized by heavy proteinuria and the nephrotic syndrome but usually does not progress to renal failure. Radhakrishnan et al[11] combined data from the trial by Ginzler et al[9] and the ALMS trial[10] and found 84 patients with pure membranous lupus, who were equally divided between the treatment groups receiving IV cyclophosphamide and mycophenolate. Consistent with the larger group's data, mycophenolate and cyclophosphamide performed similarly in terms of efficacy, but there was a slightly higher rate of side effects with cyclophosphamide.

Maintenance therapy: Mycophenolate superior to azathioprine

The ALMS Maintenance Trial[12] evaluated maintenance therapy in the same worldwide population that was studied for induction therapy. Of the 370 patients involved in the induction phase that compared IV cyclophosphamide and oral mycophenolate, 227 responded sufficiently to be rerandomized in a controlled, double-blinded trial of 36 months of maintenance therapy with corticosteroids and either mycophenolate (1 g twice daily) or azathioprine (2 mg/kg per day).

In intention-to-treat analysis, the time to treatment failure (ie, doubling of the serum creatinine level, progressing to renal failure, or death) was significantly shorter in the azathioprine group ($P = .003$). Every individual end point—end-stage renal disease, renal flares, doubling of serum creatinine, rescue immunosuppression required—was in favor of mycophenolate maintenance. At 3 years, the completion rate was 63% with mycophenolate and 49% with azathioprine. Serious adverse events and withdrawals because of adverse events were more common in the azathioprine group.

Oral agents for maintenance therapy have become the new standard

In summary, mycophenolate was superior to azathioprine in maintaining renal response and in preventing relapse in patients with active lupus nephritis who responded to induction therapy with either mycophenolate or IV cyclophosphamide. Mycophenolate was found to be superior regardless of initial induction treatment, race, or region and was confirmed by all key secondary end points.

Only one of the 227 patients died during the 3 years—from an auto accident. Again, this indicates the dramatically improved survival today compared with a decade ago.

RITUXIMAB: PROMISING BUT UNPROVEN

Rituximab (Rituxan) was originally approved to treat tumors, then rheumatoid arthritis, and most recently vasculitis. Evidence thus far is mixed regarding its use as a treatment for lupus nephritis. Although randomized clinical trials have not found it to be superior to standard regimens, there are many signs that it may be effective.

Rituximab in uncontrolled studies

Terrier et al[13] analyzed prospective data from 136 patients with systemic lupus erythematosus, most of whom had renal disease, from the French Autoimmunity and Rituximab registry. Response occurred in 71% of patients using rituximab, with no difference found between patients receiving rituximab monotherapy and those concomitantly receiving immunosuppressive agents.

Melander et al[14] retrospectively studied 19 women and 1 man who had been treated with rituximab for severe lupus nephritis and followed for at least 1 year. Three patients had concurrent therapy with cyclophosphamide, and 10 patients continued rituximab as maintenance therapy; 12 patients had lupus nephritis that had been refractory to standard treatment, and 6 had relapsing disease.

At a median follow-up of 22 months, 12 patients (60%) had achieved complete or partial renal remission.

Condon et al[15] treated 21 patients who had severe lupus nephritis with two doses of rituximab and IV methylprednisolone 2 weeks apart, then maintenance therapy with mycophenolate without any oral steroids. At a mean follow-up of 35 months (± 14 months), 16 (76%) were in complete remission, with a mean time to remission of 12 months. Two (9.5%) achieved partial remission. The rate of toxicity was low.

Thus, rituximab appears promising in uncontrolled studies.

ALMS included 370 patients worldwide, randomized to cyclophosphamide or mycophenolate for induction

Placebo-controlled trials fail to prove rituximab effective

LUNAR trial. On the other hand, the largest placebo-controlled trial to evaluate rituximab in patients with proliferative lupus nephritis, the Lupus Nephritis Assessment With Rituximab (LUNAR) trial[16] found differences in favor of rituximab, but none reached statistical significance. The trial randomized 140 patients to receive either mycophenolate plus periodic rituximab infusions or mycophenolate plus placebo infusions for 1 year. All patients received the same dosage of glucocorticoids, which was tapered over the year.

At the end of 1 year, the groups were not statistically different in terms of complete renal response and partial renal response. Rituximab appeared less likely to produce no response, but the difference was not statistically significant.

African Americans appeared to have a higher response rate to rituximab (70% in the rituximab group achieved a response vs 45% in the control group), but again, the difference did not reach statistical significance, and the total study population of African Americans was only 40.

Rituximab did have a statistically significant positive effect on two serologic markers at 1 year: levels of anti-dsDNA fell faster and complement rose faster. In addition, rates of adverse and serious adverse events were similar between the two groups, with no new or unexpected "safety signals."

This study can be interpreted in a number of ways. The number of patients may have been too small to show significance and the follow-up may have been too short. On the other hand, it may simply not be effective to add rituximab to a full dose of mycophenolate and steroids, an already good treatment.

EXPLORER trial. Similarly, for patients with lupus without nephritis, the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial[17] also tested rituximab against a background of an effective therapeutic regimen and found no additional benefit. This study had design problems similar to those of the LUNAR trial.

Rituximab as rescue therapy

The evidence so far indicates that rituximab may have a role as rescue therapy for refractory or relapsing disease. Rituximab must be used with other therapies, but maintenance corticosteroid therapy is not necessary. Its role as a first-line agent in induction therapy for lupus nephritis remains unclear, although it may have an important role for nonwhites. In general, it has been well tolerated. Until a large randomized trial indicates otherwise, it should not be used as a first-line therapy.

The US Food and Drug Administration (FDA) sent out a warning about the danger of progressive multifocal leukoencephalopathy as an adverse effect of rituximab and of mycophenolate, but this does not appear to be a major concern for most patients and is only likely to occur in those who have been over-immunosuppressed for many years.

MULTITARGET THERAPY

The concept of using multiple drugs simultaneously—such as mycophenolate, steroids, and rituximab—is increasingly being tried. Multitarget therapy appears to offer the advantages of combining different modes of action with better results, and it offers fewer side effects because dosages of each individual drug can be lower when combined with other immunosuppressives.

Bao et al[18] in China randomly assigned 40 patients with diffuse proliferative and membranous nephritis to 6 to 9 months of induction treatment with either multitarget therapy (mycophenolate, tacrolimus [Prograf], and glucocorticoids) or IV cyclophosphamide. More complete remissions occurred in the multitarget therapy group, both at 6 months (50% vs 5%) and at 9 months (65% vs 15%). Most adverse events were less frequent in the multitarget therapy group, although three patients (15%) in the multitarget therapy group developed new-onset hypertension vs none in the cyclophosphamide group.

NEW MEDICATIONS

Entirely new classes of drugs are being developed with immunomodulatory effects, including tolerance molecules, cytokine blockers, inhibitors of human B lymphocyte stimulator, and costimulatory blockers.

Belimumab offers small improvement for lupus

Belimumab (Benlysta) is a human monoclonal antibody that inhibits the biologic activity of human B lymphocyte stimulator; it has recently been approved by the FDA for lupus nephritis. In a worldwide study,[19] 867 patients with systemic lupus erythematosus were randomized to receive either belimumab (1 mg/kg or 10 mg/kg) or placebo.

The primary end point was the reduction of disease activity by a scoring system (SELENA-SLEDAI) that incorporated multiple features of lupus, including arthritis, vasculitis, proteinuria, rash, and others. Patients in the belimumab group had better outcomes, but the results were not dramatic. Because the drug is so expensive (about $25,000 per year) and the improvement offered is only incremental, this drug will not likely change the treatment of lupus very much.

Moreover, patients with lupus nephritis were not included in the study, but a new study is being planned to do so. Improvement is harder to demonstrate in lupus nephritis than in rheumatoid arthritis and systemic lupus erythematosus: significant changes in creatinine levels and 24-hour urinary protein must be achieved, rather than more qualitative signs and symptoms of joint pain, rash, and feeling better. Although belimumab is still unproven for lupus nephritis, it might be worth trying for patients failing other therapy.

Laquinimod: A promising experimental drug

Laquinimod is an oral immunomodulatory drug with a number of effects, including down-regulating major histocompatability complex II, chemokines, and adhesion-related molecules related to inflammation. It has been studied in more than 2,500 patients with multiple sclerosis. Pilot studies are now being done for its use for lupus nephritis. If it shows promise, a large randomized, controlled trial will be conducted.

Rituximab may have a role as rescue therapy for refractory or relapsing renal disease

Abatacept is in clinical trials

Abatacept (Orencia), a costimulation blocker, is undergoing clinical trials in lupus nephritis. Results should be available shortly.

INDIVIDUALIZE THERAPY

This past decade has seen such an increase in options to treat lupus nephritis that therapy can now be individualized.

Choosing IV cyclophosphamide vs mycophenolate

As a result of recent trials, doctors in the United States are increasingly using mycophenolate as the first-line drug for lupus nephritis. In Europe, however, many are choosing the shorter regimen of IV cyclophosphamide be-

cause of the results of the Euro-Lupus study.

Nowadays, I tend to use IV cyclophosphamide as the first-line drug only for patients with severe crescenteric glomerulonephritis or a very high serum creatinine level. In such cases, there is more experience with cyclophosphamide, and such severe disease does not lend itself to the luxury of trying out different therapies sequentially. If such a severely ill patient insists that a future pregnancy is very important, an alternative therapy of mycophenolate plus rituximab should be considered. I prefer mycophenolate for induction and maintenance therapy in most patients.

Dosing and formulation considerations for mycophenolate

Large dosages of mycophenolate are much better tolerated when broken up throughout the day. A patient who cannot tolerate 1 g twice daily may be able to tolerate 500 mg four times a day. The formulation can also make a difference. Some patients tolerate sustained-release mycophenolate (Myfortic) better than CellCept, and vice versa.

For patients who cannot tolerate mycophenolate, azathioprine is an acceptable alternative. In addition, for a patient who is already doing well on azathioprine, there is no need to change to mycophenolate.

Long maintenance therapy now acceptable

The ALMS Maintenance Trial[12] found 3 years of maintenance therapy to be safe and effective. Such a long maintenance period is increasingly viewed as important, especially for patients in their teens and 20s, as it allows them to live a normal life, ie, to finish their education, get married, and become settled socially. Whether 5 years of maintenance therapy or even 10 years is advisable is still unknown.

Treatment during pregnancy

Neither mycophenolate nor azathioprine is recommended during pregnancy, although their effects are unknown. Because we have much more renal transplant experience with azathioprine during pregnancy, I recommend either switching from mycophenolate to azathioprine or trying to stop medication altogether if the patient has been well controlled.

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