

Clinical Trials in Lupus Nephritis: The Challenges and the Results – Mycophenolate and Rituximab

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When Joan T. Merrill, MD, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA, was a rheumatology fellow, there were two goals in treating lupus nephritis: “cool off” the nephritis with high-dose induction and then provide less aggressive maintenance therapy. What was not clear was how long the induction and maintenance therapies should last.

The goals of lupus nephritis treatment are, in fact, more complicated than that. The ultimate goal is to prevent flares, which we are not yet able to do. The secondary goal is to treat the flares to avoid glomerular sclerosis and fibrosis while minimizing the side effects of therapy and, ultimately, reducing the higher risk of secondary morbidities that lupus nephritis patients face (eg, atherosclerosis and all-cause morbidity).

Even when patients appear to have reached remission, many still have smoldering disease. This can significantly impact long-term outcome, as demonstrated by a study from the Lupus Nephritis Collaborative Study Group [Korbet SM et al. *Am J Kidney Dis* 2000].

The trial was designed to evaluate the effect of plasmapheresis on lupus nephritis outcomes. While the study failed to reach its primary endpoint, researchers followed 86 patients with severe nephritis for 10 years. Ninety-five percent of subjects who achieved remission (n=37) within the first 6 months of a flare were still alive at 5 and 10 years, compared with 69% of subjects who did not achieve remission after 5 years and 60% at 10 years (p<0.0001). In addition, 94% of the remission group had renal survival at 10 years compared with 46% of the nonremission group at 5 years and 31% at 10 years.

A large population study of 27,998 patients with chronic kidney disease, not necessarily lupus nephritis, found a 10% to 20% death rate at 10 years, even in patients with earlier-stage kidney damage—45% in those who had later-stage damage [Keith DS et al. *Arch Intern Med* 2004].

Although new approaches that have been developed over the past 40 years have reduced the relapse rates in lupus kidney disease, including combination therapy with cyclophosphamide and prednisone, there remains a significant degree of relapse regardless [Illei GG et al. *Arthritis Rheum* 2002; Beji S et al. *Rev Med Interne* 2005; El Hachmi M et al. *Lupus* 2003; Mosca M et al. *Kidney Int* 2002; Cortes-Hernandez J et al. *Lupus* 2003].

The introduction of mycophenolate mofetil (MMF) has offered a potentially safer treatment that is at least as effective for treating acute flares as cyclophosphamide, with two of three recent trials demonstrating similar efficacy compared with cyclophosphamide [Chan TM et al. *N Engl J Med* 2000; Appel GB et al. *J Am Soc Nephrol* 2009] and one trial demonstrating superiority [Ginzler EM et al. *N Engl J Med* 2005].

Although the overall data suggest that MMF is equal to cyclophosphamide in efficacy for acute nephritis, it is worth considering the possibility that differences in the trial designs, endpoints, and populations could account for the differences in results.

The Ginzler trial had more patients who were of African-American descent than the other two trials, and in this study, mycophenolate appeared to have superior efficacy to cyclophosphamide. An earlier study by Dooley MA et al. had shown that in a single-site survey, patients of African descent had fared less well on cyclophosphamide than other patients. Although racial distinctions are a poor substitute for genetics, the notion that individual characteristics might predispose patients to be better candidates for a given treatment is an important topic for further study [Dooley MA et al. *Kidney Int* 1997].



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Adding Biologics to the Mix

Dr. Merrill next discussed the outcomes from two trials of the anti-CD20 biologics rituximab (chimeric antibody) and ocrelizumab (human antibody). In the Phase 3 LUNAR study of rituximab, 72 patients with class III/IV lupus nephritis and proteinuria (protein/creatinine ratio >1 gm protein/gm creatinine) were randomized to rituximab or placebo on Days 1, 15, 168, and 182. Although more patients in the rituximab arm responded positively to the study drug (57% versus 46%), there was no statistically significant difference in the primary outcome (percentage of patients with complete or partial renal response at Week 52) [Furie R et al. ACR 2009].

In the BELONG study of ocrelizumab, which was stopped earlier due to issues of infections with that treatment, 381 patients with active, proliferative lupus nephritis had been randomized to placebo or ocrelizumab. Patients also received one of two standard-of-care regimens: either MMF or the EuroLupus cyclophosphamide regimen (low-dose, dense-dose cyclophosphamide). Partial data were available at the time the study was stopped.

An analysis at 48 weeks found a 51% overall renal response (ORR) rate in the placebo group versus 63% in the ocrelizumab treatment group (95% CI, -1.9% to 25.7%; $p=0.075$). When the data were examined, based on which of the two standard-of-care regimens patients had received in the background, there was no difference between the ocrelizumab and placebo groups in those who were on mycophenolate, but there was a better response for those on ocrelizumab who received the EuroLupus regimen as background therapy. Whether this reflects overall superiority of mycophenolate to the EuroLupus regimen or whether the interaction with different background treatments with the test product might be different is not known. What this does illustrate is that the choice of background medications in a clinical trial might have significant impact in the ability to test the biological impact of a given medication [Mysler E et al. ACR 2010].

There were several issues in recent lupus nephritis trials that may have impacted the results, including the high bar that has been set in several trials to define response (eg, strict limits on changes in serum creatinine, near-normalization of proteinuria, and inactive urinary sediment).

Although the LUNAR (rituximab) trial did not meet its primary endpoint, it did demonstrate a favorable trend in African-Americans, once more suggesting that individual patient characteristics may be important in responses to therapy. However, whether there are predisposing features towards rituximab response that are more common in this patient group or whether this represents a more ill group of patients who are less likely to respond to background treatment remains to be determined. Nevertheless, these very preliminary data do appear to show more patients of African descent responding to the addition of rituximab than was found in other patients.

“Our clinical trials are a little marginal right now,” Dr. Merrill said. “It’s difficult to discern a real difference in response when a new drug is added, given the amount of background medication that has to be used in a serious situation, such as acute nephritis, and given endpoints which may not be as discriminatory as we would have liked.”

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