Belimumab as Add-on Therapy in Lupus Nephritis

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Nephritis, the most common serious manifestation of systemic lupus erythematosus (SLE), affects up to 50% of patients with this condition. Proliferative lupus nephritis typically manifests with microscopic hematuria, nonnephrotic proteinuria, renal insufficiency, and hypertension, whereas membranous lupus nephropathy manifests with nephrotic syndrome. Current treatment for proliferative lupus nephritis involves intensive immunosuppression, usually with cyclophosphamide or mycophenolate mofetil and high-dose glucocorticoids in a 3-to-6-month induction period, followed by a maintenance period of less intensive immunosuppression. Most patients have an initial response, but relapses are common, and treatment-resistant disease often occurs. Although long-term outcomes have improved since the 1980s, the development of end-stage kidney disease in 40% of patients with diffuse proliferative lupus nephritis and in up to 20% of those with membranous lupus nephropathy highlights a need for better treatments.[1,2]

Belimumab, a recombinant human monoclonal antibody that inhibits B-cell activating factor, was approved in 2011 for use in patients with active SLE but not in those with severe central nervous system and renal involvement. In this issue of the *Journal*, Furie et al.[3] report the results of a phase 3, 104-week, randomized, double-blind trial of belimumab as compared with placebo, plus standard therapy (mycophenolate mofetil or cyclophosphamide–azathioprine and, in most patients, glucocorticoids), in adults with active lupus nephritis. The trial was larger and longer than previous trials involving patients with lupus nephritis. The odds of having a primary efficacy renal response (odds ratio, 1.6; 95% confidence interval [CI], 1.0 to 2.3) and a complete renal response (odds ratio, 1.7; 95% CI, 1.1 to 2.7) were greater among patients who received belimumab than among those who received placebo. If these results are expressed as relative risks, patients who received belimumab were 1.3 times more likely to have a primary efficacy renal response and 1.5 times more likely to have a complete renal response than those who received placebo. Differences between the trial groups with respect to the primary efficacy renal response appeared by week 24 and were generally maintained through week 104. Renal-related events or death were also less common among patients who received belimumab than among those who received placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77). Adverse events, including infections, occurred with similar frequency in the two groups.

The investigators changed the primary trial end point in 2017 — 5 years after the trial began. The results with respect to the original primary end point, which categorized responses as complete, partial, or no response according to the level of proteinuria, the calculated glomerular filtration rate from 24-hour urine collections, and microscopic examination of urinary sediment, were not significantly different between the belimumab and placebo groups, although the results favored belimumab. The revised primary end point (the primary efficacy renal response), which is unique to this trial, did away with the partial response category, omitted the urinary sediment component, used serum creatinine levels rather urine collections to estimate renal function, and loosened the proteinuria criterion, although it was still at a level that is associated with preserved kidney function.[4] Urinary sediment examinations have been losing favor as a measure of treatment effect because the results are observer- and technique-dependent and can be confounded by nonglomerular bleeding.[5] Many trials also use estimated glomerular filtration rates rather than relying on 24-hour urine collections. A change in the primary end point may be acceptable if critical new information surfaces that affects the usefulness of the original end point, but it is important to know whether the decision to change the end point was independent of any data collected before the change.[6]

The trial does not provide information on the efficacy of belimumab as a sole primary treatment for lupus nephritis. Although post hoc analyses of previous trials of agents for systemic lupus erythematosus suggested that belimumab

may be associated with modest decreases in proteinuria and kidney flares, lupus nephritis has been reported to newly develop in patients who receive belimumab.[7-9] The current trial also does not provide information on whether belimumab has a role in treating patients in whom induction therapy fails or those with relapse. In a recent trial involving patients with relapsed lupus nephritis, belimumab did not improve outcomes in patients who had received cyclophosphamide and rituximab.[10]

In the trial conducted by Furie et al., most of the treatment effect was seen in patients who had received mycophenolate mofetil. No benefit was present in the subgroup of patients who received cyclophosphamide–azathioprine. The choice of induction treatment was not randomly assigned but selected by the treating physician, and therefore this choice was susceptible to unknown influences. If patients with more severe nephritis were preferentially treated with cyclophosphamide, a likely inclination among most physicians, the trial may be telling us that belimumab enhances responses only among less severely affected patients.

On the basis of this trial, belimumab may have a role in augmenting induction treatment with mycophenolate mofetil in patients with active lupus nephritis. Greater specification of the patients who may potentially benefit is important, as is testing whether belimumab might facilitate glucocorticoid tapering and whether the risks of end-stage kidney disease and flares decrease in patients with poor prognostic factors. Belimumab may be added to an expanding array of adjunctive treatment options for lupus nephritis, including new calcineurin inhibitors and B cell–depleting antibodies.

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