Rituximab in Membranous Nephropathy: Is It a First-Line Treatment?

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Rituximab, a B cell–depleting anti-CD20 chimeric monoclonal antibody, is Food and Drug Administration approved in the United States for the treatment of certain lymphomas, rheumatoid arthritis, and granulomatous and microscopic polyangiitis. It has been used additionally in a wide variety of glomerular disorders including lupus nephritis, IgA nephropathy, minimal change disease and focal segmental glomerulosclerosis, fibrillary glomerulonephritis, and membranous nephropathy.1,2 Although its action is predominantly through blockade of antibody production, its efficacy may also relate to antibody-independent or complement-dependent cytotoxicity, antiproliferative effects, or induction of apoptosis, among other mechanisms.2,3 Despite use in many hundreds of patients with glomerular disease, rituximab has been studied in randomized, controlled trials in only a few clinical disorders, including lupus nephritis and ANCA-positive small vessel vasculitis.4,5

Membranous nephropathy remains the most common cause of idiopathic nephrotic syndrome in Caucasians in western countries. Most idiopathic membranous nephropathy is likely related to the production of autoantibodies to the M-type phospholipase A2 receptor, which combine in situ with its antigen target in a glomerular subepithelial location.5,7 Despite its frequency, and often obvious clinical presentation with edema accompanying heavy proteinuria, idiopathic membranous nephropathy has been a difficult disease to study. It is a disorder with a high spontaneous remission rate,8 a slow progression to renal failure, and a variable partial and complete remission rate depending on the population studied and criteria for remissions. Despite these difficulties, there are controlled randomized trials, including trials with positive results, with a number of therapeutic agents, including regimens of alternating months of corticosteroids and alkylating agents, cyclosporine, and tacrolimus.9–11 Each regimen has proven superior to placebo. The responses in some case include not only greater remissions of proteinuria, but improved renal function as well.

Rituximab has not been studied in any large randomized controlled trial in idiopathic membranous nephropathy. It has been studied in many well-designed small pilot studies and the response to the agent correlates with a reduction in antibodies to the M-type phospholipase A2 receptor.12–15 In this issue of JASN, Ruggenenti et al.16 describe the course of 100 patients with persistent, angiotensin converting enzyme inhibitor–treated, idiopathic membranous nephropathy given rituximab and followed over a median time of 29 months. The study includes 68 patients with new onset disease and 32 patients with prior immunosuppressive therapy. It includes some patients with prolonged follow-up. In prospective follow-up of these patients, 27% achieved a complete and 38% achieved a partial remission of their nephrotic syndrome. Of the 65% of patients achieving some form of remission, 18 relapsed, with 11 of 18 responding to a second course of treatment. Side effects were mild and included no severe adverse events. The authors conclude, “because of its excellent safety profile rituximab might be considered as first line treatment for idiopathic membranous nephropathy, as well as for rescue therapy after other immunosuppressive regimens have failed.”

However, recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend using a regimen of alternating months of corticosteroids and alkylating agent for 6 months as first-line therapy for idiopathic membranous nephropathy, and if this fails use of a calcineurin inhibitor.17 Will the current study alter this guideline? By itself, almost certainly not. First, this study, although relatively large compared with prior studies of rituximab treatment of idiopathic membranous nephropathy and clearly providing important clinical information, is still neither randomized nor placebo controlled. We have such trials with other agents. Second, the authors cite the safety of rituximab. Although this may be true in the current study, which does not have many years of follow-up, there certainly are side effects to exposure to this antibody, including first-dose infusion reactions in as many as 10% of patients, the risk of serious infections, and risk of tumors. For example, in a controlled trial of rituximab for ANCA-positive small vessel vasculitis, tumors developed in 5% of the rituximab group and only 1% of the cyclophosphamide group. Although these tumors may not be related just to the use of rituximab, clearly more studies will be needed. Likewise, although the incidence of progressive multifocal leukoencephalopathy, a rare viral brain disease, has been very low in rheumatoid arthritis patients treated with rituximab,18 more data are needed over longer follow. Third, the authors note that even with their current regimen...
of a single dose of rituximab, the cost is much higher than with the traditional alternating steroid–alkylating agent regimen or calcineurin inhibitors. However, many investigators feel for optimal efficacy in membranous nephropathy, especially in patients who have failed other therapies, regimens of 1000 mg of rituximab intravenously require a repeat dose in 2 weeks, or regimens of 375 mg/m² of the drug weekly for four doses. This would greatly add to the cost of treatment with this monoclonal antibody.

At present, rituximab may indeed have a first-line role for treating some patients with glomerular diseases, especially some lupus patients and those with ANCA-positive small vessel vasculitis. For idiopathic membranous nephropathy, many would agree with the KDIGO guidelines, reserving rituximab for fully nephrotic patients at high risk of progression who have failed both first line treatments of alternating months of corticosteroids and an alkylating agent, or calcineurin inhibitors. Before choosing a course of rituximab, consideration should also be given to other available therapies including continuous noncyclic use of oral alkylating agents, adenocorticotropic hormone, or mycophenolate mofetil, which have also been studied in membranous nephropathy. If it is to be used, rituximab should be used in the dose regimen felt most effective at inducing remission and preventing disease complications, while minimizing potential side effects and costs. Controlled randomized trials in idiopathic membranous nephropathy will be needed to define such a regimen. Fortunately, such a controlled randomized trial comparing rituximab with cyclosporine is currently underway (ClinicalTrials.gov; identifier NCT01180036). Until the results of this trial, the current manuscript by Ruggenenti et al.16 provides valuable information to guide us when the decision has been made now to use rituximab in idiopathic membranous nephropathy.

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DISCLOSURES

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REFERENCES