Rituximab Treatment for Vasculitis

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The emergence of rituximab during the past decade as a new therapy for ANCA-associated vasculitis (AAV) has been the most important innovation in this disease area since cyclophosphamide 40 years ago. The article by Niles *et al.* (1) in this issue of *CJASN* adds to the evidence of its efficacy.

For nephrologists, vasculitis usually means a necrotizing, crescentic glomerulonephritis associated with ANCA (2). Less frequent vasculitic renal disease includes immune complex glomerulonephritides in association with Henoch-Schönlein purpura or cryoglobulinemia or intra- and extra-renovascular disease associated with polyarteritis nodosa or Takayasu arteritis. ANCA-associated renal vasculitis has an annual incidence of 10 to 15 per million population and occurs in the context of a systemic vasculitis, such as Wegener granulomatosis or microscopic polyangiitis, or as an isolated entity (renal limited vasculitis) (3). Confusingly, approximately 5% of pauci-immune, crescentic glomerulonephritis is ANCA negative at diagnosis. The typical presentation of renal vasculitis is that of a rapidly progressive glomerulonephritis. With widespread ANCA testing and increased awareness, this condition is increasingly being diagnosed at an earlier stage before advanced renal failure is present (4).

The outcomes of AAV are frequently poor: The mortality is 25% at 5 years, and 20% of survivors develop ESRD (5). Less severe chronic kidney disease persists in the majority and contributes to markedly increased rates of cardiovascular disease. GFR at diagnosis and myeloperoxidase (MPO)-ANCA positivity are predictive of both mortality and adverse renal outcome. Older patients are more likely to be MPO-ANCA positive, present with more advanced renal disease, are less tolerant of current therapies, and represent the most acute unmet need for newer therapies.

The current standard of care has evolved to comprise the combination of high-dosage glucocorticoids with cyclophosphamide. This leads to control of disease in most patients, but treatment-related toxicity, especially infection, is the major cause of early death. There is evidence that plasma exchange improves renal recovery in those who present with advanced renal failure, but it does not improve mortality (6). Concerns over the cumulative toxicity of cyclophosphamide have led to sequential regimens whereby it is replaced after 3 to 6 months by azathioprine and by the use of intravenous pulsed (as opposed to continuous oral) cyclophosphamide administration with dosage reductions for age and renal impairment; both strategies allow lower cumulative cyclophosphamide exposure (7). It is unclear how long immunosuppressive treatment should be continued; relapse of renal vasculitis is seen in one third by 5 years and increases the risk for ESRD. It is probable that although reduced cyclophosphamide intensity regimens reduce late cyclophosphamide toxicity, they are associated with a higher subsequent relapse rate. Much of the chronic morbidity of vasculitis arises from the prolonged immunosuppressive and glucocorticoid exposure, and alternative remission maintenance strategies are needed.

Rituximab was first introduced to vasculitis therapy for patients whose condition was refractory to or intolerant of standard agents and had persisting ANCA positivity on the rationale that ANCA contributed to pathogenesis and a B cell–targeted therapy would reduce ANCA levels (8,9). It had previously been shown by Fauci *et al.* (10) that cyclophosphamide was relatively B lymphocyte specific and that B cells were present at sites of inflammation in Wegener's granulomatosis. We also know that the activation status of circulating B cells correlates with disease activity and that cyclophosphamide is a particularly effective agent in this disease (11). Further evidence for B cell involvement in AAV has come from recent biopsy studies that demonstrated autoantigen-specific B cells and activated plasma cells in nasal biopsies form patients with Wegener's granulomatosis and elevated circulating levels of the B lymphocyte stimulator (BLyS) (12); however, B cells are rarely found in the kidney in ANCA vasculitis, suggesting that the therapeutic effect of rituximab is remote—either through reduction in ANCA levels or through indirect effects on autoreactive T cells. The latter is probably more likely because rituximab is effective even when ANCA is negative, and effects of rituximab on B cell:T cell co-stimulation have been shown in rheumatoid arthritis and systemic lupus erythematosus (13).

Several prospective, retrospective, and registry studies that have involved >250 patients reported a high level of efficacy of rituximab in relapsing or refractory AAV (14,15). Indeed, the evidence for rituximab for this indication is stronger than for any other agent. Two randomized, controlled trials, Rituximab for ANCA-associated Vasculitis (RAVE) and Randomised Trial of Rituximab *versus* Cyclo-

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phosphamide for ANCA Associated Renal Vasculitis (RITUXVAS), which compared rituximab- with cyclophosphamide-based regimens, were performed (16,17). They both found similar levels of response, including control of renal vasculitis, between rituximab- and cyclophosphamide-based regimens; perhaps surprising, though, neither reported a strong safety benefit of avoiding cyclophosphamide. One conclusion is that current cyclophosphamide regimens are relatively safe and adverse events are being driven by high-dosage glucocorticoids and the consequences of the underlying disease.

As with any newer therapy, many uncertainties remain. For which patients should rituximab be used, and what is the optimal dosing? Which concomitant treatment should be given with or after rituximab? Are there new safety concerns with using rituximab in vasculitis? The case for using rituximab in refractory or relapsing disease is strong, but that for new patients relies on the two randomized trials. Follow-up in the trials was short, 6 and 12 months, and more information is required before rituximab can be routinely recommended for this indication; however, it is an alternative for those in whom cyclophosphamide is contraindicated. The only AAV subgroup for which concerns over the efficacy of rituximab have been expressed are those with retro-orbital disease in Wegener granulomatosis (18). This is one of the most refractory manifestations to any therapy and usually responds to rituximab but may require more than one treatment course before an effect is seen (19). In contrast to previous studies, Niles *et al.* (1) examined the role of regular repeat rituximab dosing as maintenance therapy for those in incomplete remission or those with high relapse risk. It was previously noted that disease relapse occurs an average of 1 year after rituximab treatment of relapsing AAV and that additional rituximab courses effectively induce second and subsequent remissions (15). Rituximab has been dosed at either 375 mg/m^2 per wk for 4 weeks, which delivers a total dosage of approximately 2.5 to 3.0 g, or as 1 g for 2 weeks, for a total of 2 g. Although not formally compared, the proportion of patients who achieve peripheral B cell depletion, >95%, and the duration of benefit seem similar with both regimens (15). Niles *et al.* (1) used either the four-dose or the two-dose rituximab regimen as initial treatment and then went on to use a maintenance dose of rituximab of 1 g every 4 months; the rationale for this regimen was not argued, and other regimens, such as 1 g every 6 months, have been used (15). This was generally effective with only three of 39 patients experiencing minor relapses while receiving rituximab. As judged by the duration of B cell depletion, there is considerable variability in sensitivity to rituximab (20). No biomarkers have been convincingly shown to guide when repeat rituximab should be given, although both ANCA and B cell levels have been studied. A predominance of CD27-positive memory B cells in the reconstituted B cell repertoire has been associated with early relapse after rituximab in rheumatoid arthritis (21). It is also unclear whether a repeated course of rituximab subsequently leads to a more durable remission when the rituximab is finally stopped.

In common with other reports Niles *et al.* (1) found an immunosuppressive- and glucocorticoid-sparing effect of rituximab. A previous survey found no benefit on relapse rate in continuing an immunosuppressant after rituximab (15). For active disease in the RAVE trial, rituximab was used with glucocorticoids but without any immunosuppressant, and the results suggest that immunosuppression can be completely avoided when rituximab is used. Although glucocorticoid withdrawal has been successful once remission has been achieved after rituximab, no attempts have been made to reduce the high dosages of glucocorticoids that are used in remission induction, and this remains a future challenge.

Adverse events attributed to rituximab include infusion reactions, infections, hyogammaglobulinemia, and delayed-onset neutropenia. As a chimeric antibody, rituximab is immunogenic, and mild infusion reactions are common. Severe reactions have been more common in systemic lupus erythematosus, Churg-Strauss angiitis, and cryoglobulinemia (22). From the existing vasculitis data, it is uncertain whether rituximab contributes to rates of infection or increases the risk for rare opportunistic infections. Indeed, rituximab has been used without difficulty when cyclophosphamide use has been contraindicated by intercurrent infection. Hypogammaglobulinemia has been a particular concern in patients who have vasculitis and previously were exposed to cyclophosphamide and then receive prolonged rituximab therapy; unfortunately, Ig levels were not monitored in the study by Niles *et al.* (1), and the planned total duration of rituximab treatment was not specified (15). The mechanism of delayed-onset neutropenia, typically 3 to 6 months after rituximab, is incompletely understood; it seems to be more frequent with lymphoma when rituximab is used with cytotoxic regimens. White cell counts should be monitored after rituximab, recovery from delayed-onset neutropenia is spontaneous without sequelae, and, as in this study, recovery may be accelerated by granulocyte colony-stimulating factor.

A small proportion of patients do not respond to rituximab, and, over time, despite regular repeated courses a further minority of patients either relapse or become intolerant. Alternative agents used in refractory vasculitis include mycophenolate mofetil, gusperimus (deoxyspergualin), TNF-α blockade, alemtuzumab, and anti-thymocyte globulin (23–25). The value and safety of repeated rituximab dosing for maintaining remission in AAV is being evaluated in the ongoing MAINtenance of remission using RITuximab in Systemic ANca associated vasculitis (MAINRITSAN) trial (ClinicalTrials.gov identifier NCT00748644); however, there is the potential to improve the safety and cost-effectiveness of rituximab by the development of improved biomarkers to guide repeat dosing (26). The success of rituximab in AAV suggests that other B cell–directed therapies, including other anti-CD20 and CD22 mAbs and anti-B cell cytokine therapies, might also be effective and have potential advantages.

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See related article, "Rituximab as Maintenance Therapy for Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis," on pages 1394–1400.