Role of Rituximab Therapy in Glomerulonephritis

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ABSTRACT
B cell depletion with the monoclonal antibody rituximab is attracting increasing attention in systemic lupus erythematosus, vasculitis, and primary glomerulonephritis. Existing, uncontrolled data report high response rates in patients with refractory disease. If supported by the results of ongoing randomized trials, then rituximab and related B cell–depleting or –modulating drugs are likely to become a component in the future management of these disorders. Their use may improve patient outcomes by permitting more complete disease control and reduced exposure to glucocorticoid and traditional immunosuppressive drugs. The toxicity and infective risk of B cell–targeted agents in renal disease needs to be determined as well as their optimal dosing in combination with conventional agents.

Immunologically mediated glomerulonephritis occurs as a primary disorder or in association with a multisystem disease, such as lupus or vasculitis, and is a potentially preventable cause of ESRD. With the exception of renin and angiotensin blockade, current therapy relies on nontargeted glucocorticoids and cytotoxic or antiproliferative drugs and has changed little during the careers of currently practicing nephrologists. The emergence of evidence from investigator-initiated studies has been slow, and, with rare exceptions, glomerulonephritis has not been a target for drug development by the pharmaceutical industry. With the success of biologic agents, rituximab in particular, in autoimmune arthritis, multiple sclerosis, and transplantation, attention is turning to autoimmune renal disease.

Rituximab is a murine/human chimeric anti-CD20 mAb that depletes B cells and was licensed in 1997 for the treatment of non–Hodgkin’s lymphoma. A subsequent expansion of interest in rituximab as an immunomodulatory agent resulted in a label for rheumatoid arthritis in 2006 and preliminary reports of efficacy across the spectrum of autoimmune disease. These results have highlighted the multiple roles of the B cell in immune dysregulation, inflammation, and autoantibody synthesis. T cell autoreactivity is B cell dependent, probably through autoantigen presentation by and co-stimulatory support from B cells, and autoantigen-specific B cells and plasmablasts have been identified at sites of inflammation.

More than 20 studies of almost 300 patients reported response rates averaging 75% in refractory lupus or lupus nephritis treated with rituximab (Table 1). Responses are accompanied by falls in anti–double-stranded DNA antibodies, correction of complement depletion, and reduction in glucocorticoid requirement. Varying treatment protocols, response criteria, and positive reporting bias indicate caution is necessary in interpreting these results, compounded by the failure of the first randomized trial, EXPLORER (A Study to Evaluate the Efficacy and Safety of Rituximab in Patients With Severe Systemic Lupus Erythematosus), to demonstrate a superior response to rituximab in addition to glucocorticoids for remission induction in nonrenal lupus. It is unclear whether this result is a failure of the drug or of trial design; systemic lupus is a notoriously difficult disease in which to demonstrate differences between treatment groups. Experience in primary systemic vasculitis has also been positive but uncontrolled (Table 1). Those with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and renal involvement showed reductions in serum creatinine and predictable falls in ANCA-binding level. The duration of response in both lupus and vasculitis has been variable with relapses occurring after an average of 10 to 13 mo, but some patients enjoyed prolonged remission for several years. Re-treatment at the time of relapse has been effective, and protocol re-treatment at 4- or 6-mo intervals is under evaluation.

Two prospective, open-label studies in primary membranous nephritis have reported improvements after rituximab in 61 and 57% of cases. Responses, defined by falls in proteinuria, were generally partial rather than complete and were related to the absence of fibrotic lesions in the study by Ruggenenti et al., but this was not found in a second report.

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Table 1. Rituximab studies\textsuperscript{a}

<table>
<thead>
<tr>
<th>Study</th>
<th>Concomitant Treatments</th>
<th>Remission (Nephritis)</th>
<th>Serology Change\textsuperscript{b}</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA vasculitis</td>
<td></td>
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<tr>
<td>Keogh et al. (2005)\textsuperscript{18}</td>
<td>GC, PLEX</td>
<td>10/11 CR, 1/11 PR (4/4)</td>
<td>8/11 negative all decreased</td>
<td>2 (7, 12 mo)</td>
</tr>
<tr>
<td>Keogh et al. (2006)\textsuperscript{25}</td>
<td>GC</td>
<td>10/10 CR (7/7)</td>
<td>6/10 negative all decreased</td>
<td>1 (9 mo)</td>
</tr>
<tr>
<td>Smith et al. (2006)\textsuperscript{30}</td>
<td>GC, MMF</td>
<td>9/11 CR, 1/11 PR (6/6)</td>
<td>6/10 negative all decreased</td>
<td>6/10 (median 16.5 mo)</td>
</tr>
<tr>
<td>Stasi et al. (2006)\textsuperscript{19}</td>
<td>GC</td>
<td>9/10 CR, 1/10 PR (6/6)</td>
<td>8/10 negative all decreased</td>
<td>3/10 (12, 16, 24 mo)</td>
</tr>
<tr>
<td>SLE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Looney et al. (2004)\textsuperscript{22}</td>
<td>GC, AZA, MTX, HCQ</td>
<td>13/18 CR or PR (4/6)</td>
<td>No significant change</td>
<td>4/11 (timing NR)</td>
</tr>
<tr>
<td>Gottenberg et al. (2005)\textsuperscript{33}</td>
<td>NR</td>
<td>7/13 CR, 2/13 PR (2/4)</td>
<td>Variable</td>
<td>2/9 (9, 15 mo)</td>
</tr>
<tr>
<td>Sfikakis et al. (2005)\textsuperscript{34}</td>
<td>GC</td>
<td>5/10 CR, 3/10 PR (8/10)</td>
<td>Decrease</td>
<td>3/8 (5, 5, 8 mo)</td>
</tr>
<tr>
<td>Smith et al. (2006)\textsuperscript{30}</td>
<td>MMF, AZA GC</td>
<td>6/11 CR, 5/11 PR (6/6)</td>
<td>No significant change</td>
<td>7/11 (median 12 mo)</td>
</tr>
<tr>
<td>Vigna-Perez et al. (2006)\textsuperscript{35}</td>
<td>GC, MMF, MTX, AZA</td>
<td>18/22 improved, 5/22 CR (12/22)</td>
<td>No significant change</td>
<td>NR</td>
</tr>
<tr>
<td>Nwobi et al. (2008)\textsuperscript{36}</td>
<td>GC, MMF HCQ</td>
<td>7/18 CR, 10/18 PR (17/18)</td>
<td>Decrease</td>
<td>5/18</td>
</tr>
<tr>
<td>Podolskaya et al. (2008)\textsuperscript{16}</td>
<td>GC, CYC AZA, MMF, HCQ</td>
<td>11/19 CR, 8/19 PR (15/15)</td>
<td>Decrease</td>
<td>NR</td>
</tr>
<tr>
<td>Ng et al. (2007)\textsuperscript{14}</td>
<td>GC, CYC, HCQ</td>
<td>30/32 CR or PR (21/21)</td>
<td>Decrease</td>
<td>18/32 (mean 10 mo)</td>
</tr>
<tr>
<td>Lindholm et al. (2008)\textsuperscript{35}</td>
<td>GC, CYC MTX, MMF</td>
<td>30/33 CR or PR (11/17)</td>
<td>Decrease</td>
<td>11/30</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td></td>
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<tr>
<td>Fervenza et al. (2008)\textsuperscript{11}</td>
<td>ACE/ARB</td>
<td>8/14 response</td>
<td>–</td>
<td>NR</td>
</tr>
<tr>
<td>Ruggenenti et al. (2006)\textsuperscript{21}</td>
<td>ACE/ARB</td>
<td>14/23 response</td>
<td>–</td>
<td>2/9</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Clinical studies of rituximab in primary or secondary glomerulonephritis involving at least 10 patients. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AZA, azathioprine; CR, complete remission; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate; NR, not reported; PLEX, plasma exchange; PR, partial remission.

\textsuperscript{b}ANCA for ANCA vasculitis; anti-dsDNA for systemic lupus erythematosus (SLE).

There have been positive and negative series and case reports in cryoglobulinemia and relapsing nephritic syndrome in childhood and in recurrent posttransplantation FSGS, membranous nephropathy, and ANCA vasculitis.

A near universal finding has been the achievement of peripheral B cell (CD19\textsuperscript{+} or CD20\textsuperscript{–}) depletion below 1 × 10\textsuperscript{9}/L after rituximab, and failure to achieve depletion is correlated with poor or no clinical response.\textsuperscript{22} B cell recovery is detectable after 6 to 9 mo, and although prolonged B cell depletion is associated with a prolonged clinical response, B cell return is not closely associated with disease activity, and relapses have occurred before B cells return.\textsuperscript{20} In the minority of patients who had refractory vasculitis and were ANCA positive at the time of rituximab therapy, changes in ANCA levels have reflected changes in disease activity, but, in general, autoantibody levels in lupus and vasculitis are not predictive of relapse.\textsuperscript{18} Polymorphisms in the FcyRIII receptor influence rituximab-induced B cell lysis and associate with incomplete B cell depletion with low-dosage rituximab.\textsuperscript{23}

Rituximab dosing has copied that used in lymphoma, 375 mg/m\textsuperscript{2} per wk for 4 wk, or rheumatoid arthritis, 1000 mg repeated after 2 wk; although, superficially, responses seem similar, these regimens have not been directly compared.\textsuperscript{12} Two studies using lower dosages found lower response rates.\textsuperscript{22,24}

The role of concomitant immunosuppressive therapy at the time of rituximab or for relapse prevention after rituximab is controversial. In rheumatoid arthritis, there is a synergistic effect of methotrexate and rituximab possibly as a result of a direct reduction of synovitis by methotrexate. Immunosuppressive drugs do not contribute to the duration of B cell depletion, and there were no major differences in the duration of response between studies that continued immunosuppression after rituximab and those that did not.\textsuperscript{5,14,20,25} The development of antichimeric antibodies to rituximab (HACA) is found in up to 30% of treated patients; although in the majority of cases they seem to have no clinical effect, failure to induce depletion with repeat dosing has occurred.\textsuperscript{13,20,22}

Infusion reactions to rituximab occur in 20 to 40% and are mostly mild, although severe reactions including meningismus, anaphylaxis, and serum sickness have been reported.\textsuperscript{15,20,26} In 2006, the Food and Drug Administration reported the occurrence of progressive multifocal leukoencephalopathy in two patients with lupus after rituximab.\textsuperscript{27} Both had had prolonged previous and concurrent immunosuppressive exposure, and this severe viral infection is a rare but recognized complication of systemic lupus. It is unclear whether the frequency of infections reported in current studies with rituximab in glomerulonephritis represent any increase over what would be expected from concomitant therapy; this is an important aim of ongoing randomized trials. Late-onset neu-
tropenia is also a transient phenomenon after rituximab that may be more common in those previously exposed to cytotoxic drugs. IgG levels are unchanged after rituximab, the CD20 antigen is not present on plasma cells, but multiple courses lead to modest falls in IgG concentration. Occasional patients develop hypogammaglobulinemia and recurrent infection requiring IgG replacement. Thus, IgG levels should be monitored, and falling levels should influence decisions to repeat treatment with rituximab. As an antibody, rituximab’s half-life is reduced in nephrotic states, but it is not known how this influences responses and the need for re-treatment. Tissue resident B cells, especially in lymphoid organs and at sites of inflammation, are more resistant to depletion than circulating cells, and elevated B cell stimulating factor (BLyS), found in active lupus and vasculitis, impair rituximab-induced B cell lysis and associate with shorter clinical responses. These factors may explain cases of rituximab failure and the observation that repeated rituximab after minor or partial responses leads to a larger treatment effect. Assessing response is complicated by the variable time to response after rituximab, from days to several months, and increases in conventional therapy may be required to control a deteriorating clinical situation before a response is seen.

The preliminary results in lupus and vasculitis have stimulated the design of randomized, controlled trials with a humanized anti-CD20 mAb, ocrelizumab, and a B cell–depleting anti-CD22 mAb, epratuzumab. B cell–modulating drugs, including anti-BLyS, belimumab, and the soluble TACI receptor atacicept, which blocks BLyS and APRIL signaling, are also being studied in systemic lupus.

Rituximab is now considered an alternative therapy for refractory lupus, lupus nephritis, and vasculitis, but there is no current evidence supporting its use in routine care for remission induction or maintenance, and there is less evidence in primary glomerulonephritis. B cell–depleting or –modulating drugs have the exciting potential of improving control of glomerulonephritis and avoiding or minimizing exposure to glucocorticoids and immunosuppressive drugs. Their use is not without hazard, and important concerns over risk for infection remain. Investment in glomerulonephritis by the biologics industry is necessary to extend the current observations and offer our patients the potential for improved outcomes in the future.

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REFERENCES


