Effects of anti-CD20 monoclonal antibody as a rescue treatment for ANCA-associated idiopathic systemic vasculitis with or without overt renal involvement

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Key words: Rituximab, vasculitis, paucimmune necrotizing glomerulonephritis, Wegener’s granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis.

ABSTRACT

Background. Cyclophosphamide (CYC) is thought to be the most effective treatment for antineutrophil cytoplasmic antibody (ANCA)-associated idiopathic systemic vasculitis with severe organ or life threatening presentation. The key mechanism of action of CYC is suppression of the B lymphocyte activity. However, a considerable minority of patients either remains refractory to conventional therapy or experiences dose-limiting side effects.

Methods. In the present study, rituximab (4 weekly doses of 375 mg/m2 and 2 more doses at 1-month interval) was intravenously administered as a rescue therapy to 7 patients (4 affected by idiopathic systemic microscopic polyangiitis, 2 by Wegener’s granulomatosis, and 1 affected by Churg Strauss syndrome). The study group was made up of 3 women and 4 men, mean age 61.5 years (39-71), intolerant or refractory to more conventional therapy. Four patients had histologically confirmed paucimmune necrotizing glomerulonephritis.

Results. Significant decreases were observed in levels of serum creatinine, proteinuria, erythrocyte sedimentation rate, C-reactive protein, and ANCA titers within the first 12 months of follow-up. Arthralgia and weakness rapidly disappeared in all patients. Four out of five patients reported a decrease in the degree of paresthesia, paralleled by an improvement in the electrodiagnostic parameters. A significant improvement was observed in both Birmingham Vasculitis Activity Score and Vasculitis Damage Index. Side effects were negligible.

Conclusion. In this sample of patients with idiopathic systemic vasculitis that was refractory or intolerant to conventional treatment, rituximab was found to be a safe and effective rescue therapy.

Introduction

Steroids and cyclophosphamide have dramatically changed the natural history of anti-neutrophil cytoplasmic antibody-associated small-vessel vasculitis (AAV), a distinct subset of idiopathic systemic vasculitis that has a potentially life-threatening course (1, 2) which includes microscopic polyangiitis with or without granulomatous phenotype (so-called Wegener’s granulomatosis) and Churg-Strauss syndrome.

General experience, together with the results of controlled trials (1, 3, 4) indicates that ten percent of AAV patients present with cyclophosphamide-resistant disease, i.e., a persistently active illness despite maximally tolerated cyclophosphamide. Moreover, an even greater proportion of patients become intolerant. Finally, infertility and malignancies in younger patients, leukopenia and infections in the elderly make standard immunosuppressive treatment unappealing. Indeed, despite effective remission of vasculitic disease, patient’s quality of life remains depressed, also due to the devastating effects of current therapies. Thus, the advent of effective and safer forms of AAV management would be more than welcome.

Besides the other novel therapies, rituximab is a genetically engineered chimeric murine-human anti-CD20 monoclonal antibody that binds to the B-cell surface Ag CD20, which is expressed at the late pre-B stage (and lost during the terminal differentiation into plasma cells) and selectively depletes CD20 positive lymphocytes.

The efficacy of rituximab in patients with severe AAV refractory or intolerant to conventional therapy is examined in the present study, which specifically addresses the cost/benefit profile with regards to the indicators not only of disease activity, but also of the extent of vasculitis damage.

Competing interests: none declared.
Methods

Patients, treatment protocol and laboratory investigations

Seven patients, mean age 61.5 years (range 39-71 years) with AAV (4 with microscopic polyangiitis, 2 with Wegener’s granulomatosis, and 1 with Churg-Strauss syndrome) were deemed eligible for rituximab therapy, either because of a disease resistance to CYC (3 cases) or because of the combined impossibility to administer CYC and the resistance to alternative immunosuppressants (4 cases). All patients fulfilled the Chapel Hill definitions for vasculitides (5). Five cases presented with major urinary abnormalities: 4 had biopsy-proven diffuse necrotizing extracapillary pauciimmune glomerulonephritis and 1 case did not undergo biopsy because of concomitant anticoagulation therapy due to the presence of anti-phospholipid antibodies. The remaining 2 patients only had minimal proteinuric abnormalities and were not biopsied. Sinus lesions and lung nodules were detected in 2 cases, with massive involvement in 1 patient. Purpura with biopsy-proven leukocytoclastic vasculitis was present in 3 cases, with large necrotizing skin ulcers in 1 of them. Polynuropathy was observed in 5 patients, arthralgia and weakness were found in all 7 cases, whereas fever was present before rituximab in 3. Demographic features, diagnosis, therapeutic regimens before starting rituximab, organ involvement and extent of disease activity (as assessed by the Birmingham Vasculitis Score, BVAS) are summarized in Table I. Patients no. 3, 4, and 7 were found to be resistant to CYC. Patient no. 5 was in a relapsing phase albeit an elevated cumulative dose of CYC. Patient no. 6 had a history of severe CYC-induced leukopenia when addressed to our centre from another hospital because of a life-threatening disease. Patient no. 2 could not be treated with CYC because of a sudden pancytopenia after 1-week oral treatment at the conventional dose (2 mg/kg). Patient no. 1 refused to accept the risks of infertility related to CYC treatment.

Rituximab was administered intravenously at a dose of 375 mg/m² on days 1, 8, 15 and 22. Two more doses were administered 1 and 2 months later, according to a protocol that had been successfully employed in patients with severe cryoglobulinemic vasculitis (6). Premedication included oral antihistamines, acetaminophen (500 mg) and deflazacort (60 mg unique administration at the first infusion).

Response was evaluated by assessing the changes in clinical signs, symptoms, laboratory parameters, Visual Analogue Scale (VAS) for arthralgia, indexes of disease activity (BVAS) or damage (Vasculitis Damage Index, VDI). BVAS and VDI were assessed according to Luqmani and co-workers (7) and Exley and co-workers (8), respectively.

Laboratory studies included hemogram, serum chemistry profiles, immunoglobulin levels, erythrocyte sedimentation rate (ESR), plasma C-reactive protein (CRP), rheumatoid factor, ANCA testing, performed both by indirect immunofluorescence on ethanol-fixed neutrophils and antigen specific enzyme-linked immunosorbent assay for antitymeylperoxidase and antiproteinase 3 (2).

Statistical analysis

Student’s paired r-test was used to compare pre- versus post-therapy values of the same parameter and ANOVA Test with Dunnet’s multiple comparison post-test was used to examine the profiles of biochemical markers and clinically measurable indexes, specifically BVAS and VDI, from the start of therapy up to 12 months later. All the tests were performed using the SAS software package.

Results

Arthralgia and weakness were reported to be ameliorated in all 7 cases with a remarkable reduction in VAS score within the 1st month. Paresthesia has been reported to be improved in 4 out of 5 cases after rituximab infusions. It is of note that electrophysiological parameters, checked at 6 months in three cases (patients no. 1, 4, and 7), improved considerably in 2 of them: patient no. 4 (knee-level recording: latency 16.0 vs. 11.4 m/s, amplitude 0.3

Table I. Baseline demographic and clinical features of patients.

<table>
<thead>
<tr>
<th>Patient, Age, gender</th>
<th>Ongoing therapy</th>
<th>Organ involvement at onset</th>
<th>Active organ involvement at the time of rituximab administration</th>
<th>% of glomerular crescents</th>
<th>BVAS</th>
<th>sCr (mg/dl)</th>
<th>Proteinuria (g/24 h)</th>
<th>Hematuria (RBC / HPMF)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/39/M</td>
<td>MMF, MTX steroid pulses, IV Ig, Pl</td>
<td>K, N, J, F, S, W</td>
<td>K, N, J, F, S, W</td>
<td>nd</td>
<td>27</td>
<td>0.7</td>
<td>0.4</td>
<td>50</td>
<td>mPa</td>
</tr>
<tr>
<td>2/67/F</td>
<td>MMF, steroid pulses</td>
<td>K, F, W, J</td>
<td>K, W, J</td>
<td>40</td>
<td>11</td>
<td>1.1</td>
<td>1.1</td>
<td>50</td>
<td>mPa</td>
</tr>
<tr>
<td>3/63/M</td>
<td>Oral CYC, steroid pulses</td>
<td>K, J, W, N</td>
<td>K, J, W, N</td>
<td>30</td>
<td>11</td>
<td>2.4</td>
<td>1.3</td>
<td>40</td>
<td>mPa</td>
</tr>
<tr>
<td>4/71/F</td>
<td>Oral CYC, steroid pulses</td>
<td>N, J, F, W</td>
<td>N, J, F, W</td>
<td>nd</td>
<td>13</td>
<td>0.9</td>
<td>0.5</td>
<td>0</td>
<td>mPa</td>
</tr>
<tr>
<td>5/69/M</td>
<td>MMF, steroid pulses</td>
<td>K, N, J, F, W, UA</td>
<td>K, N, J, W</td>
<td>15</td>
<td>28</td>
<td>1.4</td>
<td>1.4</td>
<td>15</td>
<td>WG</td>
</tr>
<tr>
<td>6/62/F</td>
<td>MMF, steroid pulses, IVIgG</td>
<td>K, L, F, W, J, UA</td>
<td>K, L, F, W, J, UA</td>
<td>40</td>
<td>29</td>
<td>2.1</td>
<td>2.2</td>
<td>20</td>
<td>WG</td>
</tr>
<tr>
<td>7/60/M</td>
<td>IV CYC, steroid pulses, IV Ig</td>
<td>N, S, J, H, W</td>
<td>N, S, J, W</td>
<td>nd</td>
<td>29</td>
<td>1.2</td>
<td>0.3</td>
<td>0</td>
<td>CS</td>
</tr>
</tbody>
</table>

MMF: mycophenolate mofetil; MTX: methotrexate; IV IgG: intravenous immunoglobulin; CYC: Cyclophosphamide (oral or intravenous, IV); PE: plasma exchange; steroid pulses: methylprednisolone 15 mg/kg/day for 3 consecutive days; K: kidney; N: peripheral nervous system; J: joints; F: fever; S: skin; W: weakness; UA: upper airways (sinusitis, rhinorrea, otitis); H: heart; nd: not determined (non-biopsied case); BVAS: Birmingham Vasculitis Score; RBC/HPMF: Red Blood Cells/High Power microscopic field; mPA: microscopic polyangiitis; WG: Wegener’s granulomatosis; CS: Churg-Strauss Syndrome.
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Fig. 1. Profiles of VDI (Vasculitis Damage Index) and BVAS (Birmingham Vasculitis Activity Score) in patients with ANCA-associated vasculitis treated with anti-CD20 monoclonal antibody. A significant decrease (p<0.01) was detected both in VDI and in BVAS.

Fig. 2. Reversal of lung nodules (Panel A) and sinus granulomata (Panel B) in pt no. 6 (baseline vs. 9-month features). Panel C shows profiles of biochemical parameters in the same patient.

Levels of serum creatinine, proteinuria, erythrocyte sedimentation rate and C-reactive protein significantly decreased at 3, 6, 9 and 12 months. IgM values significantly decreased as well, whereas IgG remained stable until the 6th month (Fig. 3). The nephritic sediment disappeared within the 1st month of therapy. Trace amounts of hematuria (3-5 erythrocyte/high power microscopic field, 400x) could be detected at 3 months in patient no. 3 and no more in subsequent evaluations. On the average, ANCA levels decreased by 5-fold and in one patient negative levels had already been achieved at 1 month. Eosinophil count reversed to normal in 2 months in patient no. 7 affected by Churg-Strauss syndrome.
Apart from cases 1 and 2, patients were free from immunosuppressive drugs within 4 weeks from starting rituximab. Prednisone, administered at the dose of 0.5-1 mg/kg/day in the 1st month and 0.25-0.5 mg/kg/day in the 2nd month, was subsequently tapered by 5 mg each other week up to a maintenance dose of 5 mg/day except patient no. 4 who stopped tapering at 12.5 mg/day because of arthralgia.

No acute side effects were observed, except for dose-related bradycardia in a female with Wegener’s granulomatosis. Delayed effects, including infections, could not be detected during the follow-up.

Of note, 6 months after starting rituximab infusions patient no. 1 was in maintenance daily therapy with prednisone 5 mg combined with methotrexate 7.5 mg/week, patient no. 2 with mycophenolate mofetil 1 g and prednisone 5 mg, patient no. 4 with prednisone 12.5 mg, while the remaining patients were given either low doses prednisone (5 mg) or no therapy (patient no. 7).

**Discussion**

In the first experience with anti-CD20 monoclonal antibody in AAV, 11 patients with refractory disease were treated with high-dose corticosteroids plus 4 weekly infusions of rituximab and, in 3 cases, plasma exchange. Remission was achieved by all the patients and it was associated with a depletion of circulating B lymphocytes and a decrease in ANCA titer (9). These results were confirmed by the same group in a prospective, open-label pilot study (10). In other reports, rituximab was used in addition to cyclophosphamide, methotrexate, azathioprine or mycophenolate mofetil (11-14). Some manifestations, which are known to be especially resistant to immunosuppressive regimens (such as subglottic stenosis, sinus masses or retrobulbar granulomas) are not often successfully treated. This is probably because their anatomic site is reported as being either unresponsive (13, 14) or as regressing very slowly following rituximab administration (11). However, rituximab was found to be effective in 88 per cent of the 53 cases published by the end of 2006.

Thirty per cent of responders relapsed in 9-21 months, but good response was once again obtained in most re-treated patients (15).

In the present study, the therapeutic benefits of rituximab on organ-threatening manifestations of systemic vasculitis with renal involvement were appreciated since the first month, and consisted of a significant decrease in phlogistic indexes, proteinuria, as well as the disappearance or improvement of constitutional symptoms. However, it is worth of note that rituximab was used in escalation protocols in refractory patients or, in cases of intolerance...
to immunosuppressive drugs, was introduced in the absence of a wash-out-period. Moreover, it was administered as a rescue therapy what also explains the heterogeneous character of the patient sample.

Effective response was substantiated by a remarkable improvement in the 12 month BVAS. Also the sinuses lesions regressed in our patients with Wegener’s granulomatosis albeit with some delay as compared to other manifestations. Similarly, Brihaye et al. (15) showed that, at variance from constitutional symptoms, granulomatous manifestations regress slowly after rituximab administration. Diverse therapeutic schedules could lead to different outcomes (16-18) by affecting in different manner tissue B cells, which account for about 40% of the CD20 population and are expected to be less sensitive to rituximab, than circulating B cells. Our “4 plus 2 protocol” is consonant with the generally accepted half-life of rituximab of 7 days.

An often neglected aspect of AAV treatment is multiple mononeuritis. Some improvement was observed in critical parameters of peripheral nerve electrophysiologic studies.

Rituximab was found to be safe. A significant drop in serum IgM values was observed, which paralleled B cell depletion. IgG was found to be decreased at the 6th month and was stable at the 9th month. This profile may explain the absence of infections in rituximab-treated patients, especially when conventional immunosuppressants are no longer given after rituximab infusion.

The safety of administering rituximab is especially relevant in the management of vasculitis patients, considering the potential complications of conventional immunosuppressive therapy. Vasculitis damage indexes are strongly impacted by therapeutic manipulations. Rituximab also proved to have a good profile with regards to this particular aspect, as documented by a substantial amelioration in VDI scores within 12 months.

It is currently believed that the key mechanism of action of rituximab in vasculitis consists in removing the cellular source of the putative pathogenic autoantibodies. Whether long-lived autoantibody-producing cells are affected by anti-CD20 monoclonal antibody is questionable (17). It is more likely that rituximab mechanism of action in AAV includes depletion of the cells involved in several arms of the immune response. B cells are activated in vasculitis (19, 20) and an expansion of the B cell compartment, which multiples the number of antigen presenting cells and increases the production of a variety of cytokines (21), has been observed in vasculitis patients. This might support the long-term effects of rituximab, which could persist beyond the B cell depletion phase (6).

Of course, large controlled studies are needed to define optimum doses and protocols. Data from the present study suggest that future trials should be also addressed to compare this novel therapy to conventional treatments not only with regards to ability to promote remission induction but also to influence vasculitis damage indexes.

References


