Rituximab in refractory antineutrophil cytoplasmic antibody-associated vasculitis: what is the current evidence?

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is recognized as a chronic, relapsing and potentially fatal disease. Cyclophosphamide and steroids remain the mainstay of treatment of AAV [1]. Unfortunately, in up to 10% of patients, disease remains refractory despite conventional therapy [1]. In addition, conventional therapy has some serious side effects and hence limits its long-term use. For these refractory patients and those intolerant of conventional therapy, there are limited therapeutic options. B-lymphocytes have been implicated in the pathogenesis of AAV, by being the precursors of plasma cells (PCs), which produce ANCA [2] and in the formation of granuloma in Wegener’s granulomatosis (WG) [3]. Apart from the important role in antibody production, B-cells can also affect other aspects of the immune regulation such as immune response regulation, antigen presentation and cytokine production. This has been recognized in autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus, where the disease process is B-cell dependent and antibody independent [4,5].

Rituximab (RIT) is a chimeric monoclonal anti-CD20 antibody, which depletes B-lymphocytes, and has been proposed as salvage therapy for refractory disease.

RIT consists of human constant regions linked to murine variable domains [6]. The murine Fab domain of RIT binds the CD20 antigen, which is a transmembrane protein located on the surface of mature B-cells. The CD20 antigen is involved in regulation of the transmembrane calcium conductance and cell-cycle progression during human B-cell activation [7]. B-cell activation may differentiate into either short-lived (in the absence of T-cell help) or long-lived PCs that are regulated by ligation of CD40 provided by helper T-cells [8] (Figure 1). RIT acts through antibody-mediated apoptosis, antibody-dependent cellucytotoxicity and complement-mediated toxicity [9]. RIT induces 98% depletion of peripheral blood B-cells, but only 40–70% of lymph node B-cells are depleted [2]. Long-lived PCs do not express CD20 and this may explain why RIT-induced depletion of CD20+ B-cells in some cases does not decrease either total serum IgG levels or ANCA levels [2,10]. The rationale behind the use of RIT in AAV is based on the following three assumptions.

B-cells → ANCA → AAV

RIT can effectively deplete B-cells, which would affect the reconstitution of PCs and lead to the disruption of ANCA production. ANCA plays an important role in the pathogenesis of AAV [2]. However, AAV can relapse with negative ANCA, and the absolute level of the titre does not correlate well with disease activity as patients with AAV in remission can have high ANCA titres for many years without experiencing recurrence of the disease [11]. RIT does not effect long-lived PCs, and hence B-memory cells which do not have CD20 antigen [2]. Therefore the precise role of B-cells in the pathogenesis of AAV remains uncertain but there are several hypotheses. B-cells can act as antigen presenting cells to T-cells or provide additional co-stimulatory signals. The self reactive B-cells, derived from unusual B-cell subsets, may follow an alternative maturation process including the continued expression of CD20 during antibody production [12–14].

Following the first successful compassionate use of RIT in refractory WG [15], there have been several other case reports [12,14,16,17], case series [13,18,19] and prospective open label trials [20–22] published regarding the efficacy and safety of RIT in inducing remission in patients with AAV, mainly WG refractory to conventional therapy (Table 1). So far there are only

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three prospective open label pilot trials [20–22] and they reported contrasting results. All the 10 patients in the Keogh et al. trial [20] and nine out of 10 in Stasi et al. [22] achieved complete remission for at least 6 months as opposed to only two out of eight in the Aries et al. trial [21].

Two main observations noted for differences in response were that the cohort in the Aries et al. [21] trial, first had more granulomatous disease (five with retro-orbital granuloma, one with lung nodule and two with subglottic stenosis) than the former. Second, in this group of patients, the B-lymphocyte depletion was not associated with a significant change in ANCA titres. In the Aries et al. [21] study, their patients were refractory to standard therapy of cyclophosphamide and steroid, and anti-TNFα 3 months prior to inclusion in the study. Four doses of RIT 375 mg/m² were given at 4 weekly intervals, in addition to cyclophosphamide or methotrexate. A reduction in disease activity was observed in three patients, two of whom went into complete remission. Later, in a subsequent publication, the same authors described their successful use of intravenous azathioprine in treating the other two out of the five patients with retro-orbital granuloma, resistant to RIT [23].

Granulomatous disease seems more likely to be resistant to RIT than vasculitis disease. This observation was similarly reported by Omdal et al. [13] where two patients with granulomatous retro-orbital or sinus masses failed to achieve remission with RIT.

Granulomas, a pathognomonic feature of WG, are initiated and maintained by CD4 T-cells with a Th-1 pattern. The granulomas are made up of monocyte-derived tissue macrophages, giant cells, neutrophils, CD4+CD28− T-cells and B-cells [24–26].

It has been suggested that patients with WG may have an unbalance Th-1 cytokine response, as suggested by up-regulation of interferon-γ and tumour necrosis factor (TNF) [24,27]. It would seem therefore that etanercept or infliximab, both anti-TNFα therapies can prevent TNF from binding to cell receptors and hence the process of inflammation. However, in a randomized controlled double-blind trial, Wegener’s Granulomatosis Etanercept Trial, there were no differences in terms of rate of sustained remission, time to sustained remission or number of relapse between the etanercept and placebo in addition to standard therapy.

Keogh et al. [20] treated 10 patients with refractory WG in a prospective, open-label pilot trial with oral prednisolone (1 mg/kg/day) and four weekly infusions of RIT 375 mg/m². All patients achieved complete clinical remission by 3 months, and were tapered off glucocorticoids by 6 months. Five patients were retreated with RIT according to protocol following recurring/rising ANCA titres at 9 months follow-up.

In all patients, the peripheral blood B-cells declined to zero following the course of the treatment with RIT. This was accompanied by remission of AAV in all cases. Stasi et al. [22] studied the long-term effects of RIT 375 mg/m² weekly for 4 weeks in 10 patients with refractory AAV to conventional therapy, or in second and subsequent relapse. Eight were classified as WG. Nine patients achieved rapid response and complete remission for 6 months. With follow-up ranging from 26 to 45 months, three patients had relapsed at 12, 16 and 24 months, respectively; rechallenge with RIT at the same dose and schedule resulted in further sustained response and remission. Eriksson [19] included seven WG patients in a series of cases receiving RIT, usually at a dose of 500 mg weekly for 4 weeks. All patients responded, with six in complete remission and one partial remission at 6 months. Two patients relapsed at 12 and 13 months; the remainder were still in remission after follow-up of 6–22 months. In terms of microscopic polyangiitis, two studies by
<table>
<thead>
<tr>
<th>Authors (ref)</th>
<th>Year</th>
<th>Level of evidence</th>
<th>Type of vasculitis (no. of patients)</th>
<th>RIT regimen</th>
<th>Concomitant treatment</th>
<th>Organs involved since onset of vasculitis/start of RIT</th>
<th>BVAS score at initiation/at 6 months</th>
<th>Complete remission at 6 months</th>
<th>Complete remission at 6 months</th>
<th>Complications following RIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specks et al. [15]</td>
<td>2001</td>
<td>CR</td>
<td>1</td>
<td>WG</td>
<td>A</td>
<td>1IVMP, P 60 mg OD Concurrent D 4 mg, P 20 mg OD</td>
<td>E,J,L,K, ENT, CNS</td>
<td>7/0</td>
<td>Yes</td>
<td>RTI</td>
</tr>
<tr>
<td>Ferraro et al. [12]</td>
<td>2005</td>
<td>CR</td>
<td>1</td>
<td>WG</td>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheung et al. [14]</td>
<td>2005</td>
<td>CR</td>
<td>1</td>
<td>WG</td>
<td>B</td>
<td>Cyc 12.5 mg/kg, MMF, P</td>
<td>E, L,</td>
<td>NS</td>
<td>Yes</td>
<td>Nil</td>
</tr>
<tr>
<td>Bachmeyer et al. [16]</td>
<td>2005</td>
<td>CR</td>
<td>1</td>
<td>WG</td>
<td>A</td>
<td>MMF 1g OD maintenance</td>
<td>K, L</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Kallenbach et al. [17]</td>
<td>2005</td>
<td>CR</td>
<td>1</td>
<td>WG</td>
<td>A</td>
<td>Cyc 500 mg, MMF, P 1MTX 10 mg weekly, P 5 mg OD</td>
<td>L, 2L, 2K, S,M, 2ENT, ROG</td>
<td>NS</td>
<td>Yes</td>
<td>Nil</td>
</tr>
<tr>
<td>Omdal et al. [13]</td>
<td>2005 CS</td>
<td>3</td>
<td>WG</td>
<td>A</td>
<td>1 IVMP, P 10 mg OD 1Aza, IVMP</td>
<td>3E, 7L, 5K, 4ENT, 2S, 4J</td>
<td>3-11/0</td>
<td>Yes</td>
<td>IR, RTI, H, OM</td>
<td></td>
</tr>
<tr>
<td>Keogh et al. [18]</td>
<td>2005 CS</td>
<td>11</td>
<td>WG</td>
<td>A</td>
<td>P 1 mg/kg/OD/8 IVMP 3 TPE 5 MMF</td>
<td>4J, 7K, 4L, 5S, 7ENT, N</td>
<td>Median 6 (2-18)/0 in 8 patients, 1 in 1 Yes in 8 and 1 partial BVAS = 1</td>
<td>RTI, HZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eriksson et al. [19]</td>
<td>2005 CS</td>
<td>9</td>
<td>WG 7</td>
<td>8 B</td>
<td>MPA 2</td>
<td>1 A</td>
<td>1Aza 2 Cyc 1 P</td>
<td>6K, 4L, E, 2CNS, 5ENT, 5J</td>
<td>5-10/0</td>
<td>Yes</td>
</tr>
<tr>
<td>Keogh et al. [20]</td>
<td>2006 POL</td>
<td>10</td>
<td>WG</td>
<td>A</td>
<td>P 1 mg/kg/OD</td>
<td>6K, 4L, E, 2CNS, 5ENT, 5J</td>
<td>5-10/0</td>
<td>Yes</td>
<td>IR, HZ</td>
<td></td>
</tr>
<tr>
<td>Aries et al. [21]</td>
<td>2006 POL</td>
<td>8</td>
<td>WG</td>
<td>A</td>
<td>5 Cyc 2 MTX 1 MMF P 10–30 mg OD</td>
<td>E, 3L, 2K, 2SS, 5ROG</td>
<td>5-10/0 in 2 patients, rest 6-11</td>
<td>Only 2 out of 8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Stasi et al. [22]</td>
<td>2006 POL</td>
<td>10</td>
<td>WG</td>
<td>A</td>
<td>MPA 2</td>
<td>4 Cyc 4 TMP/SMX P up to 2 mg/kg/OD</td>
<td>2L, 6K, 2S, 5ENT</td>
<td>3-11/0 in 9 patients, 1 in 1</td>
<td>9 out of 10</td>
<td>IR</td>
</tr>
</tbody>
</table>

RIT, Rituximab; CR, Case report; CS, Case series; POL, Prospective open label; WG, Wegener’s granulomatosis; MPA, microscopic polyangiitis; A, 4 weekly infusions of Rituximab 375 mg/m²; B, Rituximab 500 mg or 1 g/infusion; K, kidney; IVMP, intravenous methylprednisolone; P, prednisolone; OD, once daily; D, dexamethasone Cyc, cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; Aza, azathioprine; TPE, therapeutic plasma exchange; CSA, ciclosporin A; TMP/SMX, trimethoprim/sulfamethoxazole; L, lung; E, eye; SS, subglottic stenosis; ENT, ear, nose, throat; J, joints; CNS, central nervous system; M, muscle; N, peripheral nerves; ROG, retro-orbital granulomas; IR, infusion related adverse event; RTI, respiratory tract infection; H, hypertension; HZ, herpes zoster; OM, osteomyelitis; NS, not specified.
Eriksson [19] and Stasi et al. [22], each having two patients, responded to RIT and remained in remission during the 12–38 month follow-up.

In the literature, the most common adverse events associated with the use of RIT in refractory AAV, were infusion related which ranged from dyspnea, dizziness, polyarthritis, fever to hypertension (volume sensitive haemodialysis patient). The most common infections were lower respiratory infections and Herpes Zoster (Table 1). All RIT regimens described in Table 1 included the use of high dose steroid which might depress serum immunoglobulin [13]. An important personal observation is that concurrent use of cyclophosphamide or plasma exchange can also decrease immunoglobulin levels. It is very important to monitor immunoglobulin levels especially when patients have infection. It is then essential to replete with intravenous immunoglobulin if serum IgG is less than the normal range to help combat the serious infections, anecdotal experience in two out of four patients [28].

In conclusion, RIT seems to be effective treatment in patients with refractory AAV, both in WG and MPA patients. In WG, patients with retro-orbital granulomas tend to be less responsive to RIT. The overall adverse events are minimal and most commonly related to the infusion. The above current evidence revealed that most of the success in treating refractory AAV is with the use of the RIT, as in dosing regimen A described in Table 1, i.e. 4 weekly infusions of 375 mg/m², which is the low-grade non-hodgkin’s lymphoma protocol [29] as opposed to dosing regimen B, i.e. two doses of 1 g with an interval of 2 weeks, as in the RA trial [30]. We therefore proposed that a multicenter randomized controlled trial of patients receiving RIT with dosing regimen A and prednisolone 1 mg/kg/day is required to evaluate the efficacy in inducing remission in AAV, as opposed to cyclophosphamide and prednisolone before RIT can be licensed and considered a standard treatment.

Conflict of interest statement. None declared.

References


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