Effectiveness of TNF-α blockade with infliximab in refractory Wegener’s granulomatosis

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Abstract

Objective. To study the effect of the chimeric monoclonal anti-tumour necrosis factor α (TNF-α) antibody infliximab in the induction of remission in six patients refractory to standard treatment with cyclophosphamide and corticosteroids. In four patients, other measures for treating refractory Wegener’s granulomatosis (WG) that have been advocated previously, i.e. intensified cyclophosphamide therapy and additional intravenous immunoglobulin, were ineffective.

Methods. Patients received infliximab (3 mg/kg in two patients and 5 mg/kg in four patients) with a 2-week interval after the first administration and 4-week intervals between infusions until remission, in addition to cyclophosphamide and corticosteroids. Vasculitis activity was assessed with the Birmingham Vasculitis Activity Score (BVAS). A standardized interdisciplinary approach was used for the follow-up of specific organ involvement.

Results. Remission was induced in five patients and corticosteroid doses could be tapered. Acute-phase responses (e.g. C-reactive protein) normalized. Titres of c-ANCA (cytoplasmic pattern antineutrophil cytoplasmic antibodies) were no longer detectable. The BVAS was reduced to zero. The higher dose of infliximab (5 mg/kg) seemed more effective in inducing remission. One patient was withdrawn because of suspected systemic infection. Five patients remained in remission for 6–24 months of follow-up.

Conclusion. The data suggest that infliximab may provide an effective and more specific therapeutic option in the treatment of active WG refractory to standard treatment.

Key words: Wegener’s granulomatosis, Treatment, Infliximab.

Wegener’s granulomatosis (WG) is an autoimmune disease of unknown origin characterized by granulomatous lesions and small-vessel vasculitis. Any organ may be affected, but pulmonary–renal syndrome is common [1, 2]. Treatment with oral cyclophosphamide (2 mg/kg per day) and corticosteroid (prednisolone 1 mg/kg per day with subsequent tapering of the dose) is still the mainstay and standard therapy for the induction of remission in WG with immediately life-threatening disease [2–5]. However, using this protocol, WG is not controlled in about 10% of patients [4, 5]. So-called intensified cyclophosphamide therapy (3–4 mg/kg per day), intravenous high-dose immunoglobulin therapy, anti-thymocyte globulin and humanized monoclonal anti-CD52 and anti-CD4 antibodies have been used in WG refractory to standard therapy. However, the benefit of these therapeutic options has not been unequivocal and there is considerable concern about side-effects [5, 6].

Blockade of tumour necrosis factor α (TNF-α)-mediated action is efficient in the treatment of various chronic inflammatory disorders, e.g. rheumatoid arthritis [7]. TNF-α plays an important role in granuloma formation and the induction of vasculitis in WG, as demonstrated by several clinical and in vitro studies [8–15]. On the basis of experimental findings and the clinical observation that TNF-α blockade by a soluble TNF-α receptor (etanercept) was well-tolerated in two phase I/II trials for non-life-threatening conditions as well as acute flares in WG [16, 17], we induced TNF-α blockade with the chimeric monoclonal anti-TNF-α antibody infliximab in six WG patients with treatment-refractory disease states.

Patients and methods

All patients fulfilled the Chapel Hill Consensus conference (CHC) definition [1] and the ACR criteria [18] for WG. WG was biopsy-proven in all patients.
TABLE 1. Manifestations of refractory WG and therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year of diagnosis</th>
<th>Biopsy from</th>
<th>Therapy before relapsea</th>
<th>Therapy before infliximab</th>
<th>Therapy before after infliximab</th>
<th>Main manifestations refractory to standard CYC/CS</th>
<th>Additional infiximab boluses</th>
<th>Status on follow-up (January 2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1981</td>
<td>K</td>
<td>MTX/CS</td>
<td>CYC³/CS</td>
<td>32/0</td>
<td>Imminent visual loss due to retro-orbital granuloma</td>
<td>6</td>
<td>Remission for 12 months (AZA)</td>
</tr>
<tr>
<td>2</td>
<td>1990</td>
<td>E</td>
<td>CYC³/CS</td>
<td>CYC³/CS</td>
<td>Ø²</td>
<td>Imminent visual loss due to retro-orbital granuloma</td>
<td>6</td>
<td>Remission for 6 months (MTX)</td>
</tr>
<tr>
<td>3</td>
<td>1993</td>
<td>E</td>
<td>MTX/CS</td>
<td>CYC³/CS</td>
<td>256/0</td>
<td>Rapidly progressive glomerulonephritis</td>
<td>3</td>
<td>Infliximab discontinued (infection?)</td>
</tr>
<tr>
<td>4</td>
<td>New</td>
<td>K</td>
<td>Ø²</td>
<td>CYC³/CS</td>
<td>1024/0</td>
<td>Rapidly progressive glomerulonephritis</td>
<td>4</td>
<td>Remission for 12 months (MMF)</td>
</tr>
<tr>
<td>5</td>
<td>1998</td>
<td>E</td>
<td>MTX/CS</td>
<td>CYC³/CS</td>
<td>512/0</td>
<td>Cavitating pulmonary nodules</td>
<td>4</td>
<td>Remission for 24 months (LEF)</td>
</tr>
<tr>
<td>6</td>
<td>1995</td>
<td>L</td>
<td>IVIG/LEF/CS</td>
<td>CYC³/CS</td>
<td>Ø²</td>
<td>Cavitating pulmonary nodules</td>
<td>4</td>
<td>Remission for 12 months (AZA)</td>
</tr>
</tbody>
</table>

E, ear, nose and/or throat; K, kidney; L, lung; CYC, cyclophosphamide; CS, corticosteroids; AZA, azathioprine; MTX, methotrexate; LEF, leflunomide; MMF, mycophenolate mofetil; Ø², no therapy; CYC³, intensification of cyclophosphamide therapy (see text); IVIG, intravenous immunoglobulin; c-ANCA, cytoplasmic pattern ANCA detected by immunofluorescence technique; Ø², no ANCA detected by immunofluorescence technique and no PR3 ANCA or ANCA against other target antigens in ELISA.

aUsing conventional doses as described previously [3–6].
bBVAS.1 represents new or worse disease activity (maximal score 63).

(1 Table 1). Patients were followed during their frequent hospital stays when WG was active, and then at regular intervals of 4–12 weeks as out-patients when remission was achieved. Vasculitis activity was assessed with the Birmingham Vasculitis Activity Score (BVAS), which is a validated instrument developed by the European Vasculitis Study Group (EUVAS) for the follow-up of disease activity in WG [6, 19] and is used routinely at our centre [3]. In brief, the BVAS considers a variety of clinical features and laboratory data to give a measure of vasculitis activity [6, 19]. BVAS.1 indicates new or worse activity and BVAS.2 indicates ongoing disease [6]. Laboratory assessment [including analysis of antineutrophil cytoplasmic antibodies (ANCA)], follow-up of organ-specific involvement, e.g. by chest radiographs, high-resolution computed tomography, bronchoalveolar lavage, MRI of the head for sinus, orbital and cerebral involvement and regularly held interdisciplinary conferences with specialists from other fields at our institution have been outlined previously [2, 3, 20, 21]. Definitions of remission and relapse followed international convention, as described elsewhere [3].

Infliximab (Remicade®; Essex Pharma, Munich, Germany) was administered in addition to standard cyclophosphamide (2 mg/kg p.o. per day) and corticosteroid therapy at a dose of 3 mg/kg in two patients (patients 1 and 3) and at a dose of 5 mg/kg in the other four patients with a 2-week interval after the first administration and 4-week intervals between infusions until remission [i.e. absence of pathological findings, tapering of corticosteroids below 7.5 mg per day (the ‘Cushing threshold’) without flare] had been induced.

Results

Case 1

A 63-yr-old woman had been suffering from WG since 1981. Major organs involved prior to the current relapse included a pulmonary–renal syndrome with pulmonary infiltrations, haemoptysis and rapidly progressive glomerulonephritis. A renal biopsy revealed focal and segmental necrotizing glomerulonephritis. Total visual loss in her left eye was caused by retro-orbital granulomas in 1987. Another relapse with demonstration of retro-orbital granulomas of the right orbit on MRI, eyelid granulomas, new pulmonary infiltrations on the chest radiograph, microscopic haematuria with dysmorphic red blood cells, nasal obstruction and MRI demonstration of sinus involvement occurred in 2000. Whereas haematuria improved, the other symptoms proved to be refractory to standard oral cyclophosphamide and continuous high-dose corticosteroid (>20 mg prednisolone p.o. per day) for 6 months. Intensified cyclophosphamide therapy (increasing the dose to 4 mg/kg over 4 weeks) did not result in improvement and was finally stopped because of leucopenia. Infliximab was then added to the standard therapy in order to prevent blindness from progressive retro-orbital granulomas. After six infusions of infliximab, improvement in ocular motility due to the regression of retro-orbital granulomas was demonstrated by MRI. All other symptoms subsided. The corticosteroid dose could be tapered and maintained at 5 mg per day. Cyclophosphamide and infliximab therapy was stopped. The patient received azathioprine (150 mg p.o. per day) for the maintenance of remission and has remained in remission for 12 months of follow-up.

Case 2

A 53-yr-old man had been suffering from WG with pulmonary infiltrations, nasal obstruction, bloody nasal discharge, episcleritis, arthritis and malaise since 1990. A nasal biopsy disclosed granulomas and vasculitis typical of WG. He had been treated with continuous oral cyclophosphamide and corticosteroid by another institution before he was referred to our centre because...
of a relapse with retro-orbital granulomas (MRI) of the left eye by the end of 2000. In addition, extensive sinus involvement and new malaise were seen. Intensified cyclophosphamide therapy and intermittent intravenous corticosteroid bolus therapy exceeding 100 mg per day over 4 weeks did not result in improvement of disease activity. Progressive retro-orbital granulomatous lesions threatened his left eye. After six infusions of infliximab, an improvement in ocular motility was documented clinically and a regression of retro-orbital granuloma was noted in the MRI. The corticosteroid dose could be tapered to 7.5 mg per day. Therapy with cyclophosphamide and infliximab was stopped and methotrexate has been given since 6 months to maintain remission.

**Case 3**

A 45-yr-old man had had WG with pulmonary–renal syndrome since 1993. A biopsy from his sinus was taken during an operation and disclosed granulomas and vasculitis typical of WG. The disease relapsed in 1999, with proptosis of the eyes due to progressive retro-orbital granulomas, severe destructive sinus involvement and new nephritic sediment. Reinstitution of standard therapy did not improve disease activity over 3 months. Imminent visual loss led to the decision to add infliximab. Infliximab therapy was stopped after three infusions without obvious evidence of regression of retro-orbital granulomas, because of suspected systemic infection, which was not confirmed later. Regression of retro-orbital granulomas was finally achieved after additional treatment options were used, i.e. orbital radiation and high-dose steroid therapy (80–250 mg per day) for 6 months. Cushing syndrome, pneumonia and thrombophlebitis were encountered during this period. Thus, regression of the retro-orbital granulomas could not be attributed to the addition of infliximab alone in this case.

**Case 4**

WG was diagnosed in a 64-yr-old previously healthy man in December 1999. He had renal involvement (nephritic sediment, creatinine 415 μmol/l), bloody nasal discharge, sinus involvement (MRI), arthralgia and malaise. A renal biopsy revealed necrotizing glomerulonephritis with crescents. Standard treatment was started. During the next 9 months the disease course was complicated by persistent renal activity, new sensory peripheral neuropathy, severe inflammatory and renal anaemia, and deep venous thrombosis. Tapering of the corticosteroid dose to 25 mg per day resulted in a new flare of renal activity with a rise in creatinine (from 220 to 330 μmol/l) within 2 weeks, nephritic sediment and new pulmonary infiltrates. Dose escalation of cyclophosphamide was soon stopped and the patient continued on a lower dose of cyclophosphamide thereafter, due to leucopenia at higher cyclophosphamide doses. Infliximab was added to the standard therapy. Pulmonary infiltrations resolved and renal function was preserved. The creatinine level remained at 200 μmol/l due to renal damage. The corticosteroid dose could be tapered to 5 mg per day. The patient received mycophenolate mofetil for the maintenance of remission because he did not tolerate azathioprine (leucopenia). He has remained in remission for 12 months.

**Case 5**

WG with pulmonary–renal syndrome and polyneuropathy were diagnosed in a 59-yr-old previously healthy man at the end of 1998. A nasal biopsy disclosed granulomas typical of WG. A renal relapse was not controlled by the standard therapy over 4 months at the end of 1999. Deteriorating renal function (rise in creatinine from 115 to 270 μmol/l and nephritic sediment), new fever and arthritis were also not controlled by intensified cyclophosphamide therapy for 4 weeks. After four infusions of infliximab, remission was achieved. Corticosteroids could be tapered from 40 to 5 mg/day. The patient was treated with leflunomide for the maintenance of remission. He has remained in remission for 24 months.

**Case 6**

Weight loss, night sweating, malaise, persistent cough and pulmonary infiltrations as well as nodules brought a 47-yr-old man to medical attention in 1995. An open-lung biopsy disclosed necrotizing granulomas and pauci-immune small-vessel vasculitis typical of WG. Relapse with pulmonary nodules, a rise in creatinine from 90 to 140 μmol/l and cutaneous nodules occurred in 1998. The patient was treated with oral cyclophosphamide and corticosteroid. During the following year, the corticosteroid dose could not be reduced below 20 mg prednisolone per day and the patient underwent repeated partial pneumectomy because of cavitation of granulomas resulting in massive pseudocaverns, and in order to exclude underlying malignancy. Addition of high-dose intravenous immunoglobulin therapy to the standard therapy did not result in sustained remission. After 3 months of leflunomide therapy for maintenance of partial remission, another relapse occurred in April 2000, with persistent cough, dyspnoea, haemoptysis, new pulmonary nodules, malaise and arthralgia. The patient was treated again with oral cyclophosphamide and corticosteroid for more than 2 months, but symptoms remained refractory. Four additional infliximab infusions resulted in complete resolution of pulmonary nodules (Fig. 1) and all other symptoms. The corticosteroid dose could be tapered to 5 mg per day. Cyclophosphamide was stopped and the patient has remained in complete and stable remission with 150 mg azathioprine p.o. per day for 12 months of follow-up.

**Discussion**

Remission was induced by the addition of infliximab to standard therapy in five of six patients with refractory WG. The dose of infliximab was chosen according to treatment recommendations from previous studies in rheumatoid arthritis [7]. It was our impression that
the higher dose of infliximab (5 mg/kg) seemed more effective. The reported data mean there is a promising new therapeutic option for a devastating situation. Because granuloma formation and the development of vasculitis are sustained by Th1-like cytokines and TNF-α, disruption of this process by targeting TNF-α may explain the response to infliximab and point to a central role of TNF-α in the pathogenesis of WG.

We encountered no serious side-effects in this small group of patients, but infections have to be surveyed carefully because re-activation of tuberculosis and other infectious problems have become apparent with TNF-α blockade [7]. Indeed, one patient was withdrawn because of suspected infection. However, the potentially organ- and life-threatening situation of the patients and the limited efficacy and side-effects of previously advocated therapeutic options for the treatment of refractory WG [5, 6] have to be weighed against the possible side-effects of infliximab. Four of our six patients received previously advocated treatment options, i.e.

intensified cyclophosphamide therapy or intravenous high-dose immunoglobulin therapy, but did not respond to them. Failure to respond to the standard therapy within a reasonable time (3–6 months, a period within which induction of remission is usually encountered in WG [5, 6]) and failure to respond to other previously advocated therapeutic options (in four of the six patients) led to the decision to begin therapy with infliximab. With the use of infliximab, corticosteroid doses were tapered successfully in all five cases responsive to infliximab. BVAS.1 and BVAS.2 were reduced to zero in all five cases. In addition, the c-ANCA titre dropped to zero in all cases in which c-ANCA had been positive at the start of treatment. Remission was seen in four of the patients; these patients were switched to maintenance therapy for 6–24 months.

This is the first report of successful therapy of WG refractory to standard cyclophosphamide/corticosteroid therapy with the chimeric monoclonal anti-TNF-α antibody infliximab. On the basis of our preliminary findings, our group is preparing a controlled study of infliximab in refractory WG.

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References


Fig. 1. Chest radiographs of patient 6. (a) Before therapy with infliximab, a 5×6 cm opacity appeared in close proximity to the left central bronchus. (b) After successful infliximab therapy, the lesion, suggestive of a large, partially cavitating granuloma, was no longer apparent.


