Infliximab or rituximab for refractory Wegener’s granulomatosis: long-term follow-up.
A prospective randomised multicentre study on 17 patients

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ABSTRACT

Objectives. To compare efficacy and tolerance of infliximab versus rituximab in patients with systemic WG refractory to, or intolerant to steroids and conservative immunosuppressant lines, including oral cyclophosphamide, who were randomly assigned to receive infliximab or rituximab and their ongoing remission. The primary endpoint was partial (PR) or complete remission (CR) at month 12. The secondary endpoint was the occurrence of adverse events. Long-term follow-up data were subjected to post-hoc analysis.

Results. Between 2004 and 2007, 9 infliximab and 8 rituximab patients were included. At M12, we observed 2 infliximab and 4 rituximab CR, 1 infliximab and 1 rituximab PR, 5 infliximab and 2 rituximab failures and 2 deaths (NS). Post-hoc analysis was conducted after 30.6±15.4 months of follow-up. Among the 15 survivors, 2 infliximab patients and 1 rituximab patient relapsed. Among 5 infliximab non-responders, 4 were successfully switched to rituximab. During follow-up, one patient from each group died. Over the long term, 10/17 (59%) patients responded to rituximab, 1 to infliximab, 2 to other strategies and 2 died. Despite the 2 deaths, tolerance of both drugs was considered acceptable in terms of WG severity before treatment and previous treatment lines.

Conclusions. Our observations demonstrate the usefulness of infliximab and/or rituximab to obtain remission of refractory WG with a trend at M12 favouring rituximab. During long-term follow-up, rituximab was better able to obtaining and maintaining remission.

Introduction

Wegener’s granulomatosis (WG) is a systemic antineutrophil-cytoplasm antibody (ANCA)-associated vasculitis, histologically characterised by small-vessel vasculitis and granulomas. Cyclophosphamide (CYC) and corticosteroids (CS) are the mainstay induction therapy, and most patients enter complete remission (CR). However, in all large series (1-4), half the patients relapsed during follow-up, during or after completing maintenance therapy. Induction therapy with intravenous (IV) CYC has been shown to be as effective as oral administration (5-7) and, because of its better safety profile, pulse CYC is prescribed for patients with refractory WG or with several lines of cytotoxic agents. Alternative treatments e.g. infliximab, an anti-tumour necrosis factor (TNF-α) recombinant monoclonal antibody or rituximab, a recombinant anti-CD20 monoclonal antibody targeting to CD20 lymphocytes, have been prescribed as rescue therapies to small series of patients, with encouraging results (9-14). Because negative observations have also been reported (15), the place of these therapies remains unclear.

This prospective randomised trial was undertaken to compare infliximab versus rituximab as an add-on treatment for patients with refractory WG or with contraindications for CYC.

Patients and methods

Patients were recruited through the French Vasculitis Study Group (FVSG) in several French hospitals between June 2004 and June 2007. All had WG deemed refractory. WG responded to
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the criteria defined by the Chapel Hill Nomenclature (16). Refractory Wegener’s granulomatosis was defined when clinical manifestations remained present or when patients flared despite optimal treatment. To be included, all patients had to have failed to respond to steroids and several immunosuppressants, prescribed alone or in combination. Among immunosuppressants, patients needed to have received at least pulses and then oral cyclophosphamide. One patient presented cytopenia to cyclophosphamide and was included in the study after failure of several other cytotoxic agents.

Before considering refractory disease, a complete evaluation was made, comprising ear-nose-&-throat (ENT) and lung CT scan, biological and immunological investigations, renal function, urine analysis, ENT consultation or other specialised consultation if needed.

After inclusion, patients were randomly assigned to receive either infliximab or rituximab, in addition to CS and immunosuppressant. The ongoing immunosuppressive regimen at inclusion, including CS, was maintained for 4 weeks, and then could be tapered or switched to another less intense immunosuppressant. Once remission was obtained, CS was tapered progressively until the lowest dose of CS was obtained. In case of severe flare-up, CS could be increased for 4 weeks; thereafter, it was compulsory to return to the dose taken before randomisation. Mycobacterial infection was sought before starting infliximab, and all patients had a tuberculin dermal test and chest radiography, in accordance with French guidelines (17).

The initial IV dose of infliximab (3 mg/kg) was administered intravenously on days 1 and 14, before the response was assessed on day 42. The initial dose was required by the French Drug Agency. When a CR was obtained, that dose was maintained for the next 6 months. When a partial remission (PR) or the absence of a response was observed, the dose was increased to 5 mg/kg, and the therapeutic response was re-evaluated 4 weeks later, on day 73. If a CR was obtained, the dose was kept unchanged for the rest of the year (14 infusions). In the absence of a response on day 73, infliximab was stopped.

Rituximab was given IV (0.375g/m²) on days 1, 8, 15 and 22. When a PR or CR was observed at month 2, the same dose was maintained for subsequent infusions at months 4, 8 and 12. When no response was observed at month 2, rituximab was stopped. Treatments are reported in Figure 1.

When the assigned treatment arm failed, patients were withdrawn from the study and other treatments were prescribed. After stopping infliximab or rituximab, the treating physician was free to choose another treatment. The primary outcome criterion was the number of PR or CR obtained at month 12. The secondary outcome measures were treatment tolerance and side effects. A post-hoc analysis of long-term follow-up data was conducted. At each visit, a physical examination was performed and the Birmingham vasculitis activity score (BVAS) was calculated (18). CR was defined as the absence of active vasculitis manifestations (BVAS=0); PR was defined as partial regression of the clinical manifestations and a BVAS decreased of >50%.

Failure was defined as the absence of WG attenuation or appearance of new clinical manifestations. At month 12 after inclusion, all patients had lung and ear-nose-&-throat (ENT) computed-tomography (CT) scans. Every patient’s serum was tested for the presence of ANCA by immunofluorescence (IF) according to the recommendations of the European Vasculitis Study Group (EC/BCR study) (19), using sera diluted by 1/16 and ethanol-fixed neutrophils. The IF assay was completed by enzyme-linked immunosorbent assay (ELISA) for patients with IF-detected ANCA. ANCA were sought at diagnosis and inclusion, and then monitored regularly during follow-up. Patients were questioned about any adverse events at each visit. These adverse events were classified according to the World Health Organisation classification (2003): severe for fatal or life-threatening events; moderate for events requiring treatment, medical procedure or hospitalisation; mild for symptoms requiring only drug discontinuation, and incidental for very mild
symptoms that did not contraindicated continuing therapy.

The protocol was approved by the Ethics Committee of Hôpital Cochin (Comité de Protection des Personnes), and each patient gave written informed consent to participate before inclusion.

Statistical analysis
The analysis was made according to the intention to treat. After the protocol’s censoring date (12 months), outcomes and late side effects were collected and a post-protocol analysis was conducted to evaluate the long-term effectiveness of the therapeutic strategy. To compare treatments groups, non parametric tests (Mann-Whitney) were used. For categorical variables, a χ² test, with Yate’s correction was applied when necessary. Statistical significance was defined as for p<0.05. Survival curves were obtained with the Kaplan-Meier method (20).

Results
Characteristics at inclusion
Between June 2004 and June 2007, 22 WG patients were screened. One patient was excluded after randomisation (rituximab group) because, due to pneumocystis jiroveci pneumonia, he did not receive rituximab and his data were not analysed. Four other patients did not meet the inclusion criteria. Ultimately, 17 cases were included in the final analysis; 8 were given rituximab and 9 received infliximab. The patients’ clinical characteristics at inclusion and outcomes are reported in Table I. Clinical characteristics, disease duration and mean BVAS at inclusion were comparable for the two groups. At WG diagnosis, 15/17 (88%) patients were ANCA-positive in IF (14 c-ANCA and 1 p-ANCA; 7 were given infliximab and 8 received rituximab), with 12 anti-proteinase 3 (PR3), 1 anti-myeloperoxidase (MPO) and 2 with no specificity in ELISA. At inclusion, 13/17 (76%) patients were ANCA-positive in IF (12 c-ANCA and 1 p-ANCA; 6 assigned to infliximab and 7 to rituximab), with 10 anti-PR3 and 3 with no specificity in ELISA. Ongoing immunosuppressive regimens at inclusion are also summarised in Table I. All but patient 15 were taking CS at inclusion, with mean±SD doses of 19.4±11.8 mg/day for the infliximab group and 41.4±28 mg/day for the rituximab group (p=0.34). Infliximab-group patients 6, 11 and 16 and rituximab-group patient 9 did not receive oral CYC after IV-CYC failure because of cytopenia (patient 6), haemorrhagic cystitis (patient 16) and high cumulated doses of CYC (patients 9 and 11, with 115 g and 45 g, respectively).

Outcome at month 12 (censoring date)
For the 9 infliximab-group patients, no CR was obtained on day 42, after two 3mg/kg infusions, and the dose was switched to 5mg/kg for all of them. Only patients 11, 16 and 17 (33%) received the 14 infusions scheduled in the protocol. Among them, patients 11 and 17 achieved CR (BVAS=0) and were asymptomatic, with complete disappearance of pulmonary nodules. Patient 17 also had persistent proteinuria, considered a sequela. Patient 16 had a PR (BVAS=1), with persistent moderate conductive hearing loss attributed to serous otitis media. The other 6 (66%) patients stopped infliximab before the end of the study. Patient 13 died of invasive aspergillosis 60 days after the first infusion. The 5 other patients had progressive disease characterised by fever and inflammation in 2 of them, persistent ENT inflammation (rhinitis or sinusitis) in 2, progression of lung nodules in 3, and progression of renal insufficiency in 1. Patients 4, 12 and 20 improved after 2 months, but relapsed between the months 4 and 6 after starting therapy. No clinical manifestation at WG onset was identified as responding better to infliximab.

At month 12, among the 6 ANCA-positive patients at inclusion, patients 6, 11 and 20 remained c-ANCA-positive (anti-PR3), and 2 had progressive disease (patients 6 and 20); patients 4, 12 and 16 became ANCA-negative, patient 16 achieved PR. Patient 13 was not tested for ANCA before she died. Patient 11, ANCA-negative at inclusion, became anti-PR3 positive despite being in CR. Patients 17 and 21 remained ANCA-negative throughout the study, the former achieved CR, and the latter had progressive disease.

At the censoring date versus inclusion, the mean BVAS was 7.5±7.7 vs. 13.1±5.5 (p=0.09); the mean CS dose was 15.2±14.8 vs. 19.4±11.84 mg/day (p=0.28). Patients 11, 16 and 17 who completed the study protocol also received immunosuppressants at inclusion: azathioprine for 1, azathioprine plus methotrexate for 1 and oral CYC for 1. Infliximab allowed immunosuppressant sparing only in patient 17, whose oral CYC could be switched to mycophenolate mofetil (MMF). Patients 11 and 16 were still on the same immunosuppressants drugs at month 12 as at inclusion.

General tolerance was good for 6 patients; patients 11 and 20 developed incidental or mild allergic reactions during infliximab infusion: facial erythema during the 12th infusion that did not recur during the next 2 infusions for patient 11, and transient bronchospasm during the 7th infusion for patient 20 that required infliximab withdrawal. Patient 13, who died of invasive aspergillosis at month 2, was noted as a severe adverse event.

Among the 8 rituximab-group patients, 5 completed the 7 planned infusions. Patients 8, 9, 15 and 18 obtained CR, and patient 10 a PR. Patients 8, 9 and 15 were clinically asymptomatic but had persistent albeit less prominent abnormalities on CT scans: chronic sinusitis or pulmonary nodules that did not regress fully. Patient 18 had persistent proteinuria and sensory peripheral neuropathy, which were considered sequelae. Patient 10 achieved a PR, but a new lung nodule <5mm was seen on the CT scan at month 12 (BVAS=10 at inclusion and 3 at outcome). Three patients did not complete the study: patient 22 succumbed to sudden death at home after the 4th infusion on day 23; patients 2 and 14 had disease progression at month 2: aggravation of bronchial stenosis and progression of inflammatory retro-ocular lesion, respectively.

At 12 months, patients 10 and 15 remained c-ANCA-positive (no specificity in ELISA and anti-PR3, respectively) despite respective PR and CR. Patients 8, 9 and 18 achieved CR and became ANCA-negative, and patient 2 remained ANCA-negative throughout.
### Table I. Clinical characteristics and outcomes of infliximab- or rituximab-treated patients with refractory WG.

<table>
<thead>
<tr>
<th>n.</th>
<th>Sex/age (years)</th>
<th>Clinical manifestations at diagnosis</th>
<th>At inclusion</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab-treated patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F/54</td>
<td>PGC, ENT, lung nodules</td>
<td>PD</td>
<td>CS + oral CYC</td>
<td>PD</td>
</tr>
<tr>
<td>6</td>
<td>F/56</td>
<td>PGC, ENT, RPGN, lung nodules, purpura, arthralgias</td>
<td>PD &amp; CYC intolerance (Cr: 144 μmol/l)</td>
<td>CS + CMX</td>
<td>PD</td>
</tr>
<tr>
<td>11</td>
<td>F/58</td>
<td>ENT, RPGN, lung nodules, scleritis, mononeuritis multiplex</td>
<td>PD &amp; CYC HDC (45 g)</td>
<td>CS + oral CYC</td>
<td>CR</td>
</tr>
<tr>
<td>12</td>
<td>F/67</td>
<td>PGC, lung nodules, mononeuritis multiplex, arthralgias</td>
<td>PD</td>
<td>CS + oral CYC</td>
<td>PD</td>
</tr>
<tr>
<td>13</td>
<td>F/56</td>
<td>PGC, ENT, lung nodules, RPGN</td>
<td>PD</td>
<td>CS + oral CYC</td>
<td>Died day 15</td>
</tr>
<tr>
<td>16</td>
<td>F/24</td>
<td>ENT, lung nodules, scleritis</td>
<td>PD &amp; CYC intolerance</td>
<td>CS + oral CYC</td>
<td>PR</td>
</tr>
<tr>
<td>17</td>
<td>M/27</td>
<td>ENT, RPGN, lung nodules, scleritis, arthralgias, purpura</td>
<td>PD</td>
<td>CS + oral CYC</td>
<td>PD</td>
</tr>
<tr>
<td>20</td>
<td>F/58</td>
<td>PGC, ENT, lung nodules</td>
<td>PD</td>
<td>CS + oral CYC</td>
<td>PD</td>
</tr>
<tr>
<td>21</td>
<td>F/76</td>
<td>ENT, lung nodules, mononeuritis multiplex</td>
<td>PD</td>
<td>CS + oral CYC</td>
<td>PD</td>
</tr>
<tr>
<td><strong>Rituximab-treated patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M/34</td>
<td>PGC, ENT, tracheal stenosis</td>
<td>PD</td>
<td>CS + IV CYC + MTX</td>
<td>PD</td>
</tr>
<tr>
<td>8</td>
<td>M/29</td>
<td>PGC, lung nodules</td>
<td>PD</td>
<td>CS + IV CYC + MTX</td>
<td>CR</td>
</tr>
<tr>
<td>9</td>
<td>M/57</td>
<td>lung nodules, pericarditis, arthralgias, purpura, orchitis</td>
<td>PD &amp; CYC HDC (&gt;115 g)</td>
<td>CS + CMX</td>
<td>CR</td>
</tr>
<tr>
<td>10</td>
<td>M/53</td>
<td>PGC, ENT, lung nodules, arthralgias</td>
<td>PD</td>
<td>CS + oral CYC</td>
<td>PR</td>
</tr>
</tbody>
</table>

**Note:** Duration of disease (months) ± SD.

**ANCA:** Anti-neutrophil cytoplasmic antibody

**BVAS:** British arterial vasculitis severity index

**CS:** Corticosteroids

**IF:** Immunofluorescence

**PR:** Partial remission

**PD:** Placebo

**MTX:** Methotrexate

**CMX:** Cyclophosphamide

**AZA:** Azathioprine

**HDC:** High dose cyclophosphamide

**M:** Months

**CR:** Complete remission

**ND:** Not determined

**ELISA:** Enzyme-linked immunosorbent assay
the study despite disease progression; patients 10 and 14 were not tested. At month 12 versus inclusion, the mean BV AS was significantly reduced: 3.4 ± 5.0 vs. 12.6 ± 7 (p=0.03); but the mean CS dose, despite being reduced (respectively 18.9 ± 18.7 vs. 41.4 ± 28.0 mg/day; p=0.17) was comparable. Among the 5 patients who completed the protocol, 4 patients were on oral (n=3) or IV (n=1) CYC at inclusion, and patient 9 was taking methotrexate. Rituximab generally allowed immunosuppressant sparing, since patients 8, 10, 15, 18 could be switched from CYC to less mild immunosuppressants: azathioprine for 2, mycophenolate mofetil for 1, or methotrexate for 1. No allergic reactions were noted. No severe infections (bronchitis, dental abscess) were observed in 3 patients. Patient 22 died suddenly on day 23; no autopsy was performed and no obvious explanation was found.

**Comparison of treatment groups**

At month 12, the number of CR or PR, and side effects did not differ significantly between the two groups. Despite this, rituximab patients generally had less severe side effects, with only 1 patient experiencing severe allergic symptoms leading to treatment withdrawal.

### Clinical manifestations at Diagnosis

<table>
<thead>
<tr>
<th>n.</th>
<th>Sex/ age (years)</th>
<th>Diagnosis</th>
<th>Inclusion</th>
<th>Reason for inclusion</th>
<th>WG duration (months)</th>
<th>ANCA IF/ ELISA</th>
<th>BVAS</th>
<th>Treatment</th>
<th>At inclusion</th>
<th>During protocol</th>
<th>Date</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>F/70</td>
<td>ENT, tracheal stenosis, subcutaneous nodules, retrocular pseudotumour</td>
<td>PD</td>
<td></td>
<td>68</td>
<td>c-ANCA/ anti-PR3</td>
<td>21</td>
<td>CS + oral CYC</td>
<td>PD</td>
<td>ND</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>M/66</td>
<td>PGC, ENT, arthralgias, purpura</td>
<td>PD</td>
<td></td>
<td>127</td>
<td>c-ANCA/ anti-PR3</td>
<td>8</td>
<td>oral CYC</td>
<td>CR</td>
<td>M12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>M/59</td>
<td>PGC, lung nodules, RPGN, mononeuritis multiplex arthralgias</td>
<td>PD</td>
<td></td>
<td>49</td>
<td>c-ANCA/ anti-PR3</td>
<td>26</td>
<td>CS + oral CYC + PE</td>
<td>CR</td>
<td>M12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>M/43</td>
<td>PGC, lung nodules, mononeuritis multiplex</td>
<td>PD</td>
<td></td>
<td>16</td>
<td>c-ANCA/ anti-PR3</td>
<td>15</td>
<td>CS + oral CYC</td>
<td>Died</td>
<td>day 23</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Severe allergic side effect leading to treatment withdrawal. PGC: poor general condition; ENT: ear, nose & throat involvement; RPGN: rapidly progressive glomerulonephritis; PD: progressive disease; CS: corticosteroids; CYC: cyclophosphamide; AZA: azathioprine; PE: plasma exchange; MTX: methotrexate; MMF: mycophenolate mofetil; IFX: infliximab; RTX: rituximab; CMX: Co-trimoxazole; HCD: high cumulated doses; PR: partial remission; CR: complete remission; ND: not done; M: month; maSD: mean ± standard deviation.

![Fig. 2. Kaplan-Meier curves of the probabilities of (A) event-free survival (EFS) and (B) relapse-free survival (RFS) after starting infliximab (IFX) or rituximab (RTX). M = month.](image-url)
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Significantly between groups. However, BVAS declined significantly only for the rituximab group. Although not significant, combined treatments were better tapered for the rituximab group. For both groups, the evolution of ANCA status did not always correspond to parallel clinical outcomes. Event-free and relapse-free survival rates are presented in Figure 2.

Long-term follow-up data was available for all patients, and mean follow-up was 30.6±15.4 months (28.9±15.4 months for the infliximab group and 32.9±16.7 months for the rituximab group) and subjected to post-hoc analysis.

For the infliximab group, among the 3 patients who achieved CR, only patient 11 remains in persistent remission under maintenance therapy with CS (10 mg/day) and mycofenolate mofetil (2 g/day), which was started on day 73 of the protocol to replace CYC, whereas patients 11 and 16 relapsed 2 and 14 months after stopping infliximab, respectively. Infliximab was again prescribed to patient 16, who developed new pulmonary nodules; she was then switched to adalimumab because of an infliximab-related skin rash. Adalimumab was ineffective and, finally, a new CR was obtained with rituximab. Patient 11 achieved CR with higher doses of CS and azathioprine. Four of the 5 (80%) patients (4, 6, 20 and 21) who failed on infliximab were successfully switched to rituximab, with persistent CR in patient 4, 6 and 21. Patient 20 finally relapsed 19 months after switching to rituximab. This patient developed bronchial stenosis and was ultimately treated successfully with methotrexate. Lastly, patient 12, who failed under infliximab and received high-dose CS and azathioprine, finally progressed to end-stage renal failure after short-term stabilisation and died of multiorgan failure 2 years later.

Patient 16 developed hepatitis subsequent to cytomegalovirus primary-infection, 9 months after the end of the protocol, under maintenance therapy with CS (5 mg prednisone), methotrexate (7.5 mg/week) and azathioprine (100 mg/day). Hepatitis resolved with antiviral therapy and withdrawal of azathioprine and methotrexate. No malignancy was observed in this group.

For the rituximab group, among the 5 patients who achieved CR or PR, patients 8, 10 and 15 are still in persistent remission, on maintenance regimens comprising low-dose CS plus methotrexate, mycofenolate mofetil or azathioprine. Patient 18 relapsed 16 months after the last rituximab infusion while on maintenance therapy with CS (7 mg) and azathioprine (150 mg/day). He once again entered CR with combined high-dose CS (1 mg/kg/day), oral CYC (2 mg/kg/day), and a new cycle of rituximab (1g days 1 and 15) and remains in CR under maintenance CS (5 mg/day) and methotrexate (15mg/week, introduced 6 months after relapse, after stopping oral CYC). Pancreatic carcinoma was diagnosed 2 months after the last infusion of rituximab in patient 9 who died 3 months later. Two survivors, despite the therapeutic failure of rituximab, were switched to IV immunoglobulins and CS and oral CYC and CS for patients 2 and 14, respectively, but their WG remained poorly controlled; they are still considered to have grumbling disease. Patient 15 was diagnosed with prostate carcinoma 27 months after the last rituximab infusion. No infectious side effect was noted in this group.

At the end of the follow-up period, independently of the assignment by randomisation, and considering treatments prescribed after biologic failure, prolonged CR or PR was obtained in...
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1 patient treated with infliximab, 9 patients treated with rituximab, 3 with other immunosuppressants combined with CS, and 2 died. Clinical outcomes are summarised in Figure 3.

Discussion

Treatment of WG relapses is especially difficult when they are multiple and refractory to cytotoxic agents, including oral CYC combined with CS, despite high doses, which can be responsible for cytopenia and major side effects. Biotherapies have often been proposed for these patients as an adjunctive therapy, with promising results for infliximab (9, 12), or rituximab (21-23).

Our study attempted to determine the efficacy of infliximab or rituximab as an add-on agent for patients with WG uncontrolled by cytotoxic drugs and CS. The choice of biotherapy was based on open studies demonstrating a benefit of adding infliximab (9, 12) or rituximab (21-23) to immunosuppressants, especially for patients whose disease failed to respond to the previous strategy (9, 12, 21). Among anti-TNF-α, infliximab was chosen because it induces cell apoptosis and has demonstrated activity against several granulomatous diseases (23). Etanercept, another anti-TNF-α was evaluated in WG patients, (24) but was not superior to methotrexate as a maintenance treatment. The initial infliximab dose was a compulsory requirement from the French Drug Agency, despite the fact that we previously showed that 5 mg/kg was more effective in obtaining a response than 3 mg/kg/infusion. Rituximab effects on granulomatous forms of WG remain controversial: positive for Seo et al. (21) and Martinez del Pero et al. (25) but negative according to Aries et al. (15). When we designed the trial, the infusion schedule was not established for autoimmune diseases, and we followed what was made for lymphoma maintenance treatment.

Based on each molecule mechanism of action, our hypothesis was to expect an infliximab therapeutic effect against granulomatous lesions and a clear regression of vasculitic lesions with rituximab. However, considering each organ involved, the responses obtained did not differ from one organ to another. It was therefore impossible, based on clinical manifestations, to predict the clinical response to each biotherapy.

Our trial results showed that both infliximab and rituximab could achieve CR or PR, in about half of the WG patients: 3/9 with infliximab, and 5/8 with rituximab. At month 12, a trend favouring rituximab was observed, but did not reach statistical differences, partly because of the small number of participating patients. Furthermore, significantly improved BVAS values were observed for the rituximab group, demonstrating its better efficacy. In addition, more CS and immunosuppressant-sparing was obtained in the rituximab group, with an observed trend for tapering CS, and oral CYC could be switched to milder immunosuppressants for all patients.

Although outcome criterion was to compare CR and PR in each group at month 12, the long-term effects of infliximab and rituximab were of major interest. For some patients it was the long-term follow-up of responders, and for others, the results obtained after switching from one drug to another, after failure of the assigned agent. In this regard, the long-term efficacy of infliximab was disappointing, as previously reported (10). Only one patient had a sustained response after censoring. Two patients who had achieved 1 CR and 1 PR under infliximab had relapsed early, 2 and 14 months after the last infusion, respectively, confirming the holding-pattern effect of infliximab (10). In contrast, more prolonged CR were obtained with rituximab, and when infliximab failed to induce remission or when a patient relapsed, rituximab was able to achieve remission for most patients. At the end of follow-up, 9 remissions could be attributed to a therapeutic strategy comprising rituximab versus 1 with infliximab.

Our results are not as good as those previously reported with infliximab (26). Indeed, PR or CR under infliximab was only reached in 33% of our patients, whereas 81% of the reported patients entered remission (26). Most of the latter had improved at 6 weeks, whereas, for 3 of our 9 infliximab-group patients, improvement was observed after 2 months, but was not maintained, with failures at 6 months. These differences are probably explained by our treatment of WG patients who did not respond to CYC and CS or other immunosuppressants prescribed at optimal dose. Moreover, the previously reported population was heterogeneous, including newly treated and refractory WG patients (26). Our findings described herein also included long-term follow-up, unlike most published papers. Some authors obtained promising results with rituximab, prescribed as rescue therapy for patients with refractory WG, (27-29), with a 90–100% remission rate and good tolerance. According those publications, WG relapse rates vary from 10% to 37%, which is comparable to our data. Pertinently, our patients who relapsed after rituximab, could again achieve remission after reintroducing rituximab.

Two of our patients did not respond to rituximab. Both had granulomatous manifestations with tracheal and bronchial stenose in 1 patient, tracheal stenose and an inflammatory retro-ocular lesion in the other. Those manifestations are usually difficult to control, though recent reports described extremely good responses of granulomatous manifestations to rituximab (25, 30). During post-protocol follow-up, 4 patients who had not responded to infliximab, and 1 patient who relapsed after stopping rituximab, achieved CR with rituximab.

In both our treatment groups, the evolution of ANCA status did not always parallel the clinical outcome. It is difficult to draw definitive conclusions concerning this point in light of the small number of participating patients, but this observation seems to agree with what has been recently published (31). Infliximab and rituximab had comparable and acceptable tolerance considering that these patients were already severely immunocompromised at inclusion. Two deaths occurred during the study, one in each group and 2 others during the post-protocol follow-up. Although according to the literature cancers are rare after rituximab exposure (28), 2 of our rituximab-group patients developed cancer during long-term follow-up. All
Two recent studies (33, 34) have demonstrated that rituximab is as effective as cyclophosphamide in inducing remission in first flare of ANCA-associated vasculitides, when prescribed in addition to steroids and cytotoxic agents.

In conclusion, although not reaching significant results, our analysis supports a better response rate with rituximab, and a higher rate of sustained CR, whereas infliximab could be useful in some cases. Future studies are needed to clarify the respective indications of these two agents for the treatment of WG.

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**Key messages**

- In the short term, infliximab and rituximab were both able to induce a remission of refractory and/or severe ANCA-associated vasculitides, when prescribed in addition to steroids and cytotoxic agents.
- In the long term, rituximab was more effective than infliximab in maintaining remission. In addition, when patients failed to respond to infliximab, rituximab was able to induce remission in most cases.

**References**


