Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study

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Abstract

Objective. To analyse the efficacy and tolerance of infliximab in refractory Takayasu arteritis (TA).

Methods. French multicentre retrospective study that included patients with TA. Clinical disease activity was defined as new vascular and/or constitutional signs.

Results. Fifteen patients with TA [median age 41 (range 17–61) years; 13 women] were included. At initiation of infliximab therapy, 14 patients were treated with CSs [prednisone; median dose 20 (range 5–35) mg/day], MTX (n = 7) or AZA (n = 4). Infliximab was used at median 5 (range 3–5) mg/kg at a median of every 6 (range 4–8) weeks. A partial or good overall response was noted in 13 (87%) of the 15 cases, 10 (77%) of the 13 cases and 8 (73%) of the 11 cases at 3, 6 and 12 months, respectively. Clinical and biological activities significantly decreased within 3 months (from 11 at baseline to 4 patients at 12 months; P < 0.05), and similarly for CS dose [from median 20 (range 5–35) mg/day at baseline to median 6 (range 2.5–30) mg/day at 12 months; P < 0.05]. Only one patient was still steroid-dependent at 12 months (vs 8 cases before infliximab). CRP regressed from a median 30 (range 4–70) mg/l to 5 (range 0–57) mg/l and 6 (0–50) mg/l at 3 and 6 months, respectively (P < 0.05). Side effects were two infusion-related reactions, one pulmonary tuberculosis, one severe bacterial infection and EBV reactivation.

Conclusion. This study confirms the interest of infliximab in terms of clinical and biological response, as well as the steroid-sparing effect in TA.

Key words: Takayasu arteritis, treatment, infliximab.

Introduction

Takayasu arteritis (TA) is a large-vessel vasculitis that affects the aorta and its primary branches and may lead to arterial segmental stenosis, occlusion and/or aneurism formation [1]. The symptoms are either non-specific and reflect systemic inflammation or related to vascular injury and induced organ-ischæmia. Even though many patients respond to CSs, relapses or steroid dependence may necessitate the use of combination therapy. AZA (2 mg/kg/day) and MTX (20–25 mg/week) have been used in patients with TA and can induce disease remission and prevent the development of new arterial lesions [2]. The addition of other immunosuppressive agents to steroid therapy may be required in a majority of patients [3].
MRI constitutes an interesting non-invasive approach to assess arterial changes during follow-up [4].

The pathogenesis of TA includes vessel injury mediated by T cells, NK cells, γδT cells and macrophages [5]. T cell and macrophage infiltrates contribute to granuloma and giant cells formation and produce IFN-γ, which stimulates the production of pro-inflammatory cytokines. This secretion of pro-inflammatory cytokines, including TNF-α and IL-6, is implicated in vascular inflammation and injury in TA [6]. The presence of B cells in the inflammatory vascular wall has also been highlighted and could contribute to the immune reaction in TA [7].

In light of these data, several studies have reported the efficacy of TNF-α inhibitors in TA, but only one observational study and a few case reports are available [8–16]. We report a French multicentre study on the efficacy and tolerance of the TNF-α inhibitor infliximab in TA.

**Patients and methods**

**Patients**

Data were collected retrospectively from physicians in charge of the patients. Physicians were asked to complete a standardized questionnaire sent online with the support of the Club Rhumatismes et Inflammation (online at http://www.cri-net.com) and Société Nationale Française de Médecine Interne (SNFMI). All patients fulfilled the ACR or Ishikawa criteria, or both, modified by Sharma [17, 18]. Infliximab was prescribed because of TA refractory to other non-steroid immunosuppressive agents and/or steroid dependence. The patients’ clinical, laboratory and radiological data as well as treatments were analysed at baseline, then at 3, 6 and 12 months and at the last visit. Routine laboratory indicators of disease activity, including haematology profile, ESR, CRP and fibrinogen serum levels were collected.

**Disease activity definition**

Clinical disease activity was considered if the patient presented one of the following features: (i) new onset of carotodynia, pain over other large vessels or new ischaemic vascular claudication; (ii) transient ischaemic episodes not attributed to other factors; (iii) new bruit or asymmetry in pulses or blood pressure; and (iv) systemic features in the absence of infection or other factors. Biological activity was defined if the patient presented two of the following features: (i) ESR > 30 mm/h; (ii) CRP > 10 mg/l; (iii) fibrinogen > 3 g/l; and (iv) leucocyte count > 10 × 10³/mm³ without any infection. Radiological activity was defined as the presence of at least two of the following features: (i) arterial wall thickening at angioscanner; (ii) arterial wall thickening with mural enhancement in MRI; and (iii) arterial hypermetabolism on PET scan. Arterial wall thickening was present before initiation of infliximab therapy at angioscanner in 10/12 cases, arterial wall thickening with mural enhancement at MRI in 5/7 cases and arterial hypermetabolism on PET scan in 6/7 cases. Steroid dependence was defined as prednisone ≥ 20 mg/day before infliximab therapy.

**Assessment of response and tolerance to TNF-α inhibitors**

Infliximab was the TNF-α inhibitor given to all patients, from 3 mg/kg (n = 5) to 5 mg/kg (n = 10), for a median of every 6 (range 4–8) weeks. Response to infliximab was evaluated globally according to the physician in charge of the patient, and separately by the presence of clinical disease and of biological activities at the 3-, 6- and 12-month follow-up visits. Radiological disease activity could not be assessed, as radiological evaluation was not performed in all patients at follow-up.

Adverse events were recorded in a specific questionnaire. Severe infection was defined as any infection with i.v. antibiotic use, hospitalization or infection-related death (WHO definition of adverse effects).

**Statistical analysis**

Data are presented as medians with extreme ranges for continuous variables and frequencies with percentages for qualitative variables. Fisher’s exact test was used to compare qualitative variables and the non-parametric Mann–Whitney U-test or Wilcoxon test for continuous variables as appropriate. A P-value < 0.05 was considered statistically significant. Statistical analyses were carried out using GraphPad Prism version 5.1 (GraphPad Software, San Diego, CA, USA, 2007).

**Results**

**Patient characteristics**

Fifteen patients [median age 41 (range 17–61) years; 13 women] were included in the study. Clinical vascular complaints were present in 6 (40%) cases, neurosensorial symptoms in 4 (27%) cases and systemic features in 8 (53%) cases. Median delay from diagnosis to infliximab treatment was 37 months (range 6–365). Laboratory data and treatments at baseline are shown in Table 1. Disease was active in all 15 patients, with clinical, biological and radiological activities in 11 (73%) of the 15 patients, respectively (all three activities in 6 cases, at least two among the three activities in 9 cases). At initiation of infliximab therapy, 14 patients were treated with steroids [prednisone; median dose 20 (range 5–35) mg/day]. Eight patients were steroid-dependent before infliximab. Fourteen patients had been previously treated with other non-steroid immunosuppressive agents (MTX in 12 cases, AZA in 7 cases, MMF in 2 cases) and 5 (33%) had more than two immunosuppressive agents before infliximab. Eleven patients (73%) were treated with other non-steroid immunosuppressive agents at initiation of infliximab, and these treatments had not been modified in the 3 months before initiating infliximab therapy (Table 1).

**Efficacy of TNF-α inhibitors**

Median follow-up after initiation of infliximab was 43 (range 4–71) months. Overall response as evaluated by the physician was noted in 13 (87%) of the 15 cases, 10 (77%) of the 13 cases and 8 (73%) of the 11 cases at 3,
Table 1 Baseline characteristics and infliximab response in 15 patients with TA during a follow-up period of 12 months

<table>
<thead>
<tr>
<th>Number of evaluable patients</th>
<th>Baseline assessment (n = 15)</th>
<th>3-month evaluation (n = 15)</th>
<th>6-month evaluation (n = 13)</th>
<th>12-month evaluation (n = 11)</th>
</tr>
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<tbody>
<tr>
<td>Clinical response</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Infliximab efficacy (by physician), n (%)</td>
<td>-</td>
<td>13 (87)</td>
<td>10 (77)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Disease clinical activity, n (%)</td>
<td>11 (73)</td>
<td>3 (20)**</td>
<td>4 (31)*</td>
<td>3 (27)*</td>
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<tr>
<td>Infliximab-associated treatments</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CSs (prednisone), n (%)</td>
<td>14 (93)</td>
<td>12 (80)</td>
<td>11 (85)</td>
<td>10 (92)</td>
</tr>
<tr>
<td>CSs (prednisone, mg/day)</td>
<td>20 (5–35)</td>
<td>15 (5–20)**</td>
<td>7.5 (5–18)*</td>
<td>6 (2.5–30)*</td>
</tr>
<tr>
<td>Steroid dependence, n (%)</td>
<td>8 (53)</td>
<td>2 (13)*</td>
<td>0*</td>
<td>1 (9)*</td>
</tr>
<tr>
<td>MTX, n (%)</td>
<td>7 (46)</td>
<td>8 (53)</td>
<td>6 (46)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>MTX, mg/week</td>
<td>15 (7.5–25)</td>
<td>15 (7.5–20)</td>
<td>15 (5–15)</td>
<td>15 (5–20)</td>
</tr>
<tr>
<td>AZA, n (%)</td>
<td>4 (27)</td>
<td>4 (27)</td>
<td>4 (31)</td>
<td>4 (36)</td>
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<tr>
<td>AZA, mg/day</td>
<td>125 (100–175)</td>
<td>125 (100–175)</td>
<td>100 (100–175)</td>
<td>100 (100–175)</td>
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<tr>
<td>Laboratory data</td>
<td></td>
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<tr>
<td>Biological activity, n (%)</td>
<td>11 (75)</td>
<td>4 (27)*</td>
<td>4 (31)**</td>
<td>4 (42)**</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>60 (12–100)</td>
<td>15 (6–32)*</td>
<td>10 (4–64)*</td>
<td>8 (2–60)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>30 (4–70)</td>
<td>5 (0–57)*</td>
<td>6 (0–50)*</td>
<td>9 (0–100)</td>
</tr>
<tr>
<td>Fibrinogen, g/l</td>
<td>5.5 (3–7.5)</td>
<td>3 (1–6.5)*</td>
<td>2.5 (2–6)*</td>
<td>2 (2–4)</td>
</tr>
<tr>
<td>Leucocyte count, 10³/mm³</td>
<td>11 (2.4–20)</td>
<td>6 (3.6–15)*</td>
<td>6 (4.2–15)**</td>
<td>6 (3.8–16)</td>
</tr>
</tbody>
</table>

Values are medians with ranges or frequencies with percentages. Steroid dependence: prednisone ≥ 20 mg/day. Associated treatments were all initiated before infliximab. *P < 0.05 vs baseline, **P < 0.005 vs baseline, ***P = 0.06.

Discussion

We report herein the French multicentre study on infliximab use in TA. In this cohort of TA patients who were refractory to other immunosuppressive agents with > 20 mg prednisone daily, infliximab enabled a significant improvement in both clinical and biological features, in addition to having a steroid-sparing effect.

Indeed, overall efficacy was noted in nearly 80% of our patients, and infliximab allowed a significant decrease in clinical and biological disease activity, and in CS dosage. Defining disease activity and correlating clinical activity with laboratory data is challenging in TA, and there are currently no consensual indicators for disease activity. Moreover, it is well established that clinical disease activity is not always correlated with routine inflammatory markers in TA. Considering the difficulty in assessing disease activity and therefore treatment response, disease activity was evaluated separately in this study with regard to clinical, radiological and biological features, as well as steroid-sparing effects. Infliximab was found to be effective in all the parameters reflecting disease activity.

Our data confirm previous reports on the efficacy of TNF-α inhibitors in refractory TA [8–16]. In reviewing the 32 cases reported in the available literature, infliximab was used most, with the majority of patients having been treated beforehand with other immunosuppressive drugs (Table 2) [8–16]. In the only prospective study of 15 patients with refractory TA, remission was achieved in 67%, with a steroid-sparing effect in 14 patients [8]. As in previous reports, TNF-α inhibitors were effective even
in refractory patients, since 75% of our patients were on other non-steroid immunosuppressive agents before TNF-α inhibitors. Furthermore, early response was notable, since clinical, biological remission and CS-sparing were achieved within 3 months in our refractory TA patients. With a median duration of treatment of 17 months, our study confirms the long-term duration of remission, similar to another previous report [12]. Infliximab doses were variable in our study, from 3 to 5 mg/kg, as there are no current guidelines for TNF-α inhibitors in TA, although dosages used were similar to those reported in the literature (Table 2). Adverse effects in our study were similar to those usually reported with TNF-α inhibitors, such as infusion reactions and pulmonary tuberculosis.

Although this is a retrospective and observational study, its multicentre design and the participation of French centres involved in the treatment of orphan diseases allows us to favourably conclude as to the efficacy of infliximab in TA. However, some imaging parameters, such as wall thickness or fluoro-2-deoxyglucose (FDG) uptake are not well-established surrogates of active disease and we could not analyse the absence of new radiological lesions in follow-up under infliximab. The presence of leucocytosis in TA is not a proven reliable marker of activity, since it could be explained by other factors, such as CS use. Even clinical and biological efficacies were noted with infliximab; in most patients, steroids and other associated immunosuppressive agents were not tapered during follow-up. On the other hand, the importance of constitutional symptoms, acute-phase response, as well as the effect of immunosuppressive agents in terms of organ damage and mortality in TA is not well established. As infliximab was used mostly in refractory TA disease in this study, its benefits as a first-line treatment option, particularly with regard to its steroid-sparing effect and in prevention of relapses, could not be assessed.

The importance of targeting pro-inflammatory cytokines in TA was recently raised by the report of the efficacy of the humanized anti-IL-6 receptor antibody (tocilizumab) [19]. As with TNF-α inhibitors, a dramatic and rapid improvement in clinical manifestations and laboratory parameters was noted. This observation of early response in even long-standing TA disease, as also noted in our study and in previous reports, supports the use of cytokine targeting therapies in TA.

In summary, our findings demonstrate that infliximab may represent an interesting alternative therapeutic option even in refractory TA. Given the limited treatment options and the number of TA cases, a multicentre randomized controlled trial may be necessary to address the benefits of first-line TNF-α inhibitor treatment in inducing remission and steroid sparing, as well as to determine the duration of TNF-α inhibitor therapy.

**Rheumatology key messages**

- Infliximab is effective in refractory TA.
- Infliximab could permit a rapid improvement in TA.
- Infliximab could have a steroid-sparing effect in TA.
Acknowledgements

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References