Tocilizumab in refractory aortitis: a study on 16 patients and literature review


Objective. Non-infectious aortitis is often refractory to standard immunosuppressive therapy. Since IL-6 has been implicated in the pathogenesis of aortitis, we assessed the efficacy of the anti-IL6 receptor monocanal antibody tocilizumab (TCZ) in a series of patients with refractory non-infectious aortitis.

Methods. Review of 16 patients (14 women/2 men) with refractory aortitis diagnosed by imaging (CT angiography, MR angiography, and/or PET) that were treated with TCZ.

Results. The mean age±SD was 51.4±20.1 years. The underlying conditions were: Takayasu arteritis (TakA) (n=7 cases), giant cell arteritis (GCA) (n=7), relapsing polychondritis (RP) (n=1), and aortitis associated with retroperitoneal fibrosis (n=1). TCZ was the first biologic drug used in all patients with GCA and in the patient with aortitis associated with retroperitoneal fibrosis but in only 2 of 7 TakA patients. In the remaining cases anti-TNF inhibitors were prescribed before TCZ (standard dose was 8 mg/kg/iv/4 weeks). After a mean±SD follow-up of 11.8±6.6 months most patients experienced clinical improvement, showing reduction of erythrocyte sedimentation rate from 43±36 mm/1st h to 3±4 mm/1st h at last visit. At TCZ onset, 25% of patients had fever and 19% polymyalgia rheumatica. These manifestations disappeared after 3 months of TCZ therapy. A corticosteroid sparing effect was also achieved (from 27±317.6 mg/day of prednisone at TCZ onset to 4 ±3.8 mg/day at last visit). TCZ had to be discontinued in a patient because of severe neutropenia.

Conclusion. TCZ appears to be effective and relatively safe in patients with inflammatory aortitis refractory to corticosteroids or to other biologic immunosuppressive drugs.

Introduction. Aortitis encompasses a wide spectrum of infectious and non-infectious pathologic conditions characterised by inflammation of the aortic wall. In some cases it may be associated with severe complications such as aneurysms, dissection and rupture of the aorta (1-4). Giant cell arteritis (GCA) and Takayasu arteritis (TakA) including in the category of large-vessel vasculitides are probably the most frequent causes of non-infectious aortitis. Nevertheless, non-infectious aortitis may present as an isolated entity or be associated with other well defined conditions (2, 5-8).

First-line treatment in non-infectious aortitis includes the use of corticosteroids, usually at high doses (9-12). Other therapies are often required to achieve control of the disease or as corticosteroid sparing agents. Different synthetic traditional immunosuppressive drugs such as methotrexate (MTX), azathioprine or cyclophosphamide have been used for this purpose (13-18). However, the efficacy of these drugs to control the activity of the disease is often insufficient and they are frequently associated with potential severe side effects.

In patients with large-vessel vasculitides, especially in GCA, a number of studies have shown the presence of abnormal production of pro-inflammatory cytokines, such as interleukin-1 (IL-1),...
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Methods

We conducted an interventional case series, open-label, multicentre study on 16 patients diagnosed as having non-infectious aortitis, either idiopathic or in the setting of well-defined autoimmune or inflammatory conditions. In all of them, TCZ therapy was given because patients were refractory to corticosteroids and standard synthetic immunosuppressive drugs and in some cases to anti-TNF-α inhibitors.

Patients and methods

Patient population

We conducted an interventional case series, open-label, multicentre study on 16 patients diagnosed as having non-infectious aortitis, either idiopathic or in the setting of well-defined autoimmune or inflammatory conditions. In all of them, TCZ therapy was given because patients were refractory to corticosteroids and standard synthetic immunosuppressive drugs and in some cases to anti-TNF-α inhibitors.

TakA fulfilled the 1990 ACR criteria for the classification for this vasculitis (51). A patient with aortitis was diagnosed as having relapsing polychondritis according to the criteria proposed by Michet et al. (52). Another patient with aortitis also fulfilled definitions for retroperitoneal fibrosis (53). Polymyalgia rheumatica (PMR) in the setting of GCA was diagnosed according to the criteria proposed by Chuang et al. (54).

In most cases management started with corticosteroids. In a second phase, synthetic traditional immunosuppressive drugs and in some cases biologic therapy was given.

Before biologic treatment, evidence of malignancy or systemic infection was excluded including hepatitis B or hepatitis C. According to national guidelines in all patients receiving biologic drugs latent tuberculosis was excluded by a tuberculin skin testing (PPD) and/or quantiferon and chest radiograph. In patients with latent tuberculosis prophylaxis with isoniazid was initiated at least 4 weeks before the onset of the biologic therapy. Overall, prophylaxis with isoniazid was maintained for 9 months. Since TCZ is an off-label indication in non infectious aortitis, written informed consent was requested and obtained from all patients.

Data collection and clinical definitions

Clinical and laboratory data were extracted from the clinical records according to a specifically designed protocol that was designed beforehand. They were stored in a computerised file. To minimise error, all the data were double-checked. The following data were assessed: clinical, laboratory, diagnosis, treatment, prognosis and adverse events. Fever was defined as a temperature >38°C, and constitutional syndrome as asthenia and/or anorexia and weight loss of at least 4 kg.

Data on routine laboratory markers of disease activity, including full blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, liver enzymes levels, creatinine serum level, proteinuria and hematuria were collected. The ESR was considered to be increased when it was higher than 20 or 25 mm/1^e hour for men or women, respectively. We defined high CRP value when it was higher than 0.5 mg/dL.

Statistical analysis

Statistical analysis was performed using the software STATISTICA (StatSoft Inc. Tulsa, Oklahoma, USA). Results were expressed as mean±SD for variables with normal distribution, or as median, range or [25th–75th interquartile range (IQR)] when they were not normally distributed.

All of the following variables were compared: clinical manifestations, ESR, CRP, and daily prednisone dose. Comparisons of these variables were made between baseline and 3, 6 and 12 months after initiation of treatment. Comparison of continuous variables was performed using the Wilcoxon test.

Results

We studied 16 patients (14 women and 2 men) with non-infectious aortitis. The mean-age ± SD was 51.4±20.1 years (range: 7–77 years). Table I summarises the main features of the patients included in this series. Aortitis was associated to the following underlying conditions: TakA (n=7 patients), GCA (n=7), relapsing polychondritis (n=1), and aortitis with retroperitoneal fibrosis (n=1).

As discussed Methods, the diagnosis of aortitis was made by imaging techniques such as FDG PET/CT scan, MR angiography, and/or CT angiography. In the patient with aortitis and retroperitoneal fibrosis the diagnosis was performed by a retroperitoneal biopsy. In 15 cases TCZ therapy was given due to aortitis refractory to standard synthetic immunosuppressive drugs and in some cases to other biologic agents. The patient with aortitis and retroperitoneal fibrosis started with TCZ without having previously received conventional immunosuppressive drugs because he was also diagnosed of secondary amyloidosis (Fig. 1).

The median duration of aortitis before TCZ onset was 12 months [IQR: 7–45]. TCZ was prescribed as monotherapy (6 cases) or combined with other traditional synthetic immunosuppressive drugs, usually MTX (7 cases), methotrexate methylfolate (2 cases), and aza-
The initial TCZ dose was 8 mg/kg every 4 weeks in 15 cases and every 2 weeks in 1 case. Most patients experienced improvement of clinical manifestations and laboratory parameters following TCZ therapy. This improvement was evident at the first available measure assessed at month 3. This response to TCZ was maintained over time (Fig. 2). An imaging technique was usually performed after TCZ onset to confirm improvement of the disease (Fig. 3 corresponding to case 14 in Table I).

Specific subtypes of aortitis

Takayasu arteritis

At TCZ onset, the 7 patients with TakA (corresponding to cases 1–7 of Table I) showed the following clinical manifestations: constitutional syndrome (n=2), fever (n=3), chest pain (n=1), abdominal pain (n=1), myalgia in the lower limbs (n=1), headache (n=1), transient ischaemic attacks (n=1), malaise (n=1) and nodular scleritis (n=1). All of them had received treatment with several traditional immunosuppressive drugs such as MTX (n=5), cyclophosphamide (n=2), azathioprine (n=2), mycophenolate mofetil (n=2) and cyclosporine A (n=1). Since they were refractory to thioprine (1 case). The initial TCZ dose was 8 mg/kg every 4 weeks in 15 cases and every 2 weeks in 1 case. Maintenance TCZ dose ranged between 4-8 mg/kg every 2 or every 4 weeks.

Table I. Main features of 16 patients before and after tocilizumab therapy.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Underlying disease</th>
<th>Diagnosis of aortitis</th>
<th>Previous traditional immunosuppressive drugs to TCZ</th>
<th>Prednisone dose (at TCZ onset) mg/d</th>
<th>Prednisone dose (at last visit) mg/d</th>
<th>CRP /ESR (at TCZ onset)</th>
<th>CRP /ESR (at last visit)</th>
<th>Follow-up with TCZ (months)</th>
<th>Serious side effects due to TCZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7/F</td>
<td>TakA MRI-A, echocardiogram</td>
<td>MTX, CYP, MM, ETN, IFX</td>
<td>30 0</td>
<td>12/72</td>
<td>&lt;0.1/5</td>
<td>24</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>57/F</td>
<td>TakA MRI-A</td>
<td>CYP</td>
<td>45 5</td>
<td>3.3/9</td>
<td>0.2/2</td>
<td>18</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>26/F</td>
<td>TakA CT-A, PET/CT</td>
<td>MTX, AZA, IFX</td>
<td>50 7.5</td>
<td>2.8/3.3</td>
<td>&lt;0.1/2</td>
<td>12</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>16/F</td>
<td>TakA MRI-A, PET/CT</td>
<td>MTX, ADA</td>
<td>50 7.5</td>
<td>0.5/14</td>
<td>0.1/7</td>
<td>12</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>45/F</td>
<td>TakA PET/CT</td>
<td>MTX, AZA, MM, IFX</td>
<td>25 0</td>
<td>&lt;0.1/2</td>
<td>0.1/5</td>
<td>13</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>41/F</td>
<td>TakA MRI-A, PET/CT</td>
<td>MTX, ADA, IFX</td>
<td>40 10</td>
<td>3.7/0.79</td>
<td>&lt;0.1/10</td>
<td>3</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>46/F</td>
<td>TakA CT, PET/CT</td>
<td>CyA</td>
<td>25 5</td>
<td>14.9/5</td>
<td>0.2/6</td>
<td>4</td>
<td>Thrombocytopenia</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>77/F</td>
<td>GCA PET/CT</td>
<td>MTX</td>
<td>10 2.5</td>
<td>3.7/120</td>
<td>1.7/7</td>
<td>5</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>59/F</td>
<td>GCA CT</td>
<td>MTX</td>
<td>60 5</td>
<td>&lt;0.1/2</td>
<td>&lt;0.1/2</td>
<td>16</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>65/F</td>
<td>GCA PET/CT</td>
<td>MTX</td>
<td>17.5 0</td>
<td>&lt;0.1/3</td>
<td>&lt;0.1/2</td>
<td>20</td>
<td>Severe neutropenia</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>67/F</td>
<td>GCA PET/CT</td>
<td>MTX</td>
<td>10 0</td>
<td>1.9/44</td>
<td>&lt;0.1/2</td>
<td>6</td>
<td>Pneumonia</td>
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<tr>
<td>12</td>
<td>74/F</td>
<td>GCA PET/CT</td>
<td>MTX</td>
<td>0 0</td>
<td>0.8/46</td>
<td>&lt;0.1/4</td>
<td>11</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>64/F</td>
<td>GCA PET/CT</td>
<td>MTX</td>
<td>15 10</td>
<td>0.1/ND</td>
<td>&lt;0.1/ND</td>
<td>3</td>
<td>Hypertension</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>53/M</td>
<td>GCA MRI-A, PET/CT</td>
<td>MTX</td>
<td>30 10</td>
<td>25.6/43</td>
<td>5.4/17</td>
<td>5</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>50/F</td>
<td>RF CT</td>
<td>MTX, CyA, LFN, CYP, IFX</td>
<td>30 5</td>
<td>0.9/13</td>
<td>&lt;0.1/13</td>
<td>20</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>75/M</td>
<td>RF CT-A</td>
<td>None</td>
<td>0 0</td>
<td>ND/98</td>
<td>ND/ND</td>
<td>17</td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

TCZ: tocilizumab; TakA: Takayasu arteritis; GCA: giant cell arteritis; RP: relapsing polychondritis; RF: retroperitoneal fibrosis; AZA: azathioprine; CyA: cyclosporine A; CYP: cyclophosphamide; LFN: leflunomide; MM: mycophenolate mofetil; MTX: methotrexate; ADA: adalimumab; ETN: etanercept; IFX: infliximab; RTX: rituximab; CRP: C-reactive protein (mg/dL); ESR: erythrocyte sedimentation rate in 1st hour; CT: computed tomography; CT-A: computed tomography angiography; MRI-A: magnetic resonance angiography; PET: positron emission tomography; ND: Not described.
these drugs, five of the seven patients were initially treated with TNF-α inhibitors. One patient undergoing treatment with adalimumab and another with etanercept were switched to infliximab. Finally, all the five patients on anti-TNF-inhibitors had to be changed to TCZ due to lack of response to anti-TNF-α inhibitors. In addition, two patients treated with non-biologic agents were also changed to TCZ. After 3 months of therapy with TCZ, 3 patients were asymptomatic, 3 patients had substantial improvement and only 1 had not experienced any improvement. Further improvement following TCZ therapy was achieved. In this regard, at last available visit, 6 patients were asymptomatic and 1 patient had mild asthenia. Moreover, in all them the dose of corticosteroids was reduced; and in 2 of them it was discontinued (cases 1 and 5). During the follow-up, imaging techniques also showed improvement in the 6 patients in whom they were performed. With respect to this, in 4 of them there was an improvement of MR angiography. In the other 2 patients there was a significant decrease in FDG PET/CT uptake following TCZ therapy.

– Giant cell arteritis
The main features of the 7 patients with GCA (corresponding to cases 8–14 of Table I) at TCZ onset were the following: PMR (n=3), constitutional syndrome (n=2), jaw claudication (n=1), headache (n=1), scapular pain (n=1), intermittent claudication of the lower extremities (n=1), and chest pain (n=1). Besides corticosteroids and before TCZ therapy, all the patients with GCA had received MTX. TCZ was started because of lack of efficacy of MTX. After 3 months on TCZ therapy, 5 patients were asymptomatic; 1 patient had mild asthenia and another patient persisted with intermittent claudication of the lower extremities. Laboratory parameters also improved. At last available visit, corticosteroid dose was reduced in all GCA patients. In 3 of them corticosteroids were completely discontinued.

– Relapsing polychondritis
A 50-year-old woman with relapsing polychondritis (case 15 of Table I) persisted with asthenia, deafness, profuse sweating, fever, abdominal pain and keratitis despite of treatment with corticosteroids, MTX, cyclosporine, leflunomide and cyclophosphamide. Because of that she was initially treated with infliximab at a dose of 5 mg/kg at 0, 2 and then every 6 weeks without improvement. Therefore, she was switched to TCZ 8 mg/kg/4 weeks showing complete clinical-laboratory improvement at month 3. Corticosteroid dose was also reduced. A CT angiography showed a significant decrease in the intimal thickness.

– Aortitis associated with retroperitoneal fibrosis
A 75-year-old man with retroperitoneal fibrosis and nephrotic syndrome due to AA amyloid deposition started with constitutional syndrome and musculoskeletal pain more intense in the dorsal region (case 16 of Table I). A CT angio-
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**Graph** showed mild aortic but intense peri-aortic inflammation. A retroperitoneal biopsy showed severe fibrosis and inflammatory cells that supported a diagnosis of periaortitis. Improvement following TCZ therapy was observed.

**Outcome**

After a mean ± SD follow-up of 11.8 ± 6.6 months, only 4 patients had experienced side effects: 1) A 46-year-old woman with TakA developed a thrombocytopenia and because of that TCZ dose had to be reduced; 2) A 64-year-old woman with GCA suffered hypotension during the second infusion of TCZ; 3) A 67-year-old woman with GCA suffered a pneumonia; 4) A 65-year-old woman diagnosed with GCA (case 10 of Table I) developed severe neutropenia (351 neutrophils) after 20 months of TCZ therapy and, because of that, the drug was discontinued.

**Discussion**

Non-infectious aortitis is frequently associated with GCA and TakA (35). These two entities have similar pathological findings (55) and share common pathogenic pathways that differentiate them from other vasculitides. Cellular immune responses involving T cells, antigen-presenting cells, and macrophages are relevant elements in GCA and TakA pathogenesis (35). However, they differ in the age at clinical onset and vascular involvement (12, 56).

GCA is a vasculitis quite common in European countries and North America involving vessels of medium and large caliber characterised by the granulomatous involvement of the aorta and its major branches with a predilection for the cranial arteries of people over 50 years of age (12, 57-59). The most common serious complication of GCA is irreversible visual loss due to optic nerve ischaemia (57, 60). GCA is associated with the upregulation of multiple proinflammatory cytokines, such as IL-6, secreted by several cell types, predominantly T-cells, macrophages, and endothelial cells (20, 61).

IL-6 plays a variety of pivotal biological functions depending on the target cell (61, 62). Thus, during physiological inflammatory responses, IL-6 participates in the synthesis of acute phase proteins, promotes the passage of acute to chronic inflammation, and facilitates development of adaptative immunity (61, 63). Moreover, IL-6 modulates activation, proliferation and differentiation of various T cell lines including CD8 T, Th17 and Treg cells. This proinflammatory cytokine also stimulates terminal differentiation of B cells and improves survival of plasma cells (61).

Increased IL-6 serum levels have been observed in patients with active GCA and a correlation of IL-6 with disease activity has also been observed (20). Also, temporal artery biopsies in GCA show an increase in the local expression of IL-6 (40-42).

TCZ is a humanised anti-IL6 receptor monoclonal antibody. This biologic agent has proved to be effective not only in rheumatoid arthritis, but also in patients with systemic inflammatory diseases such as Still’s disease (40, 64-66).
<table>
<thead>
<tr>
<th>Age / Sex</th>
<th>Clinical features</th>
<th>Previous therapy</th>
<th>Imaging technique before TCZ</th>
<th>Imaging technique after TCZ</th>
<th>ESR before / after TCZ</th>
<th>CRP before / after TCZ</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>64/M</td>
<td>Systemic manifestations</td>
<td>GCs, IFX, ETN PET/CT (FDG uptake) in numerous vessels</td>
<td>PET/CT: decreased FDG uptake in the involved vessels</td>
<td>95/4</td>
<td>5.4/0.07</td>
<td>Clinical improvement</td>
<td>Salvarani (47)</td>
<td></td>
</tr>
<tr>
<td>63/M</td>
<td>Malaise, PMR, peripheral occlusive arterial disease</td>
<td>None</td>
<td>MRI-A: aortitis</td>
<td>91/2</td>
<td>0.6/&lt;0.03</td>
<td>Clinical remission</td>
<td>Seitz (48)</td>
<td></td>
</tr>
<tr>
<td>73/M</td>
<td>Malaise, PMR, jaw claudication</td>
<td>None</td>
<td>MRI-A: aortitis</td>
<td>100/2</td>
<td>0.6/&lt;0.03</td>
<td>Clinical remission</td>
<td>Seitz (48)</td>
<td></td>
</tr>
<tr>
<td>79/F</td>
<td>Malaise, PMR, amaurosis fugax</td>
<td>GCs, MTX</td>
<td>MRI-A: aortitis</td>
<td>44/8</td>
<td>0.1/&lt;0.03</td>
<td>Clinical remission</td>
<td>Seitz (48)</td>
<td></td>
</tr>
<tr>
<td>79/M</td>
<td>Fever, night sweats and weight loss</td>
<td>GCs, AZA PET/CT: large-vessel vasculitis</td>
<td>PET/CT: no metabolic activity</td>
<td>ND/ND</td>
<td>16.8/normal (NV)</td>
<td>Clinical remission</td>
<td>Beyer (44)</td>
<td></td>
</tr>
<tr>
<td>72/F</td>
<td>Weight loss, sweats, anosmia, uveitis, sublingual haemorrhages</td>
<td>GCs, AZA, MM PET/CT (FDG uptake) in aorta, subclavian and carotid arteries</td>
<td>PET/CT: no metabolic activity</td>
<td>ND/ND</td>
<td>30.7/ Normal (NV)</td>
<td>Clinical remission</td>
<td>Beyer (44)</td>
<td></td>
</tr>
<tr>
<td>71/F</td>
<td>Systemic symptoms, headache, diplopia, night sweats, anosxia</td>
<td>GCs, MTX</td>
<td>MRI-A: subclavian and femoral artery involvement</td>
<td>ND</td>
<td>Elevated (NV)/ normal (NV)</td>
<td>Clinical remission</td>
<td>Beyer (44)</td>
<td></td>
</tr>
<tr>
<td>63/F</td>
<td>PMR, headache, fatigue, transient visual loss, anosmia, loss of weight</td>
<td>GCs, MTX, LFN, AZA PET/CT (FDG uptake) in aorta, axillary, subclavian arteries</td>
<td>PET/CT: partial response with reduction in uptake in the abdominal aorta</td>
<td>ND/ND</td>
<td>7.8/0.1</td>
<td>Clinical remission</td>
<td>Christidis (45)</td>
<td></td>
</tr>
<tr>
<td>ND/ND</td>
<td>PMR, headache, jaw and upper extremity claudication</td>
<td>GCs, CYM, IFX CT-A, MRI-A: carotid, subclavian, aorta and iliac artery involvement</td>
<td>ND</td>
<td>64/7</td>
<td>5.1/0.07</td>
<td>Clinical remission</td>
<td>Unizony (49)</td>
<td></td>
</tr>
<tr>
<td>ND/ND</td>
<td>Headache, jaw claudication</td>
<td>GCs, MTX CT-A, MRI-A: aortic involvement</td>
<td>ND</td>
<td>90/4.8</td>
<td>3.3/&lt;0.06</td>
<td>Clinical remission</td>
<td>Unizony (49)</td>
<td></td>
</tr>
<tr>
<td>72/F</td>
<td>Fever, headache, weight loss, weakness, pain of neck, shoulder and pelvic girdles, carotidynia</td>
<td>None</td>
<td>PET (FDG uptake): carotid, subclavian, thoracic and abdominal aorta</td>
<td>PET (decrease FDG uptake): carotid, subclavian arteries, thoracic and abdominal aorta</td>
<td>120/8</td>
<td>8.9/&lt;0.02</td>
<td>Clinical remission</td>
<td>Pazzola (43)</td>
</tr>
</tbody>
</table>

TCZ: tocilizumab; PMR: polymyalgia rheumatica; GCs: glucocorticoids; AZA: azathioprine; CyA: cyclosporine A; CYP: cyclophosphamide; LFN: leflunomide; MM: Mycophenolate mofetil; MTX: methotrexate; ADA: adalimumab; ETN: etanercept; IFX: infliximab; RTX: rituximab; CRP: C-reactive protein (mg/dL); ESR: erythrocyte sedimentation rate in 1st hour; FDG: fluodeoxyglucose; CT: computed tomography; CT-A: computed tomography angiography; MRI-A: magnetic resonance angiography; PET: positron emission tomography; ND: not described; NV: no numerical value.
Table III. Reported series and case reports on the use of Tocilizumab in aortitis and/or its main branches associated with Takayasu arteritis.

<table>
<thead>
<tr>
<th>Age/ Sex</th>
<th>Clinical features</th>
<th>Previous therapy</th>
<th>Imaging technique before TCZ</th>
<th>Imaging technique after TCZ</th>
<th>ESR before / CRP before</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>40/M</td>
<td>Leakage of a graft of the thoracic aorta and ischaemic pain</td>
<td>GCs</td>
<td>MRA: aortitis</td>
<td>MRA: improvement in aortitis</td>
<td>80/ 5</td>
<td>0.4/ &lt;0.03</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>27/F</td>
<td>Malaise, arms and legs claudication</td>
<td>GCs, MTX, Aza, IFX</td>
<td>MRI-A: aortitis</td>
<td>MRA: improvement in aortitis</td>
<td>40/ &lt;3</td>
<td>0.5/ &lt;0.03</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>21/F</td>
<td>Myalgia, fever, headache, bilateral carotid bruits</td>
<td>GCs, MTX</td>
<td>PET/CT (FDG uptake): multiple arteres</td>
<td>PET/CT: decrease in FDG uptake</td>
<td>45/3</td>
<td>4.0/2.06</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>40/F</td>
<td>Arthro-myalgia, fever, weight loss, carotidynia, subclavian bruit</td>
<td>None</td>
<td>PET/CT (FDG uptake): multiple arteres</td>
<td>PET/CT: decrease in FDG uptake</td>
<td>67/2</td>
<td>0.9/0.05</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>54/M</td>
<td>Malaise, myalgia, weight loss</td>
<td>None</td>
<td>PET/CT (FDG uptake): numerous vessels</td>
<td>PET/CT: decrease in FDG uptake</td>
<td>84/2</td>
<td>4.8/0.1</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>25/F</td>
<td>Myalgia, arthralgia, headache, fever, arm claudication, abdominal bruit, fatigue, carotidynia</td>
<td>GCs, MTX, MM, IFX, ADA</td>
<td>PET/CT (FDG uptake): brachiocephalic, carotid arteres. Abdominal angiography: stenosis of celiac artery; US: carotid and subclavian involvement.</td>
<td>PET/CT: decrease in FDG uptake</td>
<td>69/Normal (NV)</td>
<td>7.2/Normal (NV)</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>ND/ND</td>
<td>Upper extremitry claudication, pulse deficit, pulmatory hypertension</td>
<td>GCs</td>
<td>Cross-sectional imaging (CT-A, MRI-A): pulmonary, carotid and subclavian artery stenosis</td>
<td>ND</td>
<td>15/3.6</td>
<td>0.8/0.03</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>ND/ND</td>
<td>Lower extremitry claudication, pulse deficit, hypertension</td>
<td>GCs</td>
<td>CT-A, MRI-A: aortic arch aneurysm and external iliac artery stenosis</td>
<td>ND</td>
<td>34/8.7</td>
<td>1.7/0.56</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>20/F</td>
<td>Left cervical pain, left chest pain, syncope, weight loss</td>
<td>GCs, CyA, CYP, Aza, MM, MTX</td>
<td>Chest CT: aortitis, and stenosis of the left subclavian artery.</td>
<td>CT: reduction in aortitis</td>
<td>ND/ND</td>
<td>12.6/Normal (NV)</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>28/F</td>
<td>Arthralgia, cervicalgia, fever, weakness, sweat, weight loss, hypertension, radial pulselessness</td>
<td>GCs, MTX, CYP, MM, Aza, IFX, ADA</td>
<td>MRI-A: subclavian and axillary arteres involve</td>
<td>CT-A: reduction in aortitis; progression of stenosis in renal, subclavian and vertebral artery.</td>
<td>70/2</td>
<td>6.6/ &lt;0.3</td>
<td>Clinical improvement</td>
</tr>
</tbody>
</table>

TCZ: tocilizumab; GCs: glucocorticosteroids; AZA: azathoprine; CyA: cyclosporine A; CYP: cyclophosphamide; MM: mycophenolate mofetil; MTX: methotrexate; IFX: infliximab; ADA: adalimumab; ETN: etanercept; CRP: C-reactive protein (mg/dL); ESR: erythrocyte sedimentation rate in 1st hour; FDG: fluordeoxyglucose; CT: computed tomography; CT-A: computed tomography angiography; MRI-A: magnetic resonance angiography; PET: positron emission tomography; US: ultrasoundography. ND: not described; NV: no numerical value.
Interestingly, several studies indicate that TCZ may be a useful therapy in patients with non-infectious aortitis. Table II and Table III show available information on the use of TCZ in aortitis and/or its large branches in GCA and TakA. Of particular interest is the case reported by Salvareani et al. (47); a patient with biopsy-proven GCA that had previously been diagnosed with spondyloarthritides, having been initially treated with infliximab and then with etanercept. Besides corticosteroids, MTX had been added to etanercept for one year without improvement. The patient experienced frequent relapses, including systemic manifestations, elevated acute phase reactants and inflammation of large vessels confirmed by PET/CT when prednisone dose was decreased below 12.5 mg/day. Thus, MTX and etanercept were changed to TCZ. One month after TCZ onset the patient achieved clinical, laboratory and PET/CT improvement and the dose of prednisone was successfully tapered (47). Seitz et al. (48) published five patients with GCA treated with TCZ (8 mg/kg). The patients experienced clinical improvement that correlated with improvement in imaging techniques. Because of that, corticosteroid dose was successfully reduced (48). Beyer et al. (44) reported 3 patients with GCA that received treatment with TCZ because of active disease associated with aortitis and/or femoral inflammation on PET. Rapid and maintained improvement was found in all patients following TCZ therapy, and corticosteroid dose was successfully tapered. Unizony et al. (49) described 7 patients with GCA refractory to corticosteroid therapy and immunosuppressive agents. For this reason, they started on TCZ 4-8 mg/kg every month. They got into remission and were able to taper corticosteroid dose. Recently, Pazzola et al. (43) described a woman diagnosed with GCA and PMR. She began with TCZ as monotherapy at a dose of 8 mg/kg monthly. Clinical improvement and reduction of ESR and CRP was observed. Six months after the onset of TCZ the patient was asymptomatic and the imaging techniques showed markedly decreased of vascular FDG uptake in the affected vessels.

TakA is another large-vessel vasculitis that involves the aorta, its large branches, and the proximal portions of renal, coronary and pulmonary arteries (67). Incidence of TakA is 1.2-2.6/million per year in western population and 100-times higher approximately in the countries of The Silk Road (56, 68, 69). This entity is more common in women between 20–40 years (9, 68). Clinically it is characterised by fever, weight loss, joint pain, claudication of affected limbs, decrease or loss of pulses, carotidynia, headache, amaurosis, diplopia, renal failure, cerebrovascular events, heart failure, acute myocardial infarction and aneurysms (70-74).

As occurs in the GCA, IL-6 is also expressed in TakA tissue. Furthermore, serum levels of IL-6 are elevated in patients with TakA correlating very well with disease activity. Therefore, pharmacological blockade of IL-6 is also a potential target to be considered in this kind of vasculitis. Nishimoto et al. (46) published in 2008 the case of a 20-year-old woman diagnosed with TakA five years before. She also had ulcerative colitis. The patient was treated with corticosteroids, immunosuppressive agents and leukapheresis. Despite this, the patient could not reduce the dose of prednisolone below 30 mg/day because the symptoms recurred. For this reason, TCZ was started achieving a disease remission, allowing to taper the dose of corticosteroids. Ulcerative colitis also improved.

Salvarani et al. (47) published a study on 3 patients with TakA who experienced important improvement following TCZ therapy. Also, this group (75) reported a 25-year-old woman with TakA that started treatment with prednisone. Then, the patient received MTX, mycophenolate mofetil, infliximab and adalimumab, but none of them managed to reach control the disease activity. Therefore, TCZ was started (8 mg/kg) every 4 weeks for 6 months. Clinical activity, inflammatory markers and PET/CT findings became normal, while prednisone dosage was successfully tapered. Seitz et al. reported 2 cases of TakA (48). One of them had only been treated with corticosteroids while the other had been treated with MTX, azathioprine and infliximab. Due to lack of response, TCZ was started in both cases. Following this procedure, complete clinical response with normalisation of CRP and ESR was observed. However, one of them relapsed after 8 months of treatment. Unizony et al. (49) also described 2 patients diagnosed of TakA and treated with TCZ with good response. In contrast, Bredemeier et al. (76) described a 28-year-old woman with TakA that suffered progression of vascular stenosis despite treatment with TCZ.

RP is a rare systemic disease characterised by recurrent inflammation and destruction of cartilaginous structures as well as other structures rich in proteoglycans such as eyes, heart, blood vessels, middle ear and kidneys (77-79). Little is known on the use of TCZ in patients with RP. With respect to this, Narshi and Allard (80) described a 43-year-old woman with RP and aortitis requiring emergency aortic valve replacement. The patient had poor response to conventional therapy. Because of that, infliximab was started in combination with oral MTX and deflazacort, but she suffered a relapse of the disease associated with elevation of the laboratory markers of inflammation. Adalimumab was then started showing improvement. However, since the patient developed a recurrence of the disease despite of increasing the corticosteroid dose and the frequency of adalimumab, she was switched to TCZ (8 mg/kg/ every 4 weeks). Following TCZ the patient achieved a rapid improvement with normalisation of CRP. Other authors such as Kawai et al. or more recently Wallace and Stone also published good results in RP patients treated with TCZ (81, 82). Wendling et al. (83) reported a 46-year-old woman with RP that had received treatment with prednisone, dapsone, several disease-modifying anti-rheumatic drugs, infliximab, etanercept and anakinra, achieving clinical remission with the last one. However, when anakinra was discontinued she suffered a relapse of symptoms. At that time, she refused to start again with subcutaneous injections and because of that iv infusions of TCZ (8 mg/kg/monthly) were given.
The patient experienced clinical improvement within the first week after the first infusion of TCZ. However, subsequently, no improvement was observed and the patient had to return to anakinra.

Idiopathic isolated aortitis is characterised by giant cells or lymphoplasmacytic inflammation of the aorta. Isolated aortitis generally manifests as an ascending aortic aneurysm and it is usually discovered incidentally within a pathological study of a sample of aortic wall after surgery (8). Pazzola et al. (43) described 57-year-old man with idiopathic aortitis and diabetes mellitus that received TCZ as monotherapy at the dose of 8 mg/kg monthly for 6 months. After 2 months of treatment the patient experienced clinical improvement with normalisation of inflammation markers. A PET/CT performed after 6 months of TCZ therapy did not disclose abnormal FDG uptake.

Some authors have included within the category of idiopathic aortitis to cases of chronic periaortitis, idiopathic retroperitoneal fibrosis (Ormond disease), inflammatory abdominal aortic aneurysm, periaereural myaltritis and idiopathic isolated abdominal periaortitis (2, 84-90). We support this consideration and, because of that, we defined patient number 16 from our series (Table I) as aortitis associated with retroperitoneal fibrosis. Interestingly, a recent study conducted by Vaglio et al. supports the use of TCZ in patients with chronic periaortitis who are refractory or have contraindications for the use of corticosteroids (91). In this regard, according to the results derived from this study, TCZ should be considered in cases of chronic periaortitis refractory to other immunosuppressive drugs. TCZ added to ongoing therapy with prednisone and MTX allowed prednisone withdrawal and induced resolution of symptoms, acute-phase reactant normalisation, and reduction in FDG PET uptake in one case (91). In another case of chronic periaortitis, TCZ in monotherapy induced sustained clinical and laboratory remission, FDG uptake disappearance, and chronic periaortitis shrinkage. In conclusion, taking all these evidences together, TCZ appears to be a logistic agent effective and relatively safe in patients with inflammatory aortitis refractory to corticosteroids or to other biologic immunosuppressive drugs. However, additional studies including randomised controlled trials are needed to evaluate the long-term efficacy and safety of TCZ in patients with aortitis.

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