Case report

Tocilizumab, an effective treatment for relapsing giant cell arteritis

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ABSTRACT

Objective. Patients with giant cell arteritis (GCA) often respond to corticosteroid (CS) therapy; however, the majority of patients relapse when CS therapy is tapered or withdrawn. The purpose of this study was to assess the efficacy of tocilizumab (TCZ) in patients with relapsing GCA.

Methods. Four patients with relapsing GCA received TCZ monthly (4mg/kg or 8mg/kg). Disease activity and drug tolerability were evaluated clinically and via laboratory test results at the beginning of the study and every 3 months until the publication of this study. All four patients were still receiving TCZ monthly at the time of manuscript submission.

Results. All four patients treated with TCZ achieved clinical and laboratory response. No adverse events were detected.

Conclusion. In our small case series, TCZ was efficacious and well tolerated in patients with relapsing GCA. Proper randomised controlled trials are required to achieve confident conclusions regarding the safety and efficacy of TCZ in GCA.

Introduction

Giant cell arteritis (GCA) is characterised by inflammation of the medium- and large-sized arteries, and it affects individuals over 50 years of age. Arteries involved include the aorta, the second to fifth order aortic branches, and also the cranial and extra cranial arteries (1).

GCA is the most common primary form of vasculitis in western countries, and the vascular inflammation is usually accompanied or preceded by a systemic inflammatory process (1). The inflammatory markers associated with GCA, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are elevated in most of the cases whenever the disease active. Corticosteroids (CS) are the mainstay of treatment for GCA; however, the use of CS does not cure or induce long-term CS-free remissions.

IL-6 is a cytokine produced by T cells, B cells, macrophages, and endothelial cells. It triggers the synthesis of acute phase proteins, promotes the transition from acute to chronic inflammation, and helps with the activation of T cells and the differentiation of B cells (1).

There is evidence indicating that IL-6, which is upregulated in inflamed arteries in GCA, plays a large role in sustaining disease activity in GCA (3-5). Tocilizumab (TCZ) is a humanised anti-IL-6 receptor monoclonal antibody that blocks both soluble and membrane bound IL-6 receptors.

Case report

Case 1

A 65-year-old female was referred to us for biopsy-proven GCA that was complicated by ischaemic neuropathy, weight loss, fatigue, and jaw claudication. The patient’s GCA was also associated with elevation of the inflammatory markers ESR and CRP.

The patient’s medical history revealed that she had had GCA treated with CS; however, while on therapy for two months, she developed fatigue, anxiety, weight gain, depression, and muscle atrophy. Fifteen milligrams of methotrexate (MTX) by mouth weekly was added to her regimen to taper the steroids dose. Two months later, it was decided to initiate the patient on 4 mg/kg of TCZ per month because she had persistent elevation of inflammatory markers and significant difficulty with steroid side-effects, despite treatment with 50 mg/day of CS in combination with 15 mg/week of MTX and 1 mg/day of folic acid.
Table 1.

<table>
<thead>
<tr>
<th>Case</th>
<th>Inflammatory markers at the baseline</th>
<th>Inflammatory markers after 1st dose of TCZ</th>
<th>Inflammatory markers after 3 months</th>
<th>Inflammatory markers after 6 months</th>
<th>Inflammatory markers after 9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>ESR:34 CRP:30.6</td>
<td>ESR:5 CRP:1.0</td>
<td>ESR:0.5 CRP:3</td>
<td>ESR:0.3 CRP:2</td>
<td>ESR:0.3 CRP:1</td>
</tr>
<tr>
<td>Case 2</td>
<td>ESR:15 CRP: N/A</td>
<td>ESR:14 CRP:N/A</td>
<td>ESR:N/A CRP:N/A</td>
<td>ESR: N/A CRP: N/A</td>
<td>ESR: N/A CRP: N/A</td>
</tr>
<tr>
<td>Case 3</td>
<td>ESR:85 CRP:79.8</td>
<td>ESR:7 CRP:0.4</td>
<td>ESR:1 CRP:0.2</td>
<td>ESR:2 CRP:&lt; 0.2</td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>ESR:14 CRP:3.6</td>
<td>ESR:0.2 CRP:1</td>
<td>ESR:0.3 CRP:1</td>
<td>ESR:&lt; 0.2 CRP:1</td>
<td></td>
</tr>
</tbody>
</table>

Normal values: ESR <29; CRP: <0.8; N/A: not available.

Table II shows the levels of the inflammatory markers before and during the treatment with TCZ. The ESR and CRP improved after the second infusion and it was possible to wean the patient completely off the CS. The patient is still being treated with 4 mg/kg of TCZ monthly and there are no signs or symptoms of disease activity.

Case 2
A 71-year-old female was referred to our institution for a stiff neck that responded well to oral prednisone. However, the patient started having side-effects from the CS, such as facial swelling, insomnia, and fluid retention. Eventually she was tapered off of the CS therapy. Unfortunately during the hiatus from the steroid, the patient started to notice the return of pain in her neck, shoulder, and hip that was also associated with knee pain and swelling. Initially she was diagnosed with polymyalgia rheumatica, but later she was found to have be positive for anti-CCP antibody (15.6 units). The patient was placed on hydroxychloroquine sulfate and MTX, but did not have good response. Due to significant weight loss, weakness, and pain and swelling of her joints, a PET scan was ordered to look for malignancy. The study showed extensive uptake in her large- and medium-sized vessels including the aorta, subclavian, axillary and the common iliac arteries. Her ESR was high at 71 mm/hour. The patient was diagnosed with GCA with extra cranial compromise.

She was initially treated with 60 mg of oral prednisone per day; however, after 7 months, 10 mg/week of oral MTX was added as a steroid sparing agent due to persistent elevation of the inflammatory markers. This dose was later increased to 20 mg/week. Three months later, the patient was on 25 mg of prednisone and it was not possible to decrease the dose of the CS below 12 mg/day due to elevated levels of ESR and CRP. The patient also increased in weight, developed cingoid features, and noticed easy bruising and bleeding.

At that time it was decided to start TCZ 4 mg/kg monthly. She responded very well to the new regimen, and the inflammatory markers remained within normal limits. The CS dose was tapered to 9 mg/day and MTX remained at 15 mg/week. The patient continues to receive TCZ treatments monthly.

Case 3
A 73-year-old female was referred to our institution for severe neck and left shoulder pain. Her ESR was 102 mm/hour and she was started on prednisone 20 mg/day for polymyalgia rheumatica (PMR). One week later, her ESR was 60 mm/hour with minimal improvement of her symptoms. A magnetic resonance angiogram (MRA) was ordered and showed concentric wall thickening of the thoracic aorta that extended into the abdomen, suggesting aortitis. The patient was diagnosed with GCA and extra-cranial vessel compromise.

After three days on methylprednisolone, she was started on 60 mg/day of oral prednisone. Sixteen months later, while off CS for a few weeks, the patient developed neck, shoulder, and back pain. Her ESR was 98 mm/hour and her CRP was 135 mg/L, so 40 mg/day CS was prescribed, and she responded well.

Unfortunately, the patient developed severe swelling of the left lower extremity associated with elevation of the inflammatory markers. Her ESR was 85 mm/hour and CRP was 74.8 mg/L seven months later while she was on on 10 mg/day of prednisone. At that time, CS was increased to 30 mg/day, and 8 mg/kg of TCZ per month was initiated.

Four weeks later, the patient was symptom free and the inflammatory markers returned to normal levels. Currently the patient is is still on 8 mg/kg TCZ per month. There is no sign of disease flare and she is off CS.

Case 4
A 70-year-old female presented with throat pain and indicated that it was in the carotid area. She also had odynophagia, cough, fever, and weight-loss associated with weakness and pain in her neck, shoulders, and hips. The patient did not report headache, visual disturbances, or scalp tenderness.

Physical examination revealed the presence of a systolic murmur at the upper sternal border that irradiated to the subclavian region. At that time, the inflammatory markers were elevated. Her ESR level was 138 mm/hour and her CRP was 222.9 mg/L.

The patient had PMR-like symptoms. PET-CT demonstrated aortic, iliac, and femoral arteritis; therefore, a diagnosis of GCA with extra-cranial compromise was made.

The patient’s initial response to 60 mg/day of oral prednisone was very good and led to an improvement in her inflammatory marker levels and symptomatology. Unfortunately, with every attempt to decrease the CS dose below 15 mg/day, the patient reported a recurrence of her symptoms.

Interestingly, the inflammatory marker levels of ESR and CRP never correlated with the patient’s clinical picture. The patient was initiated on 15 mg/week of oral MTX 10 months after the
initial diagnosis; however, it did not help taper the CS dose. Due to the inability to decrease the CS dose and the lack of response to MTX, it was decided to start TCZ 8mg/kg monthly. The patient responded very well to TCZ, is currently off MTX. Additionally, the CS dose has been decreased to 6 mg/day. She is still receiving TCZ monthly.

Discussion
The use of CS is still the gold standard treatment for GCA, despite the high frequency of adverse events related to its use. IL-6 is a powerful cytokine and causes an intense pro-inflammatory reaction locally and systemically. The serum level of IL-6 is elevated in GCA (4) and plasma levels closely correlate with the systemic manifestations of the disease (6).

TCZ was very effective in decreasing inflammation and ameliorating the clinical manifestations of GCA in patients with both cranial and extracranial involvement. All four of our reviewed cases treated with TCZ had satisfactory clinical improvement. The inflammatory markers normalised after the first infusion of TCZ, except in case 4, where the ESR and CRP were already within normal limits when TCZ was initially administered. Table I shows the levels of ESR and CRP during TCZ treatment. Normalisation of acute-phase proteins is expected during the use of TCZ (5), so it is imperative that the physician responsible for the management of the GCA patient consider the clinical signs/symptoms to assess for flares or complications.

The efficacy of TCZ in the treatment of relapsing GCA is demonstrated in Table II. All four patients remained in remission during the treatment with TCZ and no adverse events were registered. Cases 1 and 3 could be completely weaned off CS, while in cases 2 and 4; the CS dose was substantially decreased during the treatment with TCZ.

Conclusion
In our case review, TCZ was proven effective in the treatment of relapsing GCA; however, it is not clear how patients treated with TCZ should be maintained over time. It remains to be established if TCZ is more effective in patients with relapsing disease compared to those with newly diagnosed GCA. Proper randomised controlled trials are required to achieve confident conclusions regarding the safety and efficacy of TCZ in GCA.

Key message
Tocilizumab is an excellent drug for the treatment of relapsing giant cell arteritis.

References

Table II.
<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical feature to start TCZ</th>
<th>TCZ treatment (other treatments)</th>
<th>CS dose at the first dose of TCZ/Last follow-up</th>
<th>CS dose at the last follow-up</th>
<th>Outcome</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Relapsing GCA</td>
<td>4mg/kg monthly (MTX)</td>
<td>Prednisone 50 mg daily</td>
<td>No CS</td>
<td>Remission (no signs or symptoms)</td>
<td>None</td>
</tr>
<tr>
<td>Case 2</td>
<td>Relapsing GCA</td>
<td>4mg/kg monthly</td>
<td>Prednisone 20 mg daily</td>
<td>Prednisone 9 mg daily</td>
<td>Remission (no signs or symptoms)</td>
<td>None</td>
</tr>
<tr>
<td>Case 3</td>
<td>Relapsing GSA</td>
<td>8mg/kg monthly</td>
<td>Prednisone 30 mg daily</td>
<td>No CS</td>
<td>Remission (no signs or symptoms)</td>
<td>None</td>
</tr>
<tr>
<td>Case 4</td>
<td>Relapsing GCA</td>
<td>8mg/kg monthly (MTX)</td>
<td>Prednisone 20 mg daily</td>
<td>Prednisone 6 mg daily</td>
<td>Remission (no signs or symptoms)</td>
<td>None</td>
</tr>
</tbody>
</table>