Case report

Rapid visual recovery following intravenous tocilizumab in glucocorticoid resistant refractory giant cell arteritis

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SUMMARY

A 72-year-old man presented with a short history of headache, jaw claudication, double vision, amaurosis fugax and distended temporal arteries. A diagnosis of giant cell arteritis (GCA) was confirmed on temporal artery ultrasound and temporal artery biopsy. Despite treatment with high-dose oral glucocorticoid (GC) and multiple pulses of intravenous methylprednisolone, his vision deteriorated to hand movements in one eye. 8 mg/kg intravenous tocilizumab, a humanised, recombinant anti-IL-6 receptor antibody, was administered within 48 hours of vision loss and continued monthly, resulting in marked visual improvement within days, as well as sustained remission of GCA. This case suggests a possible role for tocilizumab as a rescue therapy to prevent or recover visual loss in patients with GCA resistant to GC treatment, termed refractory GCA. Further research is required to elucidate the role of intravenous administration of tocilizumab in this setting.

BACKGROUND

Giant cell arteritis (GCA) is the most common form of systemic vasculitis.¹ No clear environmental cause has been identified, though the association with HLA-DRB1*04 suggests a heritable susceptibility to this condition.² Untreated, GCA carries significant risk of permanent visual loss, due to involvement of the ophthalmic artery and its branches.

GCA symptoms, which include headache, fever, weight loss, muscle ache and muscle stiffness, are common presentations in the primary care setting, so making a diagnosis on clinical grounds alone is often difficult.³ A raised erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and platelet count can support a GCA diagnosis, but they may be normal and falsely reassuring.⁴ Even temporal artery biopsy (TAB), the gold standard investigation, may give false-negative results due to the effect of glucocorticoid (GC) therapy, 'skip lesions' and inadequate biopsy length or histopathological assessment.⁵

The management of GCA is also challenging as the mainstay of treatment is long-term, high-dose systemic GC therapy, which is associated with multiple comorbidities including diabetes mellitus, hypertension, reduced bone density, gastrointestinal erosion and weight gain.⁶

This case report describes a patient with sight-impairing, GC-resistant GCA who demonstrated rapid

and sustained improvement of visual and systemic symptoms following treatment with intravenous tocilizumab (RoActemra, Roche).

CASE PRESENTATION

A 72-year-old Caucasian man presented to the emergency department with new-onset right-sided headaches, jaw claudication and transient double vision. He denied weight loss, fever, polymyalgia or arthralgia. His previous medical history was significant for hypertension, hypercholesterolaemia and borderline osteopenia. He was an active smoker. Clinical examination was unremarkable besides distended temporal arteries. GCA was suspected and treatment commenced with 60 mg (1 mg/kg) oral prednisolone once daily.

At initial ophthalmic assessment, the patient reported an episode of transient vertical diplopia, and a 'black-out' of the vision in his right eye which improved over several hours. Visual acuities measured 6/9 aided by Snellen chart in each eye. The right eye demonstrated a relative afferent pupillary defect, reduced colour vision by Ishihara testing and a constricted Humphrey visual field; the remaining examination found only early cataracts. These signs, suggestive of ocular ischaemia, raised concerns of impending visual loss and hence intravenous methylprednisolone (ivMP) was commenced (500 mg infusion once daily for 3 days) and 60 mg daily oral prednisolone continued thereafter.

On day 16 of GC treatment, the patient reported worsening jaw claudication and further transient visual loss in his right eye. The visual acuity was reduced to 6/12 and a repeat dose of 1 g ivMP was given. However, the following day his vision deteriorated in his right eye to hand movements only; the right optic disc appeared pale and swollen and 'cattle tracking' of the retinal arteries was observed. The impression was of a right ischaemic optic neuropathy and central retinal artery occlusion. High-dose (1 mg/kg/day) oral prednisolone was continued and urgent treatment with intravenous tocilizumab (8 mg/kg) was arranged.

INVESTIGATIONS

Haematological investigations demonstrated a pretreatment ESR of 3 mm/hour and a full blood count and liver function tests within normal limits. CRP on day 2 of treatment was 2.5 mg/L. A small minority of GCA patients have normal

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Figure 1 Temporal artery ultrasound. The non-compressible, hypoechoic 'halo sign' (asterisks) is seen in longitudinal (A) and cross-section (B) of the frontal branch of the patient's right temporal artery. Repeat ultrasound after 4 months of treatment with tocilizumab and a reducing dose of glucocorticoid showed resolution of the halo (C,D). Images taken with an Esaote MyLab V.7 using a 22 MHz probe.

inflammatory markers⁴ and may be at increased risk of visual complications.^{7,8}

Temporal artery ultrasound (TAUS) revealed a florid 'halo' sign (hypoechoic arterial wall thickening representing inflammation and oedema) throughout the right superficial temporal artery and its branches, with definite but patchy involvement of the left temporal artery (figure 1). Specificity of the bilateral halo sign in GCA approaches 100%.⁹ Axillary artery ultrasound, which improves sensitivity,¹⁰ was negative. CT angiography demonstrated mild thickening and calcification of the aortic arch and brachiocephalic trunk, deemed more in keeping with atherosclerotic disease than large vessel GCA. Cardiovascular risk factors and atherosclerosis may increase the severity of ischaemic complications from GCA and complicate TAUS interpretation.^{11,12}

A baseline chest radiograph and urinalysis, undertaken to exclude infection prior to immunosuppressive treatment, were unremarkable. Carotid Doppler ultrasound and a 24-hour tape also proved negative.

TAB was performed on day 22 of prednisolone treatment to support a funding request for tocilizumab therapy, given the patient's atypical blood test results and apparent resistance to glucocorticoid therapy. The biopsy sample showed focal destruction of the elastic lamina, adventitial lymphocytic inflammation and venulitis. Although no giant cells or inflammation were seen within the media or around the elastic tissue, a cardiovascular pathologist and a neuropathologist with a special interest in GCA independently concluded that the appearances were in keeping with GCA.

DIFFERENTIAL DIAGNOSIS

This patient's symptoms and signs were highly suggestive of GCA. Although a clinical diagnosis is often difficult, jaw claudication is the most specific symptom.¹³

Raised intracranial pressure may also result in headache and visual disturbances, but is usually distinguishable from GCA with a detailed history and optic disc examination for papilloedema. Raised intracranial pressure typically produces a severe, constant headache which may worsen with postural change, Valsalva or activity. Associated visual obscurations are typically brief (up to

1 min) but may be frequent. In contrast, GCA typically presents with new-onset, moderate-to-severe headache and episodes of transient, though often complete, monocular visual loss lasting up to an hour. Where papilloedema is present, neuroimaging (typically MRI head with intravenous contrast) is recommended.¹⁴

Rarely, other vasculitides or connective tissue disorders may mimic GCA. The American College of Rheumatology 1990 Classification Criteria are sensitive and specific for identifying GCA among patients with vasculitis.¹⁵ The reported case met these criteria on the basis of age, recent onset headache, clinically abnormal temporal artery and positive TAB. There were no clinical features to suggest an alternative vasculitic cause and antinuclear and antineutrophil cytoplasmic antibody tests were negative.

TREATMENT

High-dose GC is the mainstay of GCA treatment; the patient in this case was commenced on 60 mg/day (1 mg/kg) prednisolone as recommended by the 2010 British Society of Rheumatology guidelines.¹⁶ Despite this, the patient developed transient visual symptoms (diplopia, amaurosis fugax) which may portend permanent visual loss, hence a 3-day course of 500 mg ivMP was administered. In view of the side effects associated with long-term steroid use, gastric and bone protection (lansoprazole 30 mg/day, alendronic acid 70 mg/week and TheiCal once daily) were commenced.

Despite 2 weeks' high-dose GC therapy, the patient's systemic and visual GCA symptoms persisted. Funding for intravenous tocilizumab treatment was approved through the hospital as the National Institute for Health and Care Excellence (NICE) had not yet approved subcutaneous tocilizumab use for GCA in England by March 2018.

OUTCOME AND FOLLOW-UP

Intravenous tocilizumab (8 mg/kg) was first administered 2 days following near-total loss of vision in the patient's right eye. High-dose (1 mg/kg) oral prednisolone was continued at this time. By the time of review in the ophthalmology clinic 5 days later, the visual acuity had improved from hand movements to 6/9 aided and 6/6 with pinhole. A repeat ophthalmic examination found resolution of the 'cattle-tracking' of arteries and an improvement in the optic nerve appearance with only a C-shaped halo of nasal disc oedema.

Monthly intravenous tocilizumab (8 mg/kg) was continued while awaiting approval for subcutaneous therapy. At 6 months' follow-up, the oral prednisolone had been weaned from 60 to 5 mg/day, with no further visual or systemic symptoms or signs to suggest active GCA and vision maintained at 6/9 by Snellen in the affected eye.

DISCUSSION

Current guidelines recommend urgent GCA treatment with daily oral prednisolone at 1 mg/kg body weight, up to 60 mg/day.^{16,17} Treatment with ivMP has been advocated as an induction therapy in cases with evolving visual complications.^{16,17}

Even following high-dose steroid treatment, visual loss attributable to GCA recovers in just 4%–15% of patients.^{18–20} An observational study by Chan and colleagues found higher rates of visual recovery (29%) when high-dose GC was commenced within 48 hours of visual loss, indicating that prompt treatment may improve prospects for visual recovery.²¹

There is, however, no clear evidence demonstrating superiority of intravenous over high-dose oral GC in preventing or

Figure 2 Optical coherence tomography images at 6-month follow-up. (A) Infrared image of the right optic nerve head showing complete loss of the neural retinal rim inferior temporally. (B) Peripapillary retinal nerve fibre layer (RNFL) scan shows the profound loss of the RNFL. (C) RNFL thickness analysis shows that the RNFL is mostly unrecordable. (D) Infrared image of the left optic nerve head shows a floater above the optic nerve head, making it difficult to assess the disc visually. (E) Peripapillary RNFL scan shows the loss of the RNFL temporally, best seen in (F), with the patient's RNFL thickness (black line) tracking below that of normal controls within the temporal region.

recovering loss of vision in GCA. The Chan study reported significantly higher rates of visual improvement using intravenous compared with oral GC, but the treatment protocols were not standardised and the intravenous steroid group had a significantly lower mean baseline visual acuity, and therefore greater potential for visual recovery. Other studies have found no difference in visual outcomes with either route of administration.^{22 23} However, ivMP induction therapy for GCA may reduce overall treatment duration and cumulative GC doses, compared with high-dose oral GC alone.²⁴

Once all reversible symptoms have resolved and inflammatory markers have improved significantly, a gradual weaning of GC treatment is advocated. Observational cohort studies report GCA relapse rates of 34%–62%; only 15%–20% of patients achieve long-term sustained remission with GC alone.²⁵ There is little high-quality evidence to support the role of other traditional immunosuppressant agents. One meta-analysis has proposed a modest benefit with methotrexate.²⁶ However, no significant reduction in cumulative GC dose, morbidity or mortality was observed and the confidence in the effect size was low.²⁵

A phase III trial of tocilizumab showed sustained GC-free remission in 56% of patients receiving weekly subcutaneous

tocilizumab alongside a 26-week tapered course of GC, compared with 14% and 18% in the 26-week and 52-week GC taper placebo arms, respectively.²⁷ Patients treated with tocilizumab required over 40% lower cumulative doses of GC and experienced fewer GC-related adverse events compared with the placebo group. These results led to the approval of subcutaneous tocilizumab (162 mg/week) by NICE for relapsing and refractory GCA.²⁸

Intravenous tocilizumab also sustains remission in GCA. One double-blind, placebo-controlled study found that 85% of patients treated with monthly intravenous tocilizumab and tapering oral prednisolone remained relapse-free at 1 year, requiring much lower cumulative doses of GC, compared with 20% of patients given oral prednisolone and placebo.²⁹ Another study reported that 75% of patients treated with monthly intravenous tocilizumab infusions and tapering oral GC achieved remission at 26 weeks requiring a maintenance dose of prednisolone ≤ 0.1 mg/kg/day.³⁰

The pronounced deterioration of vision seen in this case occurred after 17 days of 1 mg/kg prednisolone and four pulses of ivMP, demonstrating the steroid-resistant nature of the GCA. Although non-adherence to oral GC could also explain a poor response, the patient's blood tests demonstrated a neutrophilia as is often seen with high-dose steroid treatment and his compliance with the ivMP infusions was not in question. Given the poor prognosis of GCA-related vision loss, the improvement in visual symptoms seen here was impressive. Central retinal artery occlusion causes inner retinal infarction with irreversible visual loss sustained within hours³¹; a 'pending', rather than complete occlusion, may have permitted sufficient retinal vascular perfusion to keep the retina viable.³² The profoundly reduced retinal nerve fibre layer in the right eye at 6 months' follow-up (figure 2) implies that the optic nerve head arterial supply (which includes the central retinal artery and short posterior ciliary arteries) was certainly compromised. Significant thinning of the right macula was also demonstrated (figure 3).

The rapid visual recovery observed (within days of initiating intravenous tocilizumab) may represent a delayed effect of GC treatment, but could also attest to tocilizumab's rapid onset of action. Several case reports describe patients experiencing clinical improvement of GCA symptoms within days of intravenous tocilizumab therapy.^{33 34} Progressive visual loss from anterior ischaemic optic neuropathy has also been reported in GCA, arrested by tocilizumab.³⁵

Figure 3 Optical coherence tomography macular line scan. (A) Infrared image of the right macula. The green line represents the location of the line scan (B), showing thinning of the inferior macular retinal layers and absence of photoreceptors (arrowed). (C) Infrared image of the left macula. (D) shows the corresponding normal macular retinal nerve fibres, including photoreceptors (arrowed), in the left eye.

Learning points

- Tocilizumab is a new treatment option for refractory or relapsing giant cell arteritis (GCA) and may have a role as a 'rescue therapy' in patients with sight-threatening disease.
- There is evidence that intravenous tocilizumab may induce a rapid remission of GCA, although no studies have yet directly compared the efficacy of intravenous tocilizumab to its subcutaneous form.
- There is insufficient evidence to prove superiority of intravenous over oral glucocorticoid in the prevention or recovery of visual loss in GCA.
- All patients with GCA should be advised to report visual symptoms urgently as there may be a short window of time in which permanent visual loss can be prevented.

A pharmacokinetic substudy from a trial examining tocilizumab therapy in rheumatoid arthritis found that intravenous tocilizumab achieved peak concentrations much more quickly compared with subcutaneous delivery (6 vs 74 hours).³⁶ Although no evidence correlates the time to peak tocilizumab serum concentration with speed of efficacy in GCA, these data provide a rationale for a possible benefit of intravenous over subcutaneous tocilizumab, given the highly time-critical nature of treatment in GCA-related ocular ischaemia. Further research is required to compare the efficacy of intravenous and subcutaneous tocilizumab and to investigate the potential for use as an adjunctive treatment in vision-threatening disease.

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