• Letter to the Editor •

Tocilizumab as an effective treatment option for idiopathic orbital inflammation: a case report and literature review

Hai-Yang Zhang, Hui-Jie Zhang, Hui-Fang Zhou

State Key Laboratory of Eye Health, Department of Ophthalmology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China

Correspondence to: Hui-Fang Zhou. Shanghai Ninth People's Hospital, No.639 Zhizaoju Road, Huangpu District, Shanghai 200011, China. fangzzfang@sjtu.edu.cn

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Dear Editor,

Idiopathic orbital inflammation (IOI), also known as orbital inflammatory pseudotumor, is a relatively common orbital disorder[1]. Its pathogenesis remains unclear, often regarded as a nonspecific immune-mediated response[2]. IOI presents with symptoms such as pain, photophobia, proptosis, eyelid swelling, edema, conjunctival congestion, and diplopia, with possible vision loss occurring in some cases. Based on the soft tissue structures involved, IOI can be classified into subtypes such as myositis, optic neuritis, dacryoadenitis, diffuse orbital inflammation, and orbital inflammatory masses[2].

IOI can be treated using a range of therapeutic options, including glucocorticoids, immunosuppressants, biologics, and antimetabolites[3]. Glucocorticoids are the first-line treatment with generally favorable outcomes[3]. However, responses vary, and some patients may be contraindicated due to poorly controlled diabetes, hypertension, or active ulcers. In such cases, alternative therapies should be explored to avoid side effects and ensure effective management.

Tocilizumab, a monoclonal antibody interleukin (IL)-6 receptor inhibitor, treats inflammatory and autoimmune conditions by blocking IL-6 receptors, reducing inflammation. IL-6 is crucial in several ophthalmic inflammatory diseases, including thyroid eye disease, uveitis, and scleritis[4]. While its efficacy for IOI has not been fully established, its success in similar conditions suggests potential therapeutic benefits for IOI.

In this context, we report a case of a patient diagnosed with IOI who had relative contraindications to glucocorticoid therapy. The patient achieved a favorable clinical outcome with tocilizumab treatment, with no notable side effects observed during the treatment and follow-up period.

CASE REPORT

A 34-year-old female patient presented with a one-month history of diplopia and left orbital pain. The patient had a six-year history of hypertension and diabetes, with regular use of sacubitril-valsartan and metformin. Additionally, hyperlipidemia was identified one year prior and managed through dietary interventions.

A physical examination revealed bilateral exophthalmos (right: 19 mm, left: 21 mm), eyelid edema, and elevated intraocular pressure (right: 28 mm Hg, left: 29 mm Hg). Best-corrected visual acuity was 0.9 and 0.8 in the right and left eyes, respectively. The left eye showed restricted upward, downward, and inward movement. Fundus and visual field examinations showed no abnormalities. Magnetic resonance imaging (MRI) indicated thickening of the left extraocular muscles and tendons, with the medial and inferior rectus muscles most affected (Figure 1A-1C).

The patient initially presented with suspected thyroid eye disease, but normal thyroid function tests and thyroid autoantibodies, along with unilateral muscle involvement on MRI, including tendon thickening, contradicted this diagnosis. Fundus and visual field examinations were performed, which preliminarily excluded glaucoma and other retinal diseases. After consulting a hematologist, lymphoma was excluded. A multidisciplinary discussion led to the diagnosis of myositis-type IOI in the left eye.

The patient's history included diabetes, hypertension, and hyperlipidemia, confirmed by elevated fasting blood glucose (8.4 mmol/L), glycosylated hemoglobin (8.1%), triglycerides (1.85 mmol/L), small dense low-density lipoprotein cholesterol (0.99 mmol/L), and apolipoprotein E (5.77 mg/dL). Due to contraindications to glucocorticoids and patient preferences, the Pharmacy and Treatment Committee approved off-label tocilizumab. A treatment plan was implemented with monthly intravenous infusions of tocilizumab at 8 mg/kg. The patient received four infusions from April to July 2024.

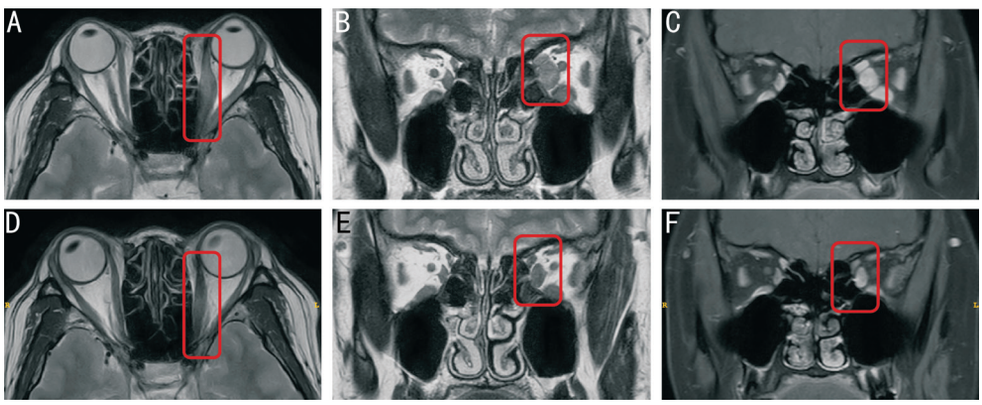

Figure 1 Comparison before and after treatment in MRI images of the patient It includes T2-weighted transverse images A and D, T2-weighted coronal images B and E, and T1-weighted coronal images with fat suppression C and F. A, B and C: The condition before treatment; D, E and F: The condition one month after completing four doses of therapy. The red box indicates the primary muscle involvement, showing the left medial rectus muscle before and after treatment. MRI: Magnetic resonance imaging.

Table 1 Ophthalmic examination results before and after treatment

Parameters	Before treatment (right/left)	After treatment (right/left)	
		One month after the first dose	One month after four doses
BCVA	0.9/0.8	0.9/0.9	0.9/0.9
IOP (mm Hg)	28/29	19/16	20/17
Exophthalmos (mm)	19/21	19/20	19/18
Diplopia	Constant diplopia	Intermittent diplopia	No diplopia
Orbital pain (Y/N)	Y	N	N
Eyelid edema (Y/N)	Y	Y	Y
Restricted ocular movement (Y/N)			
Inward	N/Y	N/Y	N/N
Outward	N/Y	N/Y	N/N
Upward	N/Y	N/N	N/N
Downward	N/N	N/N	N/N

BCVA: Best corrected visual acuity; IOP: Intraocular pressure; Y: Yes, N: No.

One month after the first treatment and before the second infusion, the patient reported significant improvement. The patient's continuous diplopia gradually became intermittent. Meanwhile, the left orbital pain decreased, and the left eye exophthalmos reduced to 20 mm. Intraocular pressure returned normal (right: 19 mm Hg, left: 16 mm Hg). However, restricted eye movement persisted in the left eye, with limitations in inward and outward movements.

After four rounds of tocilizumab, substantial improvement was observed. Diplopia and restricted eye movement resolved, and proptosis in the left eye reduced to 18 mm. However, eyelid edema persisted, with no significant change in appearance. Comparative orbital MRI revealed marked reduction in extraocular muscle thickening, particularly in the left medial and inferior rectus muscles, with decreased signal intensity (Figure 1D-1F). The patient reported no discomfort, and no side effect was observed. Relevant ophthalmic examinations are summarized in Table 1.

DISCUSSION

The diagnosis of IOI is complex and requires thorough exclusion of differential diagnoses, including infectious diseases, autoimmune disorders, hematological malignancies, and other neoplastic conditions[2]. Euthyroid thyroid eye disease refers to orbital inflammatory changes resembling thyroid eye disease but occurring in patients with normal thyroid function[5]. Differentiating IOI from euthyroid thyroid eye disease can be particularly challenging, especially when tendon involvement of the extraocular muscles is subtle and difficult to assess. IOI presents with varied symptoms, ranging from generalized orbital inflammation to localized involvement of structures like the lacrimal gland and extraocular muscles. Its onset may be acute or subacute, potentially progressing to a chronic or relapsing condition. Comprehensive evaluations are essential, including thyroid function tests, tumor markers, infectious disease markers, and autoimmune antibody assessments. Imaging studies are crucial, often revealing extraocular muscle thickening at both belly and tendon, helping distinguish IOI from other orbital inflammatory diseases. This highlights the need for a comprehensive approach to IOI diagnosis and management in clinical practice.

Table 2 Clinical presentation of published IOI cases treated with tocilizumab

Article	Age/sex	Involved eye(s)	Previous treatment	TCZ treatment regimen	Concomitant treatment	Response	Side effects
Silpa-Archa *et al*[7]	34/female	Bilateral	MTX, MMF, CSA, IFX	4 mg/kg/mo (initial) to 8 mg/kg/mo iv for 9mo	-	N	-
Artaechevarria *et al*[8]	59/female	Right	RTX, GC, MTX, LRT	8 mg/kg/mo iv for 6mo	60 mg GC qd po	Y	-
Casasnovas *et al*[9]	37/male	Bilateral	GC, CSA, MTX, MMF, IFX, ADA, LRT, RTX, IVIG	8 mg/kg/mo iv for 9mo	60 mg GC qd po	Y	-
Current study	34/female	Left	-	8 mg/kg/mo iv for 4mo	-	Y	-

IOI: Idiopathic orbital inflammation; MTX: Methotrexate; MMF: Mycophenolate mofetil; CSA: Cyclosporine; IFX: Infliximab; RTX: Rituximab; GC: Glucocorticoids; LRT: Local radiotherapy; ADA: Adalimumab; IVIG: Intravenous immunoglobulin; TCZ: Tocilizumab; Y: Yes, N: No; iv: Intravenous; qd: Once daily; po: Oral administration.

IOI offers various treatment options, but patient responses differ, necessitating tailored strategies to minimize side effects and halt disease progression. Tocilizumab has demonstrated efficacy in treating thyroid eye disease and IOI, making it a potential alternative for cases with diagnostic challenges or contraindications to glucocorticoids. This patient, unsuitable for glucocorticoids due to uncontrolled diabetes, hypertension, and hyperlipidemia, displayed tendon thickening on MRI, consistent with IOI and excluding euthyroid thyroid eye disease. Following consultation with internal medicine team and consideration of patient preferences, tocilizumab was initiated, resulting in significant clinical improvement. This decision avoided glucocorticoid-related side effects, including exacerbated comorbidities, osteoporosis, and iatrogenic Cushing's syndrome.

The pathogenesis of IOI is not fully understood but is linked to immune dysregulation[2]. IOI patients show increased orbital $CD40^+$ fibrocytes, which secrete IL-6, a key cytokine in chronic autoimmune and inflammatory diseases[6]. IL-6 fosters a pro-inflammatory environment by stimulating acute-phase proteins, regulating plasma cells, enhancing antibody production *via* dendritic cell maturation and STAT signaling, and promoting cytotoxic T cell differentiation while suppressing regulatory T cells. Targeting the IL-6 receptor, tocilizumab effectively controls inflammation in a range of ocular inflammatory diseases like IOI, thyroid eye disease, uveitis, and scleritis[4].

Reports on tocilizumab for IOI treatment are limited, with three studies documenting varying clinical characteristics and responses[7–9]. All studies summarized in Table 2 focus on refractory IOI. In these cases, prior treatments such as glucocorticoids, rituximab, methotrexate, mycophenolate mofetil, and local radiotherapy yielded poor outcomes. Tocilizumab regimens varied, with two cases combining oral glucocorticoids. Among these, two patients responded positively, achieving inflammation control and a quiescent phase, while one showed no improvement after nine months. In contrast, our patient, without additional treatments, achieved effective inflammation control and a stable prognosis in a shorter timeframe.

Tocilizumab may represent a promising therapeutic option for IOI, particularly in patients unsuitable for glucocorticoids. However, due to the relapsing nature of IOI, long-term monitoring is essential to fully understand treatment outcomes. Future studies directly comparing tocilizumab with glucocorticoids are warranted to establish optimal management strategies, including comparisons of short- and long-term efficacy, changes in clinical signs and symptoms, and the risk of disease recurrence.

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