



The Use of Tocilizumab to Treat Recurrent Thyroid Eye Disease Previously Treated with Teprotumumab

Naomi C Pang BA*, Adam S Hassan MD

Michigan State University, Eye Plastic and Facial Cosmetic Surgery, Grand Rapids, MI, USA

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*Corresponding Author

Naomi C Pang BA

Address: 15 Michigan St NE, Grand Rapids, MI 49503, USA

E-mail: pangnaom@msu.edu

Introduction

Standard treatment protocols for thyroid eye disease (TED) traditionally call for the use of systemic corticosteroids. Corticosteroid therapy may result in a rebound of TED following therapy completion.^{1,2} Moreover, associated side effects and concurrent contraindications to corticosteroid use may make this a less sought-after treatment option in some patients. Therefore, there is a need for a non-corticosteroid therapy in the treatment of TED. As our understanding of TED pathogenesis improves, more targeted biologic therapeutic options have become essential.

One of these therapeutics is teprotumumab. Teprotumumab is United States (US) FDA-approved for the treatment of TED. It is a human recombinant monoclonal IgG1 antibody against insulin growth factor 1 receptor (IGF1R).³ It blocks IGF1R-dependent induction of pro-inflammatory cytokine production as well as orbital fibroblast proliferation and differentiation.⁴ A phase III trial of intravenous teprotumumab found a reduction of proptosis by 73% in patients with active, moderate-to-severe TED compared to a placebo group. Improvements in TED-related diplopia, Graves' orbitopathy quality of life (GO-QOL) questionnaire scores, and clinical activity scores (CAS) were also observed.³

Another biologic therapy that has been used for TED is tocilizumab. Tocilizumab is a recombinant humanized monoclonal antibody against the IL-6 receptor.⁵ Use of tocilizumab for the treatment of TED is currently off-label in the United States. However, several cases have demonstrated its efficacy in treatment of corticosteroid-resistant TED as well as in patients with contraindications for steroid use.⁶⁻¹¹ Likewise, a randomized, double-masked trial in Spain confirmed these findings with improvements in CAS and European Group on Grave's Orbitopathy (EUGOGO) score as well as proptosis.¹²

Here, we describe a case with severe TED whose symptoms were alleviated with the intravenous administration of tocilizumab after TED progression following treatment with teprotumumab, corticosteroid, and orbital decompression surgery. This case is unique because it demonstrates sequential use of teprotumumab followed by tocilizumab in a single patient for the treatment of TED.

Case Report

A 72-year-old White male non-smoker was diagnosed with hyperthyroidism 15 years prior to presentation and was treated with radioactive iodine. He began having worsening TED-related ophthalmic findings over the past 4 years. A course of oral prednisone did not lead to satisfactory improvement. The patient then underwent bilateral decompression surgery in 2019. Despite this, the diplopia, bilateral proptosis, and eyelid retraction remained. This prompted the use of intravenous teprotumumab 10 mg/kg for the first 3 weeks and then 20 mg/kg every 3 weeks for a total of 8 treatments. Prior to his treatment, the CAS was 3/7. Exophthalmometry measurements were 20.0 mm on the right and 24.0 mm on the left. Extraocular movements were markedly restricted in all 4 gazes. Following treatment with teprotumumab, the patient noted substantial improvement in proptosis and eyelid retraction, but not the diplopia. Extraocular movements improved but remained mildly restricted. CAS decreased to 1/10.

Upon presentation to our clinic, one year had passed since teprotumumab treatment. His CAS had increased to 3/7. His primary concern was for exophthalmos of his right eye. Extraocular movements were restricted bilaterally, more marked on the right compared to the left. Exophthalmometry measurements increased to 24.0 mm in the right eye and decreased to 22.0 mm in the left eye. Computed tomography (CT) of the right orbit showed marked fusiform enlargement of the extraocular muscles with proptosis more pronounced on the right compared to left. Visual acuity was 20/200 in the right eye and 20/40 in the left eye. Color vision was decreased on the right (9/11 Ishihara plates) and normal on the left. Bilateral visual fields were unreliable, and bilateral pupil exams were unremarkable.

Compressive optic neuropathy (CON) on the right was suspected due to significant apical crowding of the optic nerve on the CT and reduced visual acuity and color vision testing. Oral prednisone was started. Although a relative afferent pupillary defect is usually present in the setting of CON, it was not apparent on exam. As such, the CON was thought to be mild. Optical coherence tomography was obtained. The patient underwent a prednisone taper with improvement to 20/80 and 10/11 Ishihara plates in the right eye. The reduced visual acuity and color vision that improved with systemic corticosteroid supported a diagnosis of CON. Visual fields and pupillary examination remained within normal limits.

The exophthalmos, diplopia, and conjunctival hyperemia remained unchanged. Treatment options including surgical vs medical management were discussed. Given the patient's extensive surgical history and his previous success with teprotumumab, he elected for repeat teprotumumab treatment; however, this treatment was not approved by his insurance and thus the patient declined. Instead, the patient elected to trial tocilizumab 8 mg/kg monthly for 4 treatments. He tolerated the treatment well without adverse effects. One week after his final infusion, his CAS decreased to 1/10. Conjunctival hyperemia resolved, and exophthalmometry measurements decreased to 21.0 mm in the right eye and 20.0 mm in the left eye. Extraocular movement improved bilaterally. An updated CT of the right orbit showed improved proptosis 3 months status-post treatment compared to pretreatment (Figure 1). The diplopia remained unchanged. Visual acuity improved to 20/60 in the right eye and was unchanged in the left. Color vision improved to 11/11 in the right eye.

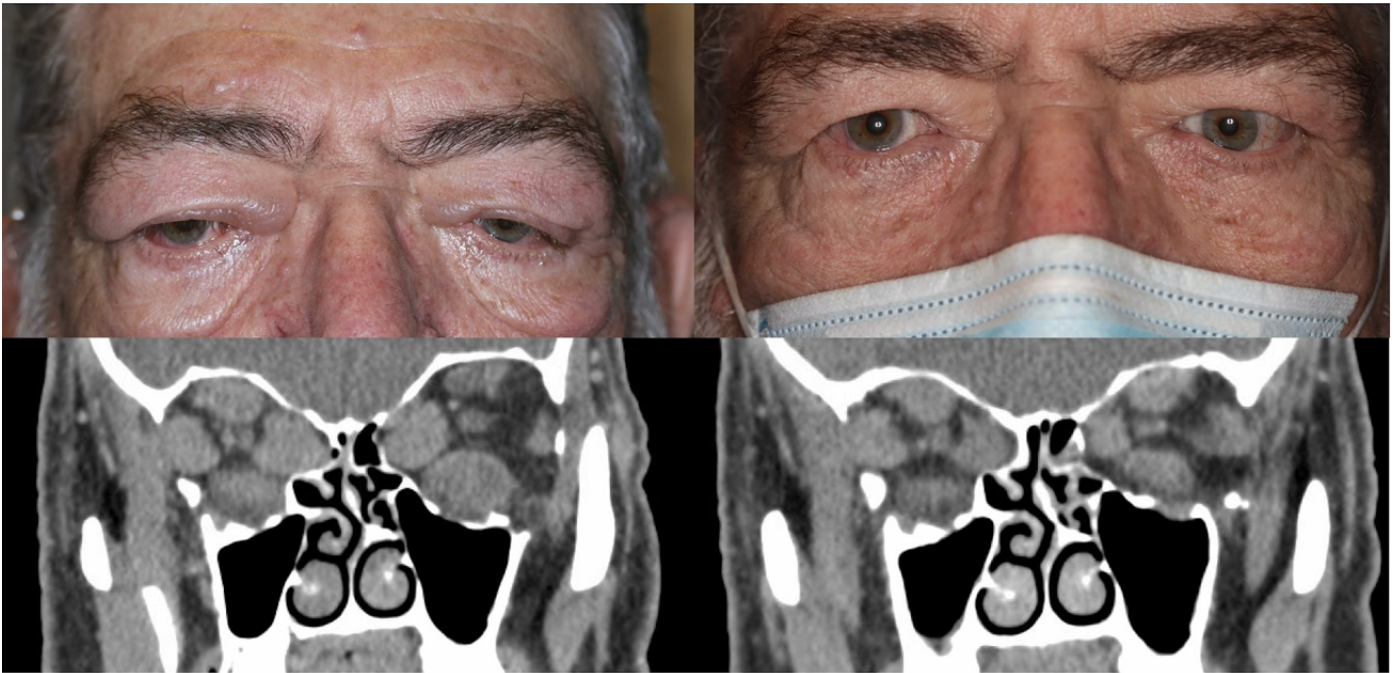


Figure 1. Left column: External photograph and computed tomography (CT) of the orbit pre-tocilizumab treatment. Note significant swelling in the periorbital area with fullness in all four eyelids and conjunctival hyperemia. On CT, note significant extraocular rectus muscle enlargement. Right column: External photograph and CT of the orbits 3 months following intravenous tocilizumab shows significant improvement.

Eighteen months following tocilizumab treatment (Figure 2), CAS, color vision, and pupil exam, and visual fields were stable. Exophthalmometry measurements remained unchanged. Right adduction improved from 40% to 75%.



Figure 2. External photograph of patient 18 months following intravenous tocilizumab showing stable external manifestations of thyroid eye disease.

Discussion

The patient presented herein has stable exophthalmos 18 months post-tocilizumab administration. He continues to have symptomatic improvement with less irritation and resolved conjunctival hyperemia. However, if it were

not for the insurance denial, an additional trial of teprotumumab may have been a suitable treatment option. The OPTIC-X extension trial found that 62.5% of patients with TED reactivation who were re-treated with teprotumumab responded favorably with reduction in proptosis, without additional safety concerns.¹³ A recent retrospective case-control study by Toro-Tobin et al. showed that both teprotumumab and tocilizumab to treat steroid-resistant TED were beneficial for up to 52 weeks, to varying degrees.¹⁴ Within this study, one patient who initially responded to tocilizumab experienced a TED flare and was subsequently treated with teprotumumab. This raises the question of treatment durability of tocilizumab vs teprotumumab and whether repeat treatment with the same therapeutic or cross-over treatment with another biologic might be more effective.

As our understanding of the pathophysiology and treatment of TED progresses, ophthalmologists may take a more targeted therapeutic approach. A recent meta-analysis comparing the rituximab, teprotumumab, and tocilizumab suggested that monoclonal antibodies may have more favorable outcomes than standard steroid therapy with regard to CAS, proptosis, diplopia, and quality of life.¹⁵

Biologics in the treatment of TED may pose some barriers to care. While teprotumumab and then tocilizumab were covered by insurance, this coverage is not necessarily the norm—especially in the case of tocilizumab since its use in TED is currently considered off-label. Additionally, coordinating care with an infusion center may delay access due to challenges with transportation and continuity of care. As an alternative, subcutaneous administration of tocilizumab has been as a more convenient and affordable option with comparable outcomes to intravenous infusion.⁷ While subcutaneous teprotumumab is currently not available for clinical use, its efficacy and safety are currently being evaluated.

Given the complexity of TED's pathophysiology, effective treatment may be elusive for some patients. Biologic therapeutics such as teprotumumab and tocilizumab have been promising in the treatment of corticosteroid-resistant TED. Our case demonstrates the potential benefits of considering such treatment options in patients who do not respond to traditional therapeutic approaches.

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Conflict of Interest Statement

The authors declare no conflicts of interest related to this topic.