



Effects of teprotumumab on patients with long-standing, active thyroid eye disease

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ABSTRACT

Purpose: Describe five cases of long-standing, active thyroid eye disease that responded to treatment with teprotumumab.

Observations: Five patients with a greater than 9-month-history of thyroid eye disease, including two patients who had previously failed orbital radiotherapy, received eight doses of teprotumumab. All five patients, including those with a history of orbital radiotherapy, achieved a proptosis reduction of at least 2 mm in each eye as well as a Clinical Activity Score reduction of at least 2 points. In addition, all cases of diplopia improved and all but one case of lagophthalmos improved.

Conclusions and Importance: Teprotumumab may be a safe and efficacious therapy for active thyroid eye disease that is of longer duration than previously studied in clinical trials, as well as disease refractory to orbital radiotherapy. In addition to robust improvement in proptosis and Clinical Activity Score, data from this series suggests diplopia and lagophthalmos may also respond to teprotumumab. Further study of teprotumumab is needed, but in the meantime these results may encourage providers to consider teprotumumab for their patients with long-standing or previously treated disease.

1. Introduction

Thyroid eye disease (TED) is a debilitating autoimmune disease of orbital soft tissue that usually occurs in the context of Graves' disease.¹ Until recently, there were no Federal Drug Administration (FDA)-approved treatment options, and the off-label therapies that existed were frustrated by dose-limiting adverse effects² and questionable long-term efficacy.^{3,4} Advances in research within the last two decades have led to the development of teprotumumab (Tepezza, Horizon Therapeutics, Deerfield, Illinois), a human monoclonal antibody against insulin-like growth factor-I receptor.^{5,6} This drug gained FDA approval in 2020 for the treatment of TED after phase II and phase III randomized controlled trials demonstrated it reduced proptosis and Clinical Activity Score (CAS) in patients with active TED of fewer than nine months' duration who were treatment-naïve^{7,8} or had been previously treated with glucocorticoids.⁷

Early, limited data suggest that teprotumumab may be efficacious in reducing proptosis and CAS in cases of chronic thyroid eye disease.⁹⁻¹¹ Data on teprotumumab's effect in cases of prior orbital radiotherapy (OR), however, are even more limited. One case report described a

positive response in dysthyroid optic neuropathy refractory to OR⁹; another small retrospective study included two patients with prior OR, but did not indicate whether they specifically responded to therapy.¹⁰ The present case series describes the effects of teprotumumab in five patients with long-standing, active TED, including two patients who had previously failed OR. The collection and reporting of all protected patient health information was compliant with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki. This case series was granted a waiver from approval by the Institutional Review Board.

2. Findings

2.1. Case 1

Patient 1 was a 63-year-old white female with Graves' disease who presented with bilateral proptosis, lagophthalmos, and severely reduced levator function. She began teprotumumab therapy 11 months after onset of symptoms. At one week following treatment, she achieved a reduction of 4.5 mm of proptosis in her right eye and 4 mm in her left

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eye. Her CAS¹² decreased by 4 points and diplopia was reduced from grade 2 to grade 1 on the Gorman diplopia score.¹³ Her levator function improved by 9 and 12 mm, respectively, with lagophthalmos improving by 3 mm in the right eye and resolving in the left eye. Adverse effects from therapy were mild, self-limited, and included leg cramping and stomach cramping.

2.2. Case 2

Patient 2 was a 79-year-old white male with Graves' disease who was noted to have marked bilateral proptosis, upper eyelid retraction, and right lagophthalmos on presentation. He initially underwent OR, which temporarily improved his proptosis by 3 mm in the right eye and 2 mm in the left eye but worsened his diplopia. He subsequently began a course of teprotumumab 11 months after symptom onset. At 22 weeks after completion of therapy, his proptosis decreased by 4 mm in the right eye and 3 mm in the left eye (see Fig. 1) and CAS improved by 4 points. His diplopia resolved from baseline grade 2, and lagophthalmos improved by 1 mm in the right eye. His adverse effects included worsening of baseline hearing loss, as well as self-resolving leg cramping, brittle nails, and loss of taste.

2.3. Case 3

Patient 3 was a 61-year-old white female with Graves' disease who presented with bilateral mild proptosis, upper eyelid retraction, and mild lagophthalmos. Prior to initial presentation, she had undergone OR with minimal improvement in diplopia. She ultimately began teprotumumab infusions after 19 months of symptoms. She was evaluated five weeks after treatment and was noted to have an improvement in proptosis of 4 mm in the right eye and 3 mm in the left eye (see Fig. 2). Her CAS improved by 7 points, diplopia resolved from baseline grade 1, and lagophthalmos resolved in both eyes. She reported self-limited mild hair loss and leg cramping.

2.4. Case 4

Patient 4 was a 61-year-old white female with a long-standing history of Graves' disease. Initial examination revealed bilateral proptosis, bilateral lagophthalmos, and right upper and lower eyelid retraction. She began therapy with teprotumumab 20 years after initial symptom onset. Two weeks following therapy, her proptosis improved by 5 mm in the right eye and 3 mm in the left eye (see Fig. 3) and CAS improved by 4 points. Her diplopia resolved from grade 1, and lagophthalmos resolved in both eyes as well. She reported no side effects from therapy.

2.5. Case 5

Patient 5 was a 19-year-old white female with Graves' disease who presented with bilateral proptosis, upper eyelid retraction, and lagophthalmos. She had a 12-month history of symptoms prior to initiation of teprotumumab. Six weeks after completion of therapy, her proptosis was reduced by 2 mm bilaterally and CAS was reduced by 3 points. In addition, her lagophthalmos improved from 5 mm to 1 mm in the right eye and remained stable at 1 mm in the left eye. She denied any adverse effects from treatment.

3. Discussion

This case series described five patients with TED of greater than nine months' duration who all responded to teprotumumab therapy (see Table 1) with only minimal, self-limited adverse effects. Namely, every patient achieved a clinically meaningful^{7,8,12} reduction in proptosis of at least 2 mm in each eye, as well as a reduction in CAS of at least 2 points after receiving eight doses of teprotumumab. These findings were true whether the patient was treatment-naïve or had previously undergone OR. To our knowledge, these are the first reported cases of treatment response in optic nerve-sparing TED refractory to OR.

Our patients, both treatment-naïve and treatment-resistant, also benefitted from teprotumumab in terms of diplopia and eyelid position. All patients with baseline diplopia experienced an improvement of at least one grade on the Gorman diplopia score,¹³ and only one case of diplopia failed to resolve with treatment. This response was more robust than what has been previously reported.¹⁰ In addition, all but one eye with baseline lagophthalmos experienced an improvement, and over half of these eyes achieved resolution. Early experience with teprotumumab in chronic TED has not shown a significant improvement in lid position as measured by margin-reflex distance or interpalpebral fissure distance,^{10,11} so the improvement in lid position as measured by lagophthalmos is an encouraging development.

Teprotumumab was well-tolerated by the five patients. Two out of the five individuals experienced no adverse effects from therapy, whereas the remaining cases reported only mild, self-limiting adverse effects. Leg cramping was most noted, whereas stomach cramping, loss of taste, worsened hearing loss, and brittle nails were more rarely described.

Given this case series' retrospective design and small sample size, generalizability is limited. Furthermore, all patients were white, so it is unclear whether patients of other races would experience the same results. Finally, our report did not account for long-term outcomes, as most post-treatment measurements were taken within eight weeks of therapy completion. It is possible that the response to teprotumumab lessens over time, as it tends to with other treatment modalities.^{3,4}

4. Conclusions

These observations support the early data that teprotumumab may be a safe and efficacious therapy for patients with active TED that is of a longer duration than previously studied in clinical trials,⁹⁻¹¹ and also suggest the benefits may extend to those who have failed OR. Contrary to previous reports,^{10,11} this series found a robust treatment-response of diplopia and lid position, which is encouraging for those patients in whom these symptoms are debilitating.

The greatest benefit of our case series, rather than drawing conclusions, is to promote the further study of teprotumumab in patients with longer-standing, previously treated, or untreated TED. In the meantime, this report may encourage providers to consider teprotumumab for their patients with similar characteristics as the patients described herein.

Patient consent

This case series was granted a waiver from approval by the affiliated Institutional Review Board because it did not contain any personal

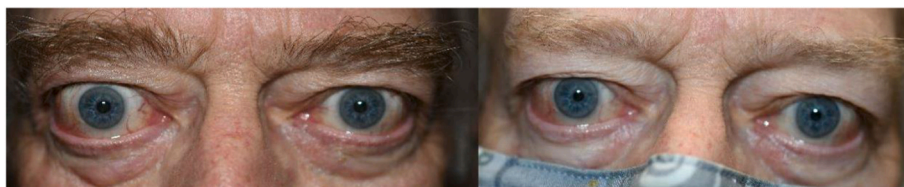


Fig. 1. External photographs of Patient 2 prior to initiation of teprotumumab therapy (left) and after completion of therapy (right).



Fig. 2. External photographs of Patient 3 prior to initiation of teprotumumab therapy (left) and after completion of therapy (right).



Fig. 3. External photographs of Patient 4 prior to initiation of teprotumumab therapy (left) and after completion of therapy (right).

Table 1

Patient characteristics and treatment response.

Patient Number	Age (years)	Duration of TED (months)	Prior OR	Δ Proptosis (millimeters, right eye/left eye)	Δ CAS	Δ Diplopia (grade)	Δ Lagophthalmos (millimeters, right eye/left eye)
1	63	11	No	-4.5/-4	-4	-1	-3/-2
2	79	11	Yes	-4/-3	-4	-2	-1/0 ^a
3	61	19	Yes	-4/-3	-7	-1	-2/-2
4	61	240	No	-5/-3	-4	-1	-3/-1
5	19	12	No	-2/-2	-3	0 ^a	-4/0

TED = thyroid eye disease, OR = orbital radiotherapy.

^a Denotes a pre-treatment measurement of 0 (e.g., diplopia score of 0 or lagophthalmos of 0 mm).

information that could lead to the identification of any of the patients.

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CRedit authorship contribution statement

Kyle B. Vinson: Investigation, Resources, Writing – original draft.
Maria Kirzhner: Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

Dr Maria Kirzhner is on the speaker’s bureau for Horizon Therapeutics. The following author has no financial disclosures: KBV.

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