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Effect of teprotumumab on intraocular pressure in thyroid-associated ophthalmopathy

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Abstract:

PURPOSE: To examine changes in intraocular pressure (IOP) in patients with thyroid eye disease (TED) following teprotumumab.

MATERIALS AND METHODS: A retrospective review of 17 patients with TED who received teprotumumab between January 2020 and September 2021 was conducted. IOP, extent of proptosis, and clinical activity score were reviewed at baseline and at 6 weeks, 12 weeks, and 24 weeks for patients undergoing teprotumumab treatment. The primary outcome measure was change in IOP, while secondary outcome measures included changes in proptosis and clinical activity score.

RESULTS: Of the 17 patients (34 eyes) with TED who were treated with teprotumumab, the mean age was 50.5 years, and 15 (88%) were female. The mean baseline IOP was 20 mm Hg (range 13–28), and the mean baseline clinical activity score was 3.8 (range 0–6). Of the 34 eyes examined at baseline, examinations were repeated in 16 at 6 weeks, 26 at 12 weeks, and 8 at 24 weeks. At week 6 of treatment, mean IOP decreased by 4.9 mm Hg ($P < 0.0001$). At week 12 of treatment, mean IOP decreased by 4.6 mm Hg ($P < 0.0001$). Mean IOP was decreased at last record of follow-up by 4.9 mm Hg ($P < 0.0001$).

CONCLUSION: Among patients with TED, teprotumumab treatment was associated with a reduction in IOP.

Keywords:

Intraocular pressure, orbital congestion, proptosis, teprotumumab, thyroid eye disease

Introduction

Thyroid eye disease (TED) is an autoimmune disease associated with facial disfigurement, diminished quality of life, and potentially vision-threatening consequences.[1] In the active, progressive stage of the disease, orbital inflammation leads to expansion and remodeling of connective tissues in the orbit.[2] These alterations result in variable ophthalmic manifestations, including proptosis, periorbital edema, eyelid retraction, diplopia, strabismus, exposure keratopathy, and compressive optic neuropathy.[2] In addition, elevated intraocular pressure (IOP) is a well-described finding in patients with TED.[3-5]

Proposed theories for elevated IOP, generally accepted to be >21 mm Hg,[6] in TED include restriction and compression of the globe by enlarged extraocular muscles, elevated episcleral venous pressure resulting from orbital congestion, or deposition of mucopolysaccharides in the trabecular meshwork limiting aqueous outflow.[7-9] Studies have demonstrated that IOP in patients with TED decreases following orbital decompression surgery, strabismus surgery, and systemic steroid treatment.[7,9-12] Orbital decompression is thought to lower

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IOP through decreasing venous congestion and orbital pressure, leading to lowered episcleral venous pressure.[10] Strabismus surgery decreases pressure on the globe after recession of "tight" muscles thus lowering episcleral venous pressure and IOP.[10] Steroids decrease orbital inflammation, which is thought to lower orbital volume and improve venous outflow.[9,12]

Teprotumumab, a novel human monoclonal insulin-like growth factor-1 receptor inhibitor, was recently approved by the Food and Drug Administration in January 2020 for the treatment of TED. In phase II and phase III randomized placebo-controlled trials, patients with active moderate-to-severe TED received 8 infusions of teprotumumab over the course of 24 weeks.[13,14] Teprotumumab was shown to be effective in reducing the clinical manifestations of TED, including proptosis, diplopia, and clinical activity score.[13,14] However, the effects of teprotumumab on IOP in TED patients remain uncharacterized. Elevated IOP may be associated with progression to glaucomatous optic neuropathy in TED.[3,4] The goal of this study was to evaluate changes in IOP in patients with TED following teprotumumab treatment.

Materials and Methods

We conducted a retrospective review of the electronic medical records of consecutive patients with TED who received teprotumumab between January 2020 and September 2021 at the Scheie Eye Institute. The study was approved by the Institutional Review Board of the University of Pennsylvania (approval number: 843923, approval date: 8/12/2020), adhered to the tenants of the Declaration of Helsinki, and was conducted in accordance with the Health Insurance Portability and Accountability Act. Adult patients over the age of 18 years with TED who received eight infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for subsequent infusions) every 3 weeks over a period of 24 weeks were included. Patients who were receiving IOP-lowering medication had a history of prior surgical treatment for TED, and with a follow-up duration of <6 weeks were excluded from the study.

Patient demographics and clinical characteristics were collected including age, sex, self-identified race, duration of TED, duration of Graves' disease, smoking status, systemic steroid use, glaucoma medication use, and teprotumumab treatment duration. In addition, data were collected on IOP, proptosis measurements, and clinical activity score at baseline and at 6 weeks, 12 weeks, and 24 weeks for patients undergoing teprotumumab treatment. The primary outcome measure was change in IOP. Secondary outcome measures were changes in proptosis and clinical activity score. IOP was measured using a Tono-Pen (Reichert Technologies, Depew, NY, USA) applanation tonometer in primary gaze. Proptosis was assessed using a Hertel exophthalmometer.

All statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Generalized estimating equations were used in linear models to account for the correlation of both eyes within a subject and across time. Mean differences in IOP, proptosis, and clinical activity scores following treatment were estimated by modeling the outcomes by time in the models. A $P < 0.05$ was considered statistically significant.

Results

A total of 17 patients (34 eyes) met the inclusion criteria. The mean age was 50.5 ± 14.3 years (range 34–65), 15 (88%) of patients were female, 8 (47%) were self-identified as White, 6 (35%) were self-identified as Black, and 2 (12%) were Asian [Table 1]. Average treatment duration was 12 weeks (range 6–24), average baseline IOP was 20 mm Hg (range 13–28), and average baseline clinical activity score was 3.8 (range 0–6). Nine out of 34 eyes had elevated baseline IOP (>21 mm Hg), with a mean of 24.1 mm Hg. Average duration of TED at the time of treatment initiation was 27.1 ± 27.9 months (range 2–120). A total of 2 patients (12%) initiated treatment between 12 and 18 months of TED onset, while 7 (41%) initiated treatment within 18 months of TED onset. Thirty-four eyes were examined and received IOP measurements at baseline, 16 at 6 weeks, 26 at 12 weeks, and 8 at 24 weeks. During the study, 10 patients underwent 2 IOP measurements, 5 patients underwent

Table 1: Baseline patient characteristics

Characteristics	Values (*n*=17 patients, 34 eyes)
Age (years), mean±SD	50.5±14.3
Sex, *n* (%)	
Male	2 (12)
Female	15 (88)
Race, *n* (%)	
White	8 (47)
Black	6 (35)
Asian	2 (12)
Other	1 (6)
Duration of thyroid eye disease (months), mean±SD	27.1±27.9
Duration of Graves' disease (years), mean±SD	6.5±7.9
Smoking status, *n* (%)	
Smoker	3 (18)
Nonsmoker	14 (82)
Systemic steroid use 12 months prior, *n* (%)	2 (12)
IOP (mmHg), mean±SD	20±3.3
Proptosis measurement (mm), mean±SD	22.4±2.4
Clinical activity score, mean±SD	3.8±1.5

SD=Standard deviation, IOP=Intraocular pressure

3 IOP measurements, and 2 patients underwent 4 IOP measurements.

Mean IOP was decreased at 6 weeks after the initiation of treatment (mean change = −4.9 mm Hg, 95% confidence interval [CI − 7, −2.9], $P < 0.0001$). Twelve weeks after initiation of treatment, mean IOP decreased by 4.6 mm Hg (95% CI [−6.3, −3.4], $P < 0.0001$) [Table 2]. At 24 weeks of treatment, mean IOP decreased by 3.9 mm Hg, which trended toward statistical significance (95% CI [−8.4, 0.4], $P = 0.07$). At the last recorded follow-up visit, mean IOP decreased by 4.9 mm Hg (95% CI [−6.3, −3.4], $P < 0.0001$). There was an average 24% reduction in IOP relative to baseline at last recorded follow-up. Figure 1 shows the IOP measurements in our study patients at 6 weeks, 12 weeks, 24 weeks, and the last recorded timepoint of teprotumumab treatment.

Mean proptosis measurements were reduced at 6 weeks (−3.7 mm, 95% CI [−6.4, −1], $P = 0.008$), at 12 weeks (−1.9 mm, 95% CI [−3, −0.8], $P = 0.0006$) and at 24 weeks of treatment (−3.4 mm, 95% CI [−5.6, −1.3], $P = 0.002$). At the last recorded follow-up visit, mean proptosis measurements decreased by 2.1 mm (95% CI [−3, −1.2], $P < 0.0001$). Mean clinical activity score was decreased at 6 weeks of treatment (−2.4, 95% CI [−3.5, −1.3], $P < 0.0001$), at 12 weeks (−2.3, 95% CI [−3.4, −1.1], $P < 0.0001$), and at 24 weeks (−2, 95% CI [−3.4, −0.1], $P = 0.03$). At the last recorded follow-up visit, mean clinical activity score decreased by 2.2 (95% CI [−3.3, −1.2], $P < 0.0001$).

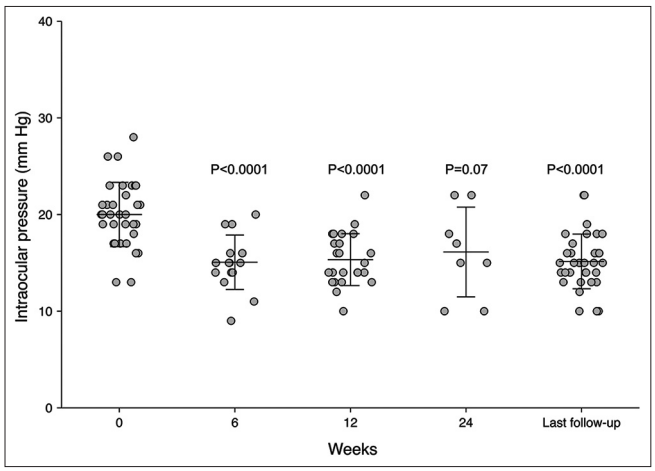

Figure 1: Distribution of intraocular pressure over time during teprotumumab treatment in patients with thyroid eye disease. Error bars represent mean ± standard deviation. *P* values shown were calculated by modeling the effect of time on IOP using generalized estimating equations. IOP = Intraocular pressure

Discussion

This study demonstrates IOP reduction following teprotumumab treatment in patients with TED. Through targeted inhibition of insulin-like growth factor-1 receptor, teprotumumab leads to improvements in proptosis, clinical activity score, and diplopia, as well as decreased extraocular muscle volume and orbital fat.[13-15] One proposed mechanism for the elevation of IOP in TED is increased volume of extraocular muscle and adipose tissue, which leads to an increase in intraorbital pressure, venous congestion, and consequently episcleral venous pressure.[7-9] Teprotumumab has been shown to decrease orbital soft tissue expansion, suggesting that the reduction of orbital connective tissue volume may mediate IOP reduction. Other postulated mechanisms of IOP elevation in TED include restriction of the globe by enlarged extraocular muscles and mucopolysaccharide deposition in the trabecular meshwork.[4,7] Teprotumumab's inhibition of insulin-like growth factor-1 receptor and consequent downstream signaling is thought to reduce glycosaminoglycan production,[16,17] which theoretically may reduce deposition in the trabecular meshwork, contributing to IOP reduction. Further, the reduction in extraocular muscle volume resulting from teprotumumab may additionally decrease IOP through alleviation of tension on the globe.[14,15]

IOP reduction occurred early following teprotumumab initiation, beginning at week 6, and significant reduction was sustained at the last recorded follow-up visit. Similarly, proptosis measurements and clinical activity score showed a significant improvement as early as week 6 in this study. These findings are consistent with prior phase II and III clinical trial results for teprotumumab which showed a significant reduction in proptosis and clinical activity score beginning at week 6.[13,14] While the reduction in IOP did not reach statistical significance at week 24, this is likely explained by the limited sample size and fewer number of eyes examined at week 24. Nevertheless, IOP reduction was found to be statistically significant at the last recorded follow-up visit. IOP reduction was observed early with teprotumumab treatment, following a similar time

Table 2: Mean intraocular pressure readings during teprotumumab treatment (mmHg)

Variable	6 weeks after initial dose (*n*=16 eyes)	12 weeks after initial dose (*n*=24 eyes)	24 weeks after initial dose (*n*=8 eyes)	Most recent record after initial dose (*n*=34 eyes)
IOP, mean±SD	15.1±2.8	15.3±2.7	16.1±4.6	15.1±2.8
Change from baseline, mean (95% CI)	−4.9 (−7–−2.9)	−4.6 (−6.3–−3.4)	−3.9 (−8.1-0.4)	−4.9 (−6.3–−3.4)
P	<0.0001	<0.0001	0.07	<0.0001

SD=Standard deviation, IOP=Intraocular pressure, CI=Confidence interval

course to improvements in clinical signs of inflammation and proptosis.

This study has several limitations. The first is the retrospective design. Second, our study included a limited number of subjects, although our sample size was comparable to recent retrospective studies on the effects of teprotumumab in TED.[15,18] Furthermore, teprotumumab's recent approval as well as delay in production due to COVID-19 vaccine development limited the national supply. Due to the lack of a control group, we were not able to make a comparison between change in IOP in subjects treated with teprotumumab and subjects receiving no treatment. However, Wémeau *et al*. found that IOP remained unchanged after 4 months in untreated patients with mild active TED.[19] We did not evaluate IOP measurements beyond 24 weeks of teprotumumab treatment, and there was no long-term follow-up to determine whether the decline in IOP was sustained after treatment. Prospective studies with longer follow-up are needed to assess the long-term impact of teprotumumab on IOP and possibly its relationship with glaucomatous and neuro-ophthalmic changes. In our study, IOP measurements were performed only in primary gaze and not in upgaze. Patients with TED may have more substantial increases in IOP on upgaze due to restriction of the globe by enlarged and fibrotic inferior rectus muscles, predominantly.[10,20] Our analysis of IOP measurements in primary position may reflect to a greater extent the impact of orbital soft tissue expansion and orbital congestion on IOP rather than isolating the effects of restrictive myopathy in upgaze. All IOP measurements in this study were performed using Tono-Pen for consistency. In support of this, a recent prospective study found no significant difference in IOP readings obtained in primary gaze using Tono-Pen compared with Goldmann applanation in patients with restrictive TED.[21]

Conclusion

The findings of this study support recent clinical studies demonstrating anatomical changes and clinical benefits associated with the use of teprotumumab in TED. In conjunction with teprotumumab's demonstrated efficacy in improving the major sequelae of TED including proptosis and diplopia, IOP reduction may represent an additional beneficial effect. The significant improvements in clinical activity score, IOP, and proptosis following teprotumumab treatment have important implications for management and may signal a transition from surgical to disease-modifying medical therapies for TED.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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