American Journal of Ophthalmology Case Reports 38 (2025) 102282

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Spectral-domain optical coherence tomography imaging findings in patients receiving teprotumumab for thyroid eye disease☆

Timothy Truong [a,1], Rona Z. Silkiss [b,c,*,1], Johnell Renz Amoroso [d], Huanye Li [f], Quan V. Hoang [e,f,g], Kasra Eliasieh [b,c], Jesse J. Jung [d,h]

[a] Department of Ophthalmology, University of Utah, Salt Lake City, UT, USA
[b] Department of Ophthalmology, California Pacific Medical Center, San Francisco, CA, USA
[c] Silkiss Eye Surgery, Oakland, CA, USA
[d] East Bay Retina Consultants, Inc, Oakland, CA, USA
[e] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[f] Singapore Eye Research Institute, Singapore National Eye Centre, Singapore
[g] Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia College of Physicians and Surgeons, New York, NY, USA
[h] Department of Ophthalmology, University of California, San Francisco, San Francisco, CA, USA

ARTICLE INFO

Keywords:
Choroidal thickness
Ganglion cell analysis
Insulin-like growth Factor-1
Insulin-like growth factor Receptor-1 inhibition
Retinal nerve fiber layer
Spectral-domain optical coherence tomography
Teprotumumab
Thyroid eye disease

ABSTRACT

Purpose: Prior studies have demonstrated the potential side effects of insulin-like growth factor-1 (IGF-1) inhibition for thyroid eye disease (TED) including hearing loss. In this study, we assessed changes in functional vision including visual field testing and best-corrected visual acuity (BCVA), clinical examination parameters, and spectral-domain optical coherence tomography (SD-OCT) biomarkers in patients who received insulin growth factor receptor-1 (IGF-R1) inhibition with teprotumumab for TED.

Design: Retrospective, noncomparative cohort.

Subjects: 22 eyes of 12 TED patients.

Methods and outcomes measures: Retrospective chart review was conducted, with demographics, clinical examination, BCVA, Humphrey visual field (HVF), and SD-OCT data: central foveal thickness (CFT), sub-foveal choroidal thickness (SFCT), choroidal vascular index (CVI), retinal nerve fiber layer (RNFL), and ganglion cell-inner plexiform layer (mGCIPL) thickness compared between before and after an 8-infusion course of teprotumumab. Linear regression modeling with clustering was used for statistical analysis. Statistical significance was set at $p < 0.05$.

Results: Proptosis, clinical activity scores, and intraocular pressure improved. SFCT -35.7μm ($p = 0.038$), RNFL -5.41μm ($p = 0.001$), and mGCIPL −7.35μm ($p = 0.010$) decreased after six months. CFT and CVI did not statistically differ. BCVA and HVF mean deviation remained stable.

Conclusions: There were statistically significant decreases in SFCT, RNFL, and mGCIPL in TED patients treated with teprotumumab, but no differences in CFT and CVI. Functional testing, with HVF and BCVA, was not affected, but there were significant systemic side effects including hearing loss noted in several patients. Further research is needed to understand the potential effects of IGF-1R blockade on the retina and optic nerve.

1. Introduction

Thyroid eye disease (TED) is characterized by orbital inflammation secondary to excessive autoimmune fibroblast activation.[1] It is most commonly associated with Graves' Disease, in which thyroid-stimulating immunoglobulins (TSI) bind the thyrotropin receptor to stimulate thyroid hormone production, enlarge the thyroid gland, and activate orbital and pretibial fibroblasts with resultant inflammation.[1–3] However, the inflammatory response seen in TED is not completely understood.[1–4] TSI is thought to bind with antigens on the

☆ Meeting Presentation: This work was presented at the annual International Retinal Imaging Symposium on May 31, 2024 in Los Angeles, California, USA.

* Corresponding author. Silkiss Eye Surgery, 400 29th St. Suite 315, Oakland, CA, 94609, USA.
E-mail address: DrSilkiss@silkisseyesurgery.com (R.Z. Silkiss).

[1] These authors contributed equally and are shared first authors.

https://doi.org/10.1016/j.ajoc.2025.102282
Received 12 October 2024; Received in revised form 6 January 2025; Accepted 14 February 2025
Available online 18 February 2025

orbital fibroblast such as insulin-like growth factor-1 (IGF-1) to stimulate hyaluronic acid accumulation and cytokine production. This leads to fibroblastic differentiation, connective tissue remodeling and edema, and enlargement of extraocular muscles and orbital adipose tissue.[1–4]

In 2020, teprotumumab became the first monoclonal antibody targeting insulin-like growth factor-1 receptor (IGF-1R) to be FDA-approved for the treatment of adults with moderate-severe, active TED.[4,5] Teprotumumab has been shown to decrease clinical manifestations of TED including proptosis, diplopia, and clinical activity scores.[4–6] However, significant audiologic side effects have been shown to occur with IGF-1R inhibition.[7–14] In a literature review of known IGF-1 effects in the human eye, Truong and Silkiss postulated that the retina is a potential target tissue that may be impacted in the systemic administration of these biologic pharmaceuticals,[15] especially because IGF-1R has been found in all layers of the retina.[15,16] Other basic science studies have demonstrated that IGF-1 may play a role in angiogenesis, with some studies suggesting that there may be a future benefit of IGF-1R inhibition in the treatment of retinal disease, including retinopathy of prematurity and age-related macular degeneration.[15–19] Despite this, there is little in the literature discussing the ramifications of TED treatment on optical coherence tomographic (OCT) and OCT angiography (OCT-A) measurements of the retina and optic nerve.[20–25] To the best of the authors' knowledge, OCT measurements of the retina thickness, choroid, and/or nerve fiber layer after treatment of TED patients have only been evaluated in response to pulsed methylprednisolone therapy and orbital decompression.[22–27] Herein, this is the first study to utilize a combination of clinical assessment, functional visual testing including Humphrey visual field (HVF), and spectral-domain optical coherence tomography (SD-OCT) measurements to better understand the potential impact of teprotumumab, a systemically administered, IGF-1R inhibitor, on the retina and optic nerve.

2. Methods

This retrospective chart review was completed between mutual patients of two clinical practices in Northern California (Silkiss Eye Surgery [RZS, KE, Oakland, CA, USA] and East Bay Retina Consultants, Inc. [JJJ, Oakland, CA, USA]). Approval from the California Pacific Medical Center Institutional Review Board was obtained, and this exempt study adhered to the tenets of the Declaration of Helsinki. This study was retrospective so patient consent was not obtained.

2.1. Participants

Patients with a known diagnosis of moderate-severe, active thyroid eye disease and a history of teprotumumab treatment were evaluated prior to and after treatment with clinical evaluation, functional visual testing, and multimodal imaging between December 2019 and April 2024 were included in this study. Patients were treated with Teprotumumab intravenously 8 times, once every 3 weeks following standard protocol (10 mg/kg for the first infusion then 20 mg/kg for the following 7 infusions).[5] Exclusion criteria included the presence of ocular pathologies (age-related macular degeneration, retinal dystrophy, retinal vascular disease such as diabetic retinopathy or retinal vascular occlusion, retinal detachment, macular pathology such as epiretinal membrane or macular hole, any form of glaucoma, high myopia (refraction $<$ -6.00 diopters) that would significantly alter the visual functional testing and multimodal imaging measurements at any timepoint, previous treatment with teprotumumab, and/or premature termination of teprotumumab infusions due to severe side effects.

2.2. Ophthalmological examination

Demographic data (age, ethnicity, sex), medical and ophthalmic history were obtained from each patient's record starting from the visit prior to the date of initiation of the first teprotumumab infusion. Clinical side effects of teprotumumab were also documented. Baseline and follow-up clinical evaluation including best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity (BCVA), intraocular pressure (IOP) by Goldmann applanation, Hertel measurement and clinical activity score (CAS) determined by a two, board-certified, oculoplastic surgeons (RZS, KE), and dilated fundus examination findings by JJJ were collected. Humphrey visual field 24-2 or 30-2 (HVF) were also obtained to assess optic nerve function, and mean deviation (MD) was used for comparison prior to and after treatment with teprotumumab.

2.3. Optical coherence tomography imaging

SD-OCT data was obtained from the Zeiss Cirrus 5000/6000 SD-OCT (Carl Zeiss Meditec, Inc. Dublin, CA, USA) with the automated Macular Cube 512x128 and Optic Disc 200x200 protocols. Images were centered on the fovea and standard OCT tracking software was utilized to minimize motion artifacts. Scans had to have a signal strength between 7 out of a possible 10 to a full 10 out of 10, uniform illumination without areas of darkness, well-focused, and no significant evidence of motion artifact. The Macular Cube 512x128 protocol included the ETDRS macular central foveal thickness (CFT, radius of curvature 1 mm) and the average ganglion cell-inner plexiform layer (mGCIPL) thickness from the ganglion cell analysis (GCA).[28] The Zeiss Cirrus Software (Cirrus Software 10.0, Carl Zeiss Meditec, Inc., Dublin, CA, USA) GCA algorithm automatically identified the macular retinal nerve fiber layer (RNFL) and inner plexiform layer (IPL) outer boundaries. The distance between the RNFL and IPL outer boundaries was defined as mGCIPL thickness.[28] The Optic Disc 200x200 protocol automatically calculated the average circumferential peripapillary retinal nerve fiber layer thickness (RNFL). The sub-foveal choroidal thickness (SFCT) was manually calculated by a single, board-certified, vitreoretinal surgeon (JJJ) with the Zeiss Cirrus software calipers as the vertical distance between the retinal pigment epithelium's (RPE) outer surface and the choroidal scleral interface from the high-definition (HD) 12 lines-radial scan pattern, which images the posterior pole with each line being averaged 8 times.

The choroidal vascular index (CVI) calculation process utilized MATLAB (MATLAB version:9.13.0, Natick, Massachusetts: The MathWorks Inc., 2022) and involved several steps to ensure accurate measurements. Initially, to counteract light attenuation's impact on OCT images, post-processing techniques such as compensation and contrast enhancement were applied to all B-scans. This approach effectively eliminated shadows caused by blood vessels, aiding subsequent segmentation processes and enhancing tissue visibility at considerable depths.[29–31] Utilizing the Reflectivity software,[32] a contrast exponent threshold of 2 was selected through extensive parameter testing to accentuate tissue boundaries. Additionally, a decompression threshold of 2 and compression exponent of 6 optimized image clarity. Following image enhancement, the boundaries between the sclera and choroid in the B-scans were reviewed and agreed upon by two independent graders (QVH and JJJ). CVI was obtained by binarizing OCT images and defined as the proportion of luminal area (LA) to total cross-sectional choroidal area (TCA).[33] To find the Total Cross-Sectional Choroidal Area (TCA), an algorithm in MATLAB automatically detected the RPE boundary on OCT B-scan images. The RPE regions were identified based on pixel intensity thresholding, and statistical analysis helped identify and remove outliers. Within the central foveal region, a 3000-μm horizontal area around the central fovea was selected. The (TCA) was confirmed after arbitration. The B-scan image was then downscaled to 8-bit and adjusted with Niblack auto local threshold. The CVI was computed as the ratio of luminal area (LA) to total choroidal area (TCA) within this specific region (Fig. 1).

2.4. Statistical analysis

ETDRS BCVA was converted to LogMAR acuity for statistical

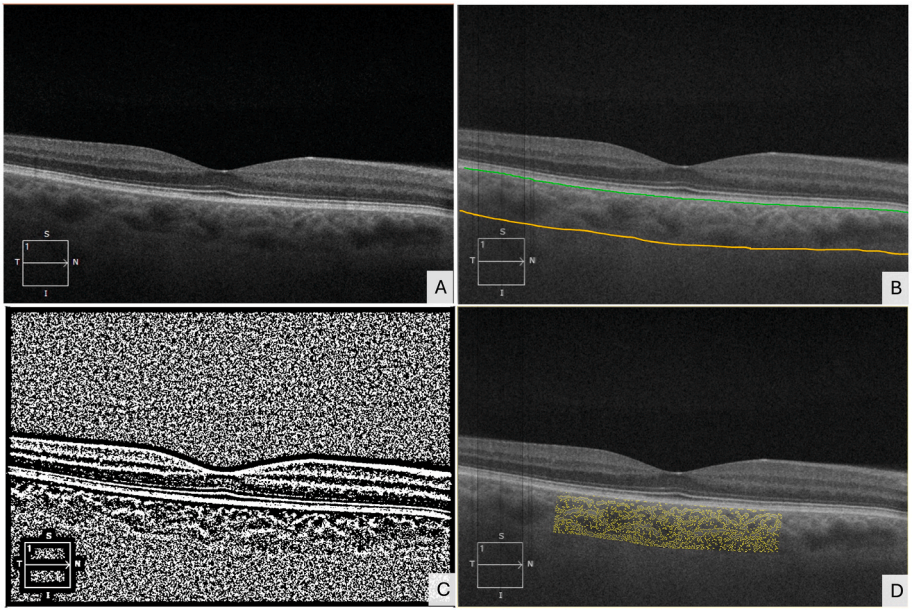

Fig. 1. Sample Image Binarization and Identification of the Luminal Area and Total Choroidal Area. Fig. 1A. Original OCT B-scan image. Fig. 1B. Compensation and constant-enhanced OCT B-scan, processed in Reflectivity. RPE boundary (green) was detected automatically using image processing techniques in MATLAB, and the boundary between sclera and choroid (yellow) was manually marked. These boundaries were validated by two independent graders. Fig. 1C. Niblack thresholded image. Dark pixels represent the luminal area (LA). Fig. 1D. Total choroidal area (TCA) was selected within the 3000-μm horizontal region around the central fovea. The CVI was computed by dividing the luminal area by the total choroidal area.

analysis. All other variables were continuous. Statistical analysis was performed using linear regression model with clustering to account for the inclusion and correlation between the two eyes of the same patient. The outcome variables including clinical examinations and clinical image findings were regressed on 'time' (baseline versus after completion of a teprotumumab course) and 'eye' (right versus. left), with clustering at the patient level. This approach adjusts for the within-subject correlation between eyes, ensuring robust standard errors. Statistical significance was set at p-value <0.05.

3. Results

34 eyes of 17 patients were initially evaluated. Two patients (4 eyes) were excluded due to premature termination of teprotumumab infusions due to side effects. Three patients (6 eyes) were also excluded due to underlying primary open-angle glaucoma. One eye of one patient was excluded due to underlying neovascular age-related macular degeneration, and 1 eye of another was excluded due to the development of a rhegmatogenous retinal detachment during interval follow-up not believed to be associated with therapy. 22 eyes of 12 patients were included for final analysis. Full demographics and thyroid eye disease data can be found in Table 1. Nine (75.0%) patients were female. Average period of known active of thyroid eye disease prior to initiation of teprotumumab was 118.8 (Range: 10–372) months. 11 patients (91.7%) had known extraocular muscle involvement. One patient (8.3%) had previously required orbital decompression. All patients had trialed a course of intravenous steroids.

Clinical examination results are summarized in Fig. 2. Baseline average logMAR visual acuity (±standard deviation (SD)) was 0.16 (±0.16); post-treatment VA was 0.20 (±0.15). Regression with clustering for inclusion of both eyes indicated no significant changes introduced by treatment (coefficient = −0.015, p = 0.569). Mean pre-treatment Hertel measurement was 23.16 (±3.38) mm, while mean post-treatment Hertel measurement was 20.86 (±2.84)mm, which significantly decreased after treatment (coefficient = −2.30, p = 0.002). Mean pre-treatment CAS score improved significantly from 5.17 (±1.34) to 2.42 (±1.75) post-treatment (coefficient = −2.75, p = 0.002). Mean pre-treatment IOP declined from 18.5 (±3.26) to 15.6 (±4.04) after treatment (coefficient = −2.91, p = 0.031). HVF MD values did not significantly change, from mean −1.96 dB (±6.89) to −2.03 dB (±3.21) (coefficient = −0.08, p = 0.524). Eye (left versus right) was included in all regression models except CAS score and was not a significant predictor for any outcome variables.

Clinical SD-OCT imaging findings are summarized in Fig. 3. Mean CFT did not significantly change before and after treatment, from 254.41 μm (±25.65) to 254.95 μm (±24.93) (regression coefficient for treatment = 0.55, p = 0.764). CVI also remained stable at 0.60 (0.05) before and 0.60 (0.07) after treatment (coefficient = 0.002, p = 0.812). SFCT declined significantly from 345.95 μm (±147.39) to 312.86 μm (±123.73) (coefficient = −33.09, p = 0.038). Average RNFL thickness decreased significantly from 89.32 μm (±9.38) to 83.95 μm (±11.62) (coefficient = −5.36, p = 0.001). Average mGCIPL thickness also declined significantly from 74.15 μm (±9.32) to 67.5 μm (±13.21) (coefficient = −6.65, p = 0.010) after treatment. Eye (left versus right), although included in all regression models, was not a significant predictor for any outcome variables. The regression with patient-level clustering results were summarized in Figs. 2 and 3.

Side effects are listed in Table 1. Eight patients (66.7 %) experienced side effects to teprotumumab. These included hearing loss, tinnitus, hyperglycemia, unintentional weight loss, hair loss, brittle nails, muscle cramps, gastrointestinal issues and worsened systemic hypertension.

4. Discussion

Herein, we report the first SD-OCT findings in a series of patients who presented with moderate to severe TED with extraocular muscle involvement that were treated with teprotumumab. After treatment, there was a noticeable improvement in CAS and over 2 mm of proptosis reduction on Hertel. We observed a significant decrease in SFCT (p = 0.038), average RNFL thickness (p = 0.001), and average mGCIPL thickness (p = 0.010) after treatment. There were no changes in vision (p = 0.57) or with MD on HVF (p = 0.52) over the follow-up period. Most patients (8 out of 12, 66.7%) did experience side effects including hearing loss.

Table 1
Full demographics and thyroid eye disease data of patients studied

Patient	Demographics					Past Ocular History	Past Medical History	Medications	Prior treatment for TED	History of TED (months)	Self-reprted side effects from teprotumumab
	Age (years)	Sex	Race/ Ethnicity	History of Smoking	Eyes included						
3	73	Female	Asian	No	OD	Dry AMD OD, Wet AMD OS (OS excluded)	Graves' Disease, Breast Cancer (remission)	None	IV methylprednisolone	10	Elevated glucose, muscle cramps, brittle nails, loss of hair
4	81	Female	White	No	OU	CEIOL OU, peripheral retinal tear OS s/p retinopexy (stable)	Graves' Disease, Sjogren's, Heart Disease	Levothyroxine, Metoprolol, Restasis, Timoptic	IV methylprednisolone	180	25 lb weight loss, hair loss, loss of taste
5	40	Male	Asian	No	OU	None	Graves' Disease, Hypertension, GERD	Amlodipine, Methimazole, Famotidine, Propranolol	IV methylprednisolone	24	None
6	66	Male	Asian	Yes	OU	None	Diabetes, Hypertension, High Cholesterol, Atrial fibrillation	Methimazole, apixaban, atorvastatin, gabapentin, losartan, metoprolol succinate, metformin	History of thyroidectomy, IV methylprednisolone	24	25 lb weight loss, hyperglycemia, hypertension
7	45	Male	Asian	Yes	OU	None	Graves' Disease	Methimazole	IV methylprednisolone	24	None
8	80	Female	White	No	OS	CEIOL OU; retinal detachment OD (OD excluded)	Graves' Disease, Hypertension, Arthritis, GERD, HLD	levothyroxine, metroprolol, losartan, pantoprazole, simvastatin	Iodine-131, IV methylprednisolone	36	Hearing loss
9	40	Female	Asian	No	OU	Myopia OU (stable)	Graves' Disease	Methimazole, Oral contraceptive	IV methylprednisolone	36	Irregular menses, brittle nails
10	41	Female	Asian	No	OU	Pseudophakia OU	Graves' Disease, Hypertension	Methimazole, Losartan	IV methylprednisolone	2	Weight loss, leg cramps
11	46	Female	Hispanic	No	OU	None	Graves' Disease	Methimazole	IV methylprednisolone	10	None
12	48	Female	Asian	Yes	OU	LASIK OU	Graves' Disease, Depression	Methimazole, Venlafaxine	IV methylprednisolone	24	None

OD: right eye; OS: left eye; OU: both eyes; TED: Thyroid Eye Disease; HLD Hyperlipidemia; GERD: Gastroesophageal Reflux Disease; LASIK: Laser-assisted in situ keratomileusis; lb: pounds.

Clinically, there was a statistically significant reduction in intraocular pressure as demonstrated in Fig. 2, which was also observed in a series of 9 patients by Chu.[34] Many TED patients demonstrate elevated IOP, likely due to extraocular muscle restriction and elevated episcleral venous pressure.[35,36] The observed decrease in IOP may be due to a reduction in prolonged orbital congestion in these patients.[35–38] Importantly, Chu et al. emphasize that this improvement in IOP does not substitute the need for appropriate follow-up and management in patients with underlying glaucoma, due to potential increased susceptibility of the optic nerve.[34]

As mentioned previously, the SD-OCT parameters of RNFL and mGCIPL typically used to monitor optic nerve disease such as glaucoma also decreased after teprotumumab treatment. It is not fully understood whether the decline seen in RNFL and mGCIPL thickness after treatment with teprotumumab is simply the resolution of pre-existing optic nerve edema[23,39,40] or damage to the ganglion cells and nerve fiber layer axons themselves.[41] In a systematic literature review, Chien et al. found that RNFL, combined RNFL/GCIPL, and mGCIPL were similar in TED patients without dysthyroid optic neuropathy (DON) and healthy controls; the only patients demonstrating decline in these biomarkers were patients with known DON or those undergoing orbital decompression for TED.[24] Similarly, Hsia et al. found that orbital decompression was associated with decreased RNFL measurements in both patients with and without DON prior to surgery.[24,27] Having excluded patients with pre-existing disc edema, they postulated that this decline in RNFL thickness may be attributed to surgical traction on the optic nerve and supplying blood vessels, and possible compression from post-operative tissue swelling. Eyes without prior DON did not demonstrate changes in visual field mean deviation, visual field index, or logMAR visual acuity.[27] To our knowledge, no other studies have specifically analyzed mGCIPL changes in response to treatment in TED. Although our study was limited, all eyes of all patients demonstrated reduction in mGCIPL thickness. Wu et al. examined the inner retinal thickness of patients with and without dysthyroid optic neuropathy, and found that mGCIPL was decreased in both groups and may precede visual dysfunction.[41] While other SD-OCT parameters such as CFT remained stable, the decrease in mGCIPL may indicate damage to the ganglion cells themselves rather than resolution of pre-existing retinal edema.[24] Further research will be needed to understand the effect of teprotumumab or other therapeutics on retinal ganglion cells. IGF-1R has been found to be ubiquitous throughout the human body and in each layer in the retina,[15,16] and IGF-1 may have a neuroprotective effect by modulating the activity of retinal microglia.[16] In vitro studies have similarly shown that IGF-1R activation is essential for the regulation of apoptosis, axonal regeneration, and photoreceptor turnover.[15,16,42–45] Given the multiple potential mechanistic effects from TED causing increased IOP, it is plausible that RNFL and mGCIPL decreased after treatment with teprotumumab and served as surrogate biomarkers of potential damage from elevated IOP during the active phase of TED.[34–36] Alternatively, the observed decline in RNFL and mGCIPL may be indicative of loss of neuroprotective effects of IGF-1R in the retina when blocked by a biologic inhibitor,[15,16,42–45] similar to observed hearing loss after treatment teprotumumab.[7–14] Further research will be required to better understand the pathophysiology of IGF-1R blockade on the retina and optic nerve.

We also observed that SFCT decreased after teprotumumab treatment. The mechanism of choroidal expansion and thickening is thought to be due to venous congestion and impaired ocular blood flow secondary to orbital congestion.[20,23,37–40] Alimgil et al. found that TED patients had elevated intraorbital pressure associated with increased venous pressure, choroidal vascular resistance, and overall decreased ocular blood flow.[37] These mechanisms of venous congestion have been implicated in venous overload choroidopathy[46] and likely correlate with increased SFCT in TED patients. Our patients responded to teprotumumab as expected, with SFCT declining after treatment. Our results did not demonstrate any statistical differences in CVI before or after treatment, though this may be due to the way CVI is calculated. CVI is the

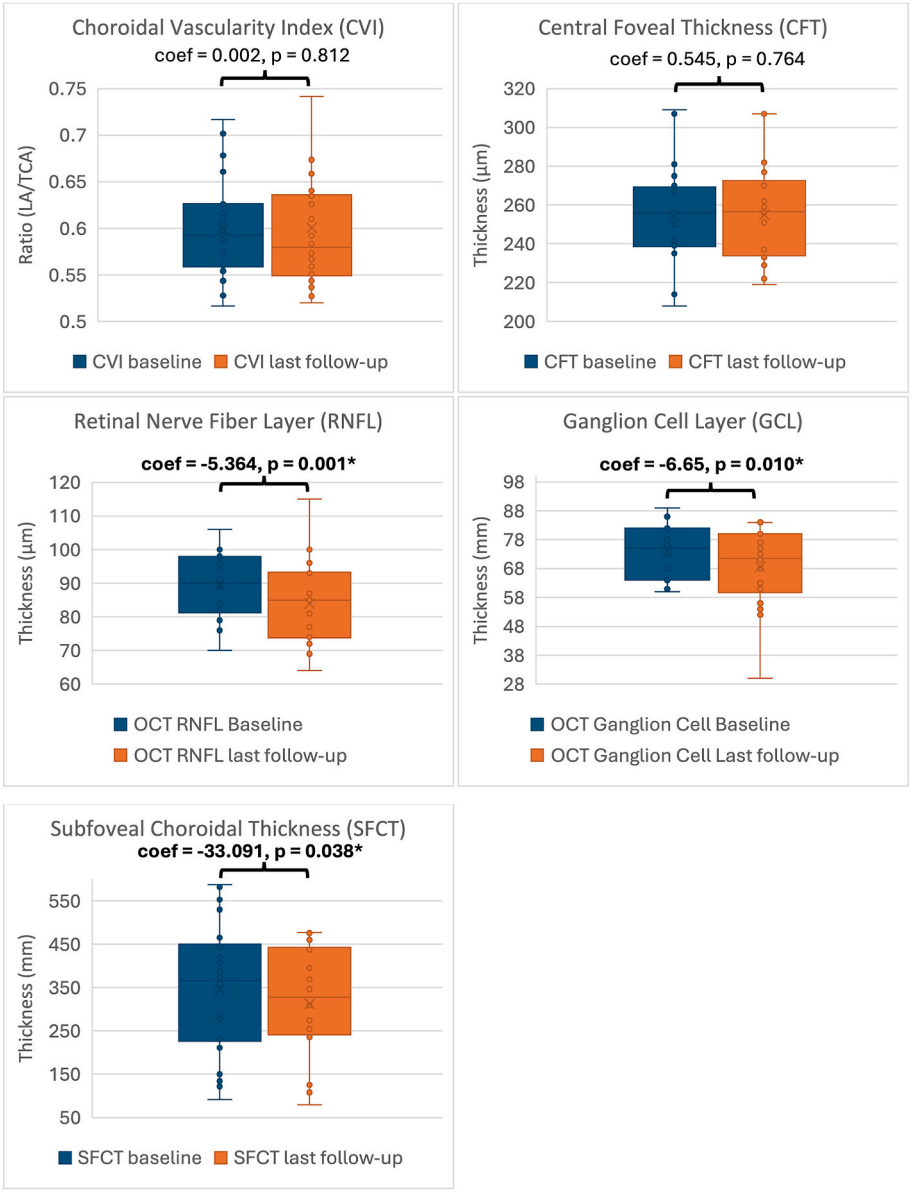

Fig. 2. Change in Clinical Examination from baseline (T0) to six-nine months after Teprotumumab (T1).

ratio of the choroidal vascular volume to the total choroidal volume, and only changes when the choroidal vascular volume changes without a concomitant change in the choroidal stroma.[47] After teprotumumab, it is possible that the choroidal vascular and stroma volume both changed proportionately, and therefore CVI was unchanged after treatment. Lee and Lee similarly found a decline in choroidal thickness on OCT after glucocorticoid therapy without change in CVI.[22] Rafizadeh et al. also found a statistically significant reduction in SFCT without a significant change in CVI, suggesting a proportional decline in both LA and TCA.[26] Additionally, we observed no change in CFT in response to treatment, whereas some studies assert that there is a general thinning effect, especially in the fovea, but others assert that there may be thickening or no effect from active TED.[23,38–40]

There were limitations to our study, including a small sample size, lack of a control comparison cohort, and retrospective nature. However, given the increased use of teprotumumab for TED, our study contributes to a better understanding and possible concerns of off-target tissue effects of this therapeutic class of medication. Obtaining angiographic studies and functional testing such as electroretinography may serve as a future avenue of study. Despite these limitations, we believe that this study serves as a basis for understanding the impact of IGF-1R inhibition on the retina and optic nerve. Physicians should carefully monitor their patients and consider pre-infusion and post-infusion image screening in these patients.

5. Conclusion

In summary, we observed reduced SFCT, RNFL, and mGCIPL thickness levels in the retina and optic nerve after treatment for TED with teprotumumab. There was also a reduction in CAS, proptosis, and intraocular pressure, with preservation of BCVA and HVF mean deviation. While teprotumumab remains a powerful method to treat TED, there may be a potential impact on the retina and optic nerve that needs to be verified in larger, longitudinal studies. Given the continued, interest in this class of IGF-R1 inhibitor medications, including different routes of administration (intravenous, subcutaneous, and oral), it remains important for ophthalmologists to be aware of and interested in identifying the potential consequences of these therapeutics. Use of these biologics continues to expand, including earlier treatment in the disease cycle to prevent disease progression or symptom development. It

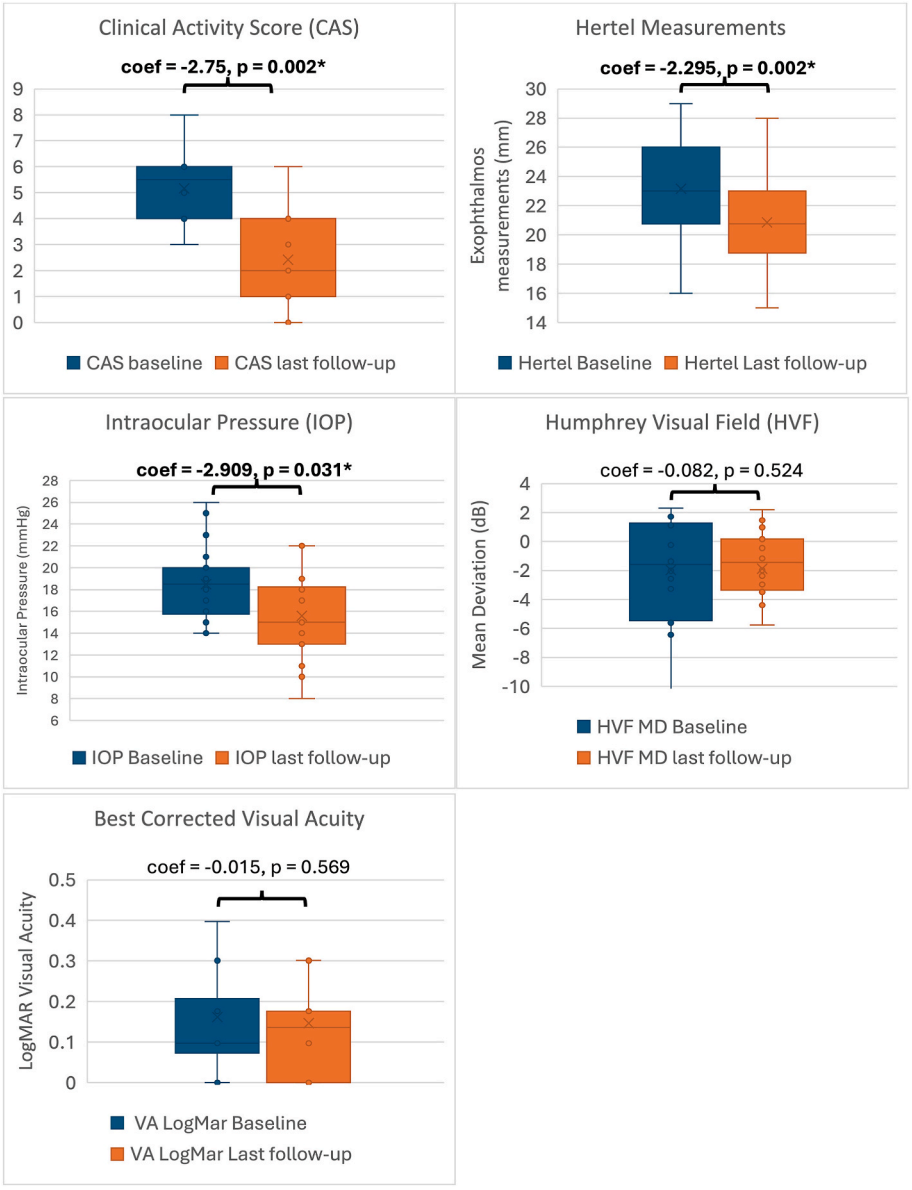

Fig. 3. Change in Spectral-Domain Optical Coherence Tomography (SD-OCT) value from baseline (T0) to six months after Teprotumumab (T1).

is critical that we understand the impact of these molecules, especially before they become more widely used, perhaps pre-emptively, in otherwise asymptomatic patients.

b) Financial Disclosures: TT: None; JJJ: Consultant: Carl Zeiss Meditec, Regeneron, Genentech, Iveric Bio; JRA: None; HL: None; QHV: None; KE: None; RZS: None
c) Design of the study (TT, RZS, JJJ); Conduct of the study (TT, RZS, JJJ); Collection of data (TT, JRA, KE, RZS, JJJ); Management of the data (TT, HL, JRA, QVH, RZS, JJJ); Analysis of the data (TT, JRA, HL, QVH, JJJ); Interpretation of the data (TT, HL, QVH, JJJ); Preparation of the manuscript (TT, QVH, RZS, JJJ); Review of the manuscript (TT, HL, JRA, QVH, RZS, JJJ); and Approval of the manuscript (TT, HL, JRA, QVH, RZS, JJJ)
d) Approval was obtained from the California Pacific Medical Center Institutional Review Board (San Francisco, CA, USA) for this Health Insurance Portability and Accountability Act-compliant, retrospective cohort study, and all research adhered to the tenets of the Declaration of Helsinki. The IRB was completed prospectively for this exempt research design.

CRediT authorship contribution statement

Timothy Truong: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Rona Z. Silkiss:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Johnell Renz Amoroso:** Project administration. **Huanye Li:** Software, Methodology, Investigation, Formal analysis. **Quan V. Hoang:** Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis. **Kasra Eliasieh:** Data curation. **Jesse J. Jung:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation.

Claim of priority

After conducting a literature review on September 1, 2023 utilizing PubMed and Google Scholar using the key words “thyroid eye disease,” “teprotumumab,” and “optical coherence tomography,” we did not find

any reports of optical coherence tomography imaging of patients having received teprotumumab for thyroid eye disease.

Precis

Although functional testing with visual field and acuity did not change, spectral-domain optical coherence tomography findings showed decreased sub-foveal choroidal thickness, ganglion cell/inner plexiform layer, and nerve fiber layer thickness after treatment with teprotumumab.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

a) Funding/Support: This work was supported in part by the Pacific Vision Foundation as well as by an unrestricted grant from Research to Prevent Blindness (RPB) under QVH. The sponsor or funding organization had no role in the design or conduct of this research.

References

1. Pritchard J, Han R, Horst N, Cruikshank WW, Smith TJ. Immunoglobulin activation of T cell chemoattractant expression in fibroblasts from patients with Graves' disease is mediated through the insulin-like growth factor I receptor pathway. *J Immunol*. 2003;170(12). https://doi.org/10.4049/jimmunol.170.12.6348.
2. Griffin SM, Silkiss RZ. Orbital lymphocyte populations in three states of thyroid eye disease. *Am J Ophthalmol Case Rep*. 2023;31. https://doi.org/10.1016/j.ajoc.2023.101865.
3. Douglas RS, Gupta S. The pathophysiology of thyroid eye disease: implications for immunotherapy. *Curr Opin Ophthalmol*. 2011;22(5). https://doi.org/10.1097/ICU.0b013e3283499446.
4. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4). https://doi.org/10.1056/nejmoa1910434.
5. Horizon Therapeutics. Tepezza (teprotumumab) [package insert]. *U.S. Food and Drug Administration website*; January 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761143s000lbl.pdf. Accessed May 31, 2024.
6. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18). https://doi.org/10.1056/nejmoa1614949.
7. Chern A, Dagi Glass LR, Gudis DA. Thyroid eye disease, teprotumumab, and hearing loss: an evolving role for otolaryngologists. *Otolaryngol Head Neck Surg*. 2021;165(6). https://doi.org/10.1177/01945998211004240.
8. Chow A, Silkiss RZ. Teprotumumab-associated chronic hearing loss screening and proposed treatments. *BMJ Case Rep*. 2022;15(4). https://doi.org/10.1136/bcr-2021-248335.
9. Ding AS, Mahoney NR, Campbell AA, Creighton FX. Sensorineural hearing loss after teprotumumab therapy for thyroid eye disease: a case report. *Otol Neurotol*. 2022;43(2). https://doi.org/10.1097/MAO.0000000000003428.
10. Highland J, Gordon S, Reddy D, Patel N. Ototoxicity and teprotumumab. *Ann Otol Rhinol Laryngol*. 2022;131(8). https://doi.org/10.1177/00034894211042740.
11. Sears CM, Azad AD, Amarikwa L, et al. Hearing dysfunction after treatment with teprotumumab for thyroid eye disease. *Am J Ophthalmol*. 2022;240. https://doi.org/10.1016/j.ajo.2022.02.015.
12. Najjar W, Yu J. Audiologic demonstration of ototoxicity from teprotumumab treatment in a patient with thyroid eye disease. *OTO Open*. 2022;6(2). https://doi.org/10.1177/2473974X221097097.
13. Reed DS, Kostosky N, Davies BW, Epstein A, Durairaj VD. Rifle blast exacerbating hearing loss in a patient treated with teprotumumab for thyroid eye disease. *Ophthalmic Plast Reconstr Surg*. 2022;38(2). https://doi.org/10.1097/IOP.0000000000002078.
14. Keen JA, Correa T, Pham C, et al. Frequency and patterns of hearing dysfunction in patients treated with teprotumumab. *Ophthalmology*. 2024;131(1). https://doi.org/10.1016/j.ophtha.2023.08.001.
15. Truong T, Silkiss RZ. The role of insulin-like growth factor-1 and its receptor in the eye: a review and implications for IGF-1R inhibition. *Ophthalmic Plast Reconstr Surg*. 2023;39(1). https://doi.org/10.1097/IOP.0000000000002146.
16. Arroba AI, Campos-Caro A, Aguilar-Diosdado M, Valverde ÁM. IGF-1, inflammation and retinal degeneration: a close network. *Front Aging Neurosci*. 2018;10(JUL). https://doi.org/10.3389/fnagi.2018.00203.
17. Stahl A, Hellstrom A, Smith LEH. Insulin-like growth factor-1 and anti-vascular endothelial growth factor in retinopathy of prematurity: has the time come? *Neonatology*. 2014;106(3). https://doi.org/10.1159/000365132.
18. Cha DM, Woo SJ, Kim HJ, Lee C, Park KH. Comparative analysis of aqueous humor cytokine levels between patients with exudative age-related macular degeneration and normal controls. *Investig Ophthalmol Vis Sci*. 2013;54(10). https://doi.org/10.1167/iovs.13-12730.
19. Sengupta N, Afzal A, Caballero S, et al. Paracrine modulation of CXCR4 by IGF-1 and VEGF: implications for choroidal neovascularization. *Investig Ophthalmol Vis Sci*. 2010;51(5). https://doi.org/10.1167/iovs.09-4137.
20. Del Noce C, Roda M, Ferro Desideri L, Traverso CE, Vagge A. Evaluation of macular blood flow after intermittent intravenous infusion of high-dose corticosteroids (pulse therapy) in patients with thyroid-associated orbitopathy (TAO) using angio-OCT. *Graefe's Arch Clin Exp Ophthalmol*. 2022;260(2). https://doi.org/10.1007/s00417-021-05336-4.
21. Rafizadeh SM, Heidari M, Aghajani A, et al. Superficial ocular vascular changes after orbital decompression in patients with thyroid ophthalmopathy measured by anterior segment OCT angiography; an observational study. *Sci Rep*. 2024;14(1). https://doi.org/10.1038/S41598-024-64925-5.
22. Lee J, Lee DC. Changes in clinical activity, serum autoantibody levels, and chorioretinal vessels after systemic glucocorticoid therapy in thyroid eye disease. *Ophthalmol Ther*. 2023;12(4). https://doi.org/10.1007/s40123-023-00696-y.
23. Guo J, Li X, Ma R, Gan L, Qian J. The changes of retinal nerve fibre layer and ganglion cell layer with different severity of thyroid eye disease. *Eye (Basingstoke)*. 2022;36(1). https://doi.org/10.1038/s41433-021-01453-w.
24. Chien L, Go CC, Lahaie Luna GM, Briceño CA. Changes in retinal nerve fiber layer, ganglion cell complex, and ganglion cell layer thickness in thyroid eye disease: a systematic review. *Taiwan J Ophthalmol*. 2023;14(2):217–224. https://doi.org/10.4103/TJO.TJO-D-22-00110.
25. Tehrani MJ, Ebrahimiadib N, Eye F, et al. Assessment of retinal and choroidal vessel density and nerve fiber layer thickness changes after orbitotomy in sever NON-active thyroid orbitopathy patients (A retrospective study). *Int Ophthalmol*. 2022. https://doi.org/10.21203/RS.3.RS-2267065/V1. Published online November 16.
26. Rafizadeh SM, Momeni A, Rahimi M, et al. Effect of orbital decompression surgery on the choroidal profile in patients with thyroid eye disease. *Sci Rep*. 2024;14(1). https://doi.org/10.1038/S41598-024-65884-7.
27. Hsia Y, Hsiao CC, Wei YH, Lai IW, Lin CW, Liao SL. The changes in optic nerve after orbital decompression surgery for thyroid eye disease and case reports of ischemic optic neuropathy. *BioMed Res Int*. 2022;2022, 4808194. https://doi.org/10.1155/2022/4808194.
28. Yum HR, Park SH, Park HYL, Shin SY. Macular ganglion cell analysis determined by Cirrus HD optical coherence tomography for early detecting chiasmal compression. *PLoS One*. 2016;11(4). https://doi.org/10.1371/journal.pone.0153064.
29. Lai FHP, Iao TWU, Ng DSC, et al. Choroidal thickness in thyroid-associated orbitopathy. *Clin Exp Ophthalmol*. 2019;47(7). https://doi.org/10.1111/ceo.13525.
30. Girard MJA, Strouthidis NG, Ross Ethier C, Mari JM. Shadow removal and contrast enhancement in optical coherence tomography images of the human optic nerve head. *Investig Ophthalmol Vis Sci*. 2011;52(10). https://doi.org/10.1167/iovs.10-6925.
31. Foin N, Mari JM, Davies JE, Di Mario C, Girard MJA. Imaging of coronary artery plaques using contrast-enhanced optical coherence tomography. *Eur Heart J Cardiovasc Imaging*. 2013;14(1). https://doi.org/10.1093/ehjci/jes151.
32. Ophthalmic Engineering & Innovation Library. Reflectivity. Ophthalmic engineering & innovation library - oeil. www.ophthalmic.engineering/reflectivity.html. Accessed May 31, 2024.
33. Agrawal R, Gupta P, Tan KA, Cheung CMG, Wong TY, Cheng CY. Choroidal vascularity index as a measure of vascular status of the choroid: measurements in healthy eyes from a population-based study. *Sci Rep*. 2016;6. https://doi.org/10.1038/srep21090.
34. Chu M, Sung J, Song M, Song A, Song J. Intraocular pressure improvement in patients receiving teprotumumab for the treatment of thyroid eye disease: a case series. *J Med Case Rep*. 2022;16(1). https://doi.org/10.1186/s13256-022-03375-x.
35. Betzler BK, Young SM, Sundar G. Intraocular pressure and glaucoma in thyroid eye disease. *Ophthalmic Plast Reconstr Surg*. 2022;38(3). https://doi.org/10.1097/IOP.0000000000002049.
36. Delavar A, Radha Saseendrakumar B, Lee TC, et al. Associations between thyroid eye disease and glaucoma among those enrolled in the national institutes of Health all of us research program. *Ophthalmic Plast Reconstr Surg*. 2023;39(4). https://doi.org/10.1097/IOP.0000000000002310.
37. Alimgil ML, Benian Ö, Esgin H, Erda S. Ocular pulse amplitude in patients with Graves' disease: a preliminary study. *Acta Ophthalmol Scand*. 1999;77(6). https://doi.org/10.1034/j.1600-0420.1999.770618.x.
38. Casini G, Marinò M, Rubino M, et al. Retinal, choroidal and optic disc analysis in patients with Graves' disease with or without orbitopathy. *Int Ophthalmol*. 2020;40(9). https://doi.org/10.1007/s10792-020-01392-7.
39. Meirovitch SB, Leibovitch I, Kesler A, Varssano D, Rosenblatt A, Neuderfer M. Retina and nerve fiber layer thickness in eyes with thyroid-associated ophthalmopathy. *Isr Med Assoc J*. 2017;19(5).
40. Ogmen BE, Ugurlu N, Bilginer MC, et al. Thicknesses of the retinal layers in patients with Graves' disease with or without orbitopathy. *Int Ophthalmol*. 2022;42(11). https://doi.org/10.1007/s10792-022-02339-w.
41. Wu Y, Tu Y, Wu C, et al. Reduced macular inner retinal thickness and microvascular density in the early stage of patients with dysthyroid optic neuropathy. *Eye and Vision*. 2020;7(1). https://doi.org/10.1186/s40662-020-00180-9.
42. Bu SY, Yu GH, Xu GX. Expression of insulin-like growth factor 1 receptor in rat retina following optic nerve injury. *Acta Ophthalmol*. 2013;91(6). https://doi.org/10.1111/aos.12096.
43. de Figueiredo CS, Raony Í, Medina SV, de Mello Silva E, dos Santos AA, Giestal-de-Araujo E. Insulin-like growth factor-1 stimulates retinal cell proliferation via

activation of multiple signaling pathways. *Current Research in Neurobiology*. 2023;4. https://doi.org/10.1016/j.crneur.2022.100068.
44. Dupraz S, Grassi D, Karnas D, Nieto Guil AF, Hicks D, Quiroga S. The insulin-like growth factor 1 receptor is essential for axonal regeneration in adult central nervous system neurons. *PLoS One*. 2013;8(1). https://doi.org/10.1371/journal.pone.0054462.
45. Rajala A, Teel K, Bhat MA, et al. Insulin-like growth factor 1 receptor mediates photoreceptor neuroprotection. *Cell Death Dis*. 2022;13(7). https://doi.org/10.1038/s41419-022-05074-3.
46. Spaide RF, Gemmy Cheung CM, Matsumoto H, et al. Venous overload choroidopathy: a hypothetical framework for central serous chorioretinopathy and allied disorders. *Prog Retin Eye Res*. 2022;86. https://doi.org/10.1016/j.preteyeres.2021.100973.
47. Zhang Y, Zhou SW, Noam N, et al. Influence of carotid endarterectomy on choroidal perfusion: the INFLATE study. *Ophthalmol Retina*. 2024;8(1). https://doi.org/10.1016/j.oret.2023.07.026.