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https://doi.org/10.1007/s00417-024-06491-0

OCULOPLASTICS AND ORBIT

Teprotumumab improves light sensitivity in patients with thyroid eye disease

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Received: 24 November 2023 / Revised: 1 April 2024 / Accepted: 11 April 2024

Abstract

Background Teprotumumab, a novel IGF-1R antibody, has been shown to significantly reduce the signs of acute and chronic Thyroid Eye Disease (TED). Light sensitivity is a reported symptom in patients with TED. There is a lack of a prospective study that has explored the effects on light sensitivity in a large cohort of patients with acute and chronic TED following treatment with teprotumumab.

Methods Consecutive patients who were diagnosed with TED and reported light sensitivity at baseline were considered for study eligibility. All patients had measurements of Visual Light Sensitivity Questionnaire-8 (VLSQ-8), proptosis, clinical activity score (CAS), and MRD1 (distance between the upper eyelid margin and corneal reflex, mm) and MRD2 (distance between the lower eyelid margin and corneal reflex, mm) before and after treatment.

Results Ninety patients (41 acute, 49 chronic) met the inclusion criteria. The mean (SD) age was 47.3 (14.3). Eighty-six (95.6%) patients completed all 8 infusions. There was a significant reduction in the total score and across all categories of the VLSQ-8 ($p < 0.01$ for all). Seventy-two (80%) patients had a clinically significant improvement (≥2 reduction) in at least one category. There was no significant difference in the total VLSQ-8 score between the acute and chronic group ($p = 0.8$).

Conclusion Teprotumumab improves light sensitivity in patients with acute and chronic TED.
The results of this study highlight that the improvements in light sensitivity following treatment are not directly related to the mechanical changes in TED, suggesting another underlying mechanism is potentially involved.

Keywords Thyroid eye disease · Thyroid · Orbit · Thyroid eye disease treatment

Key messages

What is known:

- Light sensitivity is a reported symptom in patients with thyroid eye disease. Teprotumumab can improve light sensitivity in patients with both acute and chronic disease

What is new:

- This study has a large cohort of patients with both acute and chronic TED, while prior research has only compared only a small sample of patients. The data revealed that improvements in light sensitivity were not directly related to the mechanical changes seen in patients following treatment with teprotumumab. These findings suggest there may be another underlying mechanism that impacts light sensitivity in TED.

Introduction

Teprotumumab, a monoclonal antibody that blocks the insulin-like growth factor-1 receptor (IGF-1R) has been approved in 2020 by the US Food and Drug Administration for the treatment of thyroid eye disease (TED). The

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Published online: 19 April 2024

overexpression of IGF-1R and its interaction with the thyrotropin receptor (TSH-R) [1] is a key pathological feature in both acute and chronic TED [2]. The impact of teprotumumab on common signs and symptoms of TED such as Clinical Activity Score (CAS), proptosis, and inflammation has been well-studied in Phase 2 and 3 randomized, double-masked, placebo-controlled clinical trials (NCT01868997 and NCT03298867) [3, 4]in patients with active TED [3]. Subsequent research has shown a similar effect in signs such as CAS, proptosis, and inflammation in chronic TED [5]. Data from the recently presented Phase 4 clinical trial (NCT04583735) provided evidence that teprotumumab can significantly improve proptosis and visual functioning in patients with chronic/inactive/low CA [6]. Light sensitivity is a reported symptom in patients with TED, but there is a paucity of literature regarding the prevalence and improvement with various treatment options. In one study, a total of 48% of patients reported at the time of their TED diagnosis of having experienced light sensitivity [7]. The patient's quality of life was assessed using The Graves' Ophthalmopathy Quality of Life instrument (GO-QOL) and the reports showed that light sensitivity was one of the main determining symptoms that placed patients in a low GO-QOL group versus the high GO-QOL tercile [7]. We recently documented improvements in light sensitivity in patients treated with teprotumumab, but a limitation of that study was the small sample of 20 patients [8]. In that sample, there were only 10 patients in both the acute and chronic TED subgroups. There is a lack of a prospective study that has explored the effects on light sensitivity in a large cohort of patients with acute and chronic TED following treatment with teprotumumab. We present this prospective study and review the potential relationships between light sensitivity and other features of TED.

Methods

This prospective observational study was performed between March 2020 and April 2023. The study adhered to the tenets of the Declaration of Helsinki and was performed in accordance to the Health Insurance Portability and Accountability Act (HIPAA). The study was approved by the WCG-IRB (WCG, Puyallup, WA, USA) institutional review board (IRB No. 20210376). All patients provided written informed consent to participate in the study.

Patients

In this prospective longitudinal study, patients who were diagnosed with TED and presented to our institution for treatment with teprotumumab were considered for study eligibility. Patients who reported light sensitivity at baseline were considered for inclusion. Patients received infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the following 7 infusions) every 3 weeks with the intention to complete a full course of treatment over a period of 24 weeks. Patients with disease duration > 24 months were assigned to the chronic group and ≤ 24 months to the acute group. The primary outcome measure was change in light sensitivity following treatment with teprotumumab. Secondary outcome measures included change in proptosis (mm), clinical activity score (CAS), and MRD1 (marginal reflex distance 1 [distance between the upper eyelid margin and corneal reflex, mm]) and MRD2 (marginal reflex distance 2 [distance between the lower eyelid margin and corneal reflex, mm]). All clinical measurements were assessed at baseline and 3 weeks following the last infusion by the same examiner.

Light sensitivity assessment

Light sensitivity was assessed using the Visual Light Sensitivity Questionnaire-8 (VLSQ-8). An improvement of ≥2 in any of the 8 categories is deemed clinically significant. This validated questionnaire has been developed and used to assess light sensitivity in ocular and neurologic conditions [8–10]. The questionnaire included the following eight questions: Q1. In the past month, how often did you have visual light sensitivity outdoors during daylight? Q2. In the past month, how often did you have a sense of glare in your eyes? Q3. In the past month, how often did you have visual light sensitivity from flickering lights or bright colors? Q4. Please rate the severity of the worst visual light sensitivity you experienced in the past month. Q5. When you have sensitivity to light, do you also experience headache? Q6. When you have sensitivity to light, how often is your vision blurry? Q7. How often does sensitivity to light limit your ability to read, watch TV or use the computer? Q8. In the past month, how often did you need to wear dark glasses on cloudy days or indoors? Questions 1-5 were answered as 1 (never), 2 (rarely), 3(sometimes), 4 (often), or 5 (always). Question 4 was answered from 1 to 5 with 1 as none, 3 as moderate, and 5 as severe.

Clinical activity score

A 7-point CAS was used to assess the activity of TED. The CAS assigns a point each of the following signs: retrobulbar eye pain, pain on eye movement, eyelid erythema, eyelid swelling, conjunctival redness, chemosis, and inflammation of the caruncle or plica [11].

Proptosis

Proptosis was measured in millimeters (mm) using the same exophthalmometer at all visits. The eye with the higher proptosis was assigned as the study eye (SE), and the contralateral eye was designated as the fellow eye (FE), which is consistent with the design of previous teprotumumab clinical trial protocols [3, 4]. If both eyes had the same proptosis value, the eye with the higher CAS was designated the SE. If both eyes had the same CAS, then the study eye was randomly assigned.

Eyelid measurements

Photographs were taken of each participant under standardized lighting conditions at each visit. All participants were asked to look straight ahead with a neutral facial expression and relaxed brows for each photo. One experienced grader independently measured MRD1 and MRD2. The pixel length on each photograph was determined using a standard corneal white-to-white diameter of 11.77 mm for males and 11.64 mm for females was used as described in previous studies on eyelid measurements [12]. The measurements were completed on each digital photograph using ImageJ software (National Institute of Health, Bethesda, MD, USA).

Statistical analyses

Statistical analysis was performed using SPSS statistics software (version 22.0; SPSS, Inc., Chicago, Illinois, USA). Statistical significance was defined as $p < 0.05$. The differences in baseline and post treatment measurements in exophthalmometry, CAS, and VLSQ-8 was analyzed using a two-tailed paired *t* test. Differences in VLSQ-8 scores between the acute and chronic groups was analyzed using an independent *t* test. The relationship between VLSQ-8, CAS, proptosis, and MRD1/2 was examined using a Pearson's correlation analysis. Chi-Square test was used to compare score differences on the VLSQ-8 between the acute and chronic TED group.

Results

A total of 90 consecutive patients (77 females, 13 males) met the inclusion criteria. The mean (SD) age was 47.3 (14.3). The mean (SD) duration of TED prior to treatment was 51.3 (73.3) months. Eighty-six (95.6%) patients completed all 8 infusions. Eighty-six (95.6%) patients were nonsmokers at time of treatment. All patients were euthyroid at time of treatment. Forty-nine patients had chronic TED (disease duration > 24 months), and 41 patients had acute TED disease duration ≤24 months). Demographic details are presented in Table 1.

Clinical measurements

Visual light sensitivity assessment

There was a statistically significant reduction across each of the categories in the VLSQ-8 ($p < 0.01$ for all) and in the total score ($p < 0.01$). Seventy-two (80%) patients had a clinically significant improvement (≥2 reduction) in at least one category. A ≥ 2 reduction was seen in 46.7% of patients for Q1, 34.4% for Q2, 35.6% for Q3, 36.7% for Q4, 22.2% for Q5, 35.6% for Q6, 43.3% for Q7, and 25.6% for Q8 (Figs. 1 and 2).

Proptosis

The mean (SD) exophthalmometry in the SE was 21.3 mm (3.1) at baseline and 18.2 mm (2.7) following therapy ($p < 0.01$) with a mean change of 3.1 mm (1.7). In the FE, the mean (SD) exophthalmometry was 20.0 mm (3.1) at baseline and 17.8 mm (2.8) following therapy ($p < 0.01$), with a mean change of 2.2 mm (1.6).

CAS

The mean (SD) CAS in the SE was 2.8 (1.6) at baseline and 0.8 (0.8) following therapy ($p < 0.01$), with a mean change of 2.0 (1.7). In the FE, the mean (SD) CAS was 2.6 (1.6) at baseline and 0.8 (0.9) following therapy ($p < 0.01$).

Eyelid measurements

The mean (SD) MRD1 score in the SE was 4.2 (1.8) at baseline and 3.9 (1.5) following therapy ($p < 0.05$), with a mean change of 0.3 (1.1). In the FE, the mean (SD) MRD1 score was 3.8 (1.5) at baseline and 3.7 (1.3) following therapy ($p = 0.3$), with a mean change of 0.1 (1.1). The mean (SD) MRD2 score in the SE was 6.4 (1.6) at baseline and 6.1 (1.4) following therapy ($p < 0.01$), with a mean change of 0.3 (0.9). In the FE, the mean (SD) MRD2 score was 6.2 (1.3) at baseline and 6.1 (1.2) following therapy ($p = 0.2$), with a mean change of 0.1 (1.0). There was a statistically significant seen in MRD1 and 2 in the SE, but not in the fellow eye. However, there was no clinically significant reduction in MRD1 and MRD2 in the either the SE or FE (Fig. 3) (Table 2).

Table 1 Demographic details of patients

Case	Age	M/F	Duration of TED Prior to First Infusion (months)	Smoking History	Case	Age	M/F	Duration of TED Prior to First Infusion (months)	Smoking History
1	53	Female	3.2	No	46	82	Male	360.4	No
2	37	Female	8.8	Former	47	47	Male	89.1	No
3	53	Female	10.2	No	48	51	Female	7.6	No
4	43	Male	8.2	No	49	63	Female	56.6	No
5	38	Male	3.5	Former	50	36	Female	5.3	No
6	29	Female	82.7	No	51	40	Male	9.5	Former
7	70	Female	5.8	No	52	48	Female	2.5	Former
8	69	Female	39.8	No	53	47	Female	62.4	Former
9	49	Female	25.8	No	54	32	Female	18.6	No
10	53	Female	2.9	No	55	25	Male	64.6	No
11	64	Female	21.9	No	56	67	Female	35.4	No
12	58	Female	10.2	No	57	75	Female	1.4	No
13	31	Male	9.4	No	58	58	Female	57.5	No
14	82	Male	5.0	No	59	49	Female	47.6	Former
15	37	Female	23.1	No	60	49	Female	36.2	No
16	35	Male	25.6	No	61	45	Female	2.5	No
17	48	Female	67.5	No	62	41	Female	252.7	Former
18	19	Female	2.1	No	63	32	Female	35.9	Former
19	57	Female	44.1	No	64	39	Female	3.4	Former
20	51	Female	152.8	Former	65	57	Female	61.4	No
21	34	Female	57.5	No	66	39	Female	6.8	No
22	46	Female	22.6	No	67	47	Female	110.1	Yes
23	34	Female	0.8	No	68	51	Female	48.1	No
24	74	Male	0.8	No	69	42	Female	4.2	No
25	45	Female	80.6	No	70	64	Female	146.4	Former
26	43	Female	10.0	Former	71	42	Female	170.6	No
27	36	Female	8.7	Former	72	62	Female	194.8	No
28	28	Female	108.0	No	73	33	Female	4.8	No
29	53	Female	47.4	No	74	59	Female	2.0	No
30	35	Female	6.2	No	75	30	Female	9.4	No
31	38	Male	102.2	Former	76	67	Female	4.7	No
32	63	Female	23.9	No	77	19	Female	2.6	Former
33	48	Female	22.9	No	78	47	Female	1.2	No
34	54	Female	280.4	Former	79	54	Female	0.9	Yes
35	49	Female	4.4	Yes	80	45	Female	27.0	Former
36	45	Female	63.9	No	81	44	Female	305.1	No
37	54	Female	22.5	No	82	45	Female	3.3	No
38	63	Female	148.1	Former	83	45	Female	8.6	No
39	19	Male	21.1	No	84	50	Female	6.8	Former
40	44	Female	17.3	Yes	85	22	Female	0.4	No
41	28	Female	126.2	No	86	71	Female	246.5	No
42	75	Female	1.2	No	87	26	Male	44.0	No
43	66	Female	78.3	No	88	44	Female	116.3	No
44	35	Female	36.8	No	89	43	Female	6.9	No
45	61	Female	91.1	Former	90	38	Female	3.2	No

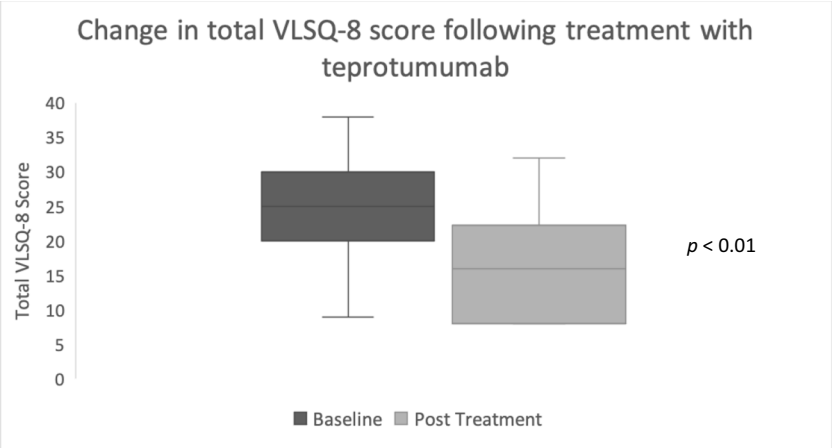

Fig. 1 Changes in the total VLSQ-8 score following treatment with teprotumumab

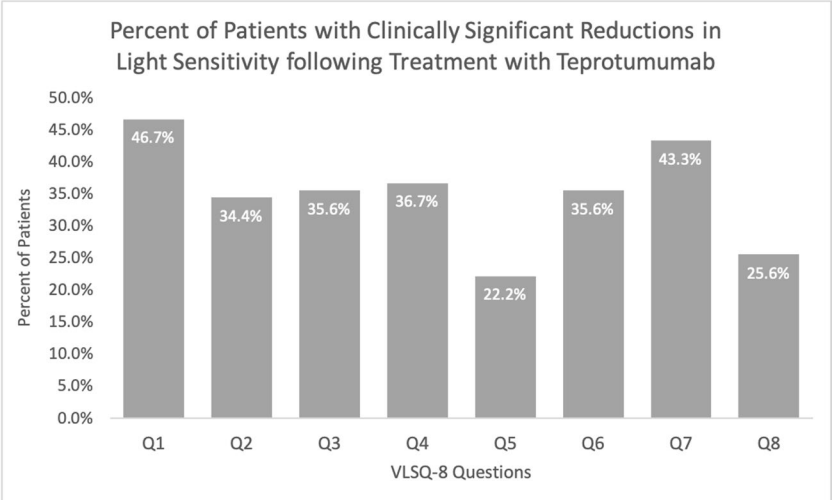

Fig. 2 Responses on the Visual Light Sensitivity Questionnaire-8 following treatment

Acute versus chronic TED

Following treatment, there was no significant difference in the total VLSQ-8 score between the acute and chronic group ($p = 0.8$) (Fig. 4). All questions asked about light sensitivity and its effects in the past month. There was no significant difference ($p > 0.05$) seen across seven of the eight categories (Q1 to Q7) of the VLSQ-8 when analyzing the percentage of patients who experienced a clinically significant (≥2 point) reduction (Fig. 3). There was a significant difference in only Q8 ($p < 0.05$).

Relationships between visual light sensitivity and other clinical characteristics of TED

The correlation between changes in light sensitivity and changes in proptosis was not significant in the SE and the FE ($p = 0.1$ and 0.7, respectively). Further, there was no correlation between changes in light sensitivity and changes for CAS for the study or fellow eye ($p = 0.1$ and 0.2, respectively). There was no correlation between changes in light sensitivity and changes in MRD1 for the study or fellow eye ($p = 0.3$ and $p = 0.9$, respectively). Finally, there was no correlation between changes in light sensitivity and changes in MRD2 for the study or fellow eye ($p = 0.8$ for both).

Discussion

Teprotumumab has been shown to reduce proptosis, inflammation, lacrimal gland volume, aqueous tear production, diplopia, and soft tissue expansion in patients with acute and chronic TED [5, 8]. In this study, we found that there was a reduction in the VLSQ-8 following treatment with teprotumumab, with 80% of patients having a clinically significant reduction in at least one category. A similar improvement was seen in patients with both acute and chronic TED. The findings in this study provide further insight on the effects on

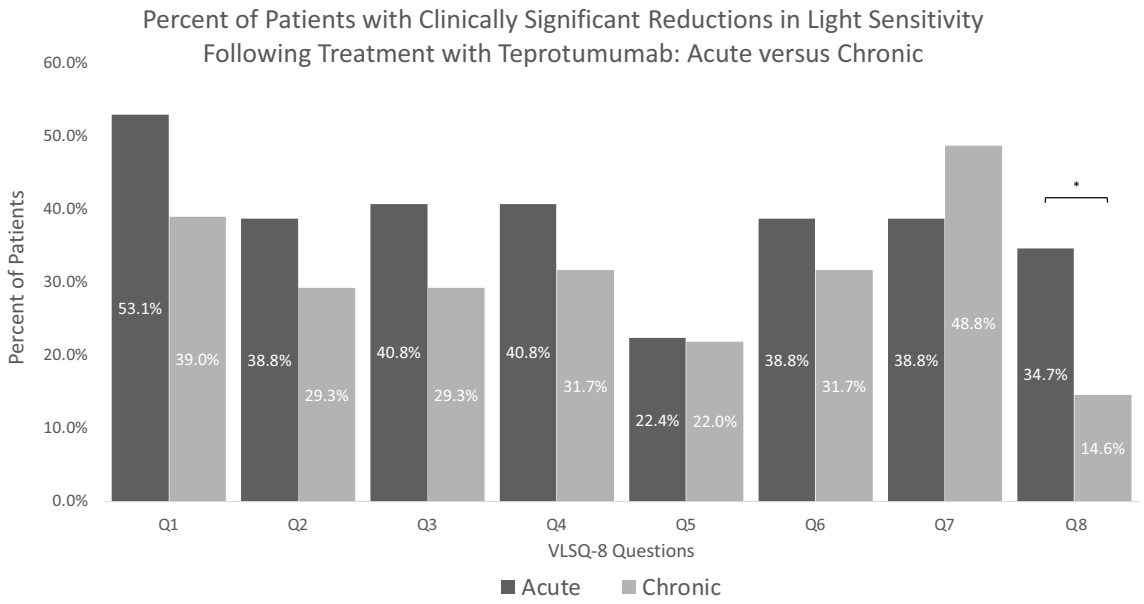

Fig. 3 Responses on the Visual Light Sensitivity Questionnaire-8 in patients with acute and chronic TED. * $p < 0.05$

light sensitivity following treatment teprotumumab in both acute and chronic TED.

Light sensitivity relationship with other clinical parameters

There was no correlation between changes in light sensitivity and changes in CAS, proptosis, MRD1 or 2 in either the SE or FE. This suggests that there may be another underlying mechanism that may be contributing to reduction in light sensitivity following treatment with teprotumumab that is not entirely explained by mechanical factors such as exposure.

Acute versus chronic TED

In our subgroup analysis, there was no change in the total VLSQ-8 score in patients with acute or chronic TED. Across the 8 categories, there was a difference in only one question between the two groups. Prior research has shown that the overexpression of IGF-1R is evident in both the acute and chronic phase of TED [2]. Therefore, it is reasonable that teprotumumab, an inhibitor of the IGFR-1R pathway, has shown a similar effect in light sensitivity and other clinical parameters in both groups.

Limitations

One limitation is that the VLSQ-8 has not been validated for TED. In addition, corneal changes were not assessed in this study. While we maintained the same lighting conditions in the pre and post treatment period, we did not measure the pupil diameter at these time points. There is a possibility that the incident light on the retina could have varied according to proptosis, thereby, potentially affecting lid height in response. Further studies that include measurement of the pupil diameter during treatment with teprotumumab would provide further information. The prospective longitudinal nature and large sample size were the primary contributing factors to the strength of this study.

Table 2 Clinical characteristics pre and post treatment

	Study Eye			Fellow Eye		
	Baseline	Post-Treatment	*p* Value	Baseline	Post-Treatment	*p* Value
Exophthalmometry (mm)	21.3 (3.1)	18.2 (2.7)	< 0.01	20.0 (3.1)	17.8 (2.8)	< 0.01
CAS	2.8 (1.6)	0.8 (0.8)	< 0.01	2.6 (1.6)	0.8 (0.9)	< 0.01
MRD1 (mm)	4.2 (1.8)	3.9 (1.5)	< 0.05	3.8 (1.5)	3.7 (1.3)	0.3
MRD2 (mm)	6.4 (1.6)	6.1 (1.4)	< 0.01	6.2 (1.3)	6.1 (1.2)	0.2

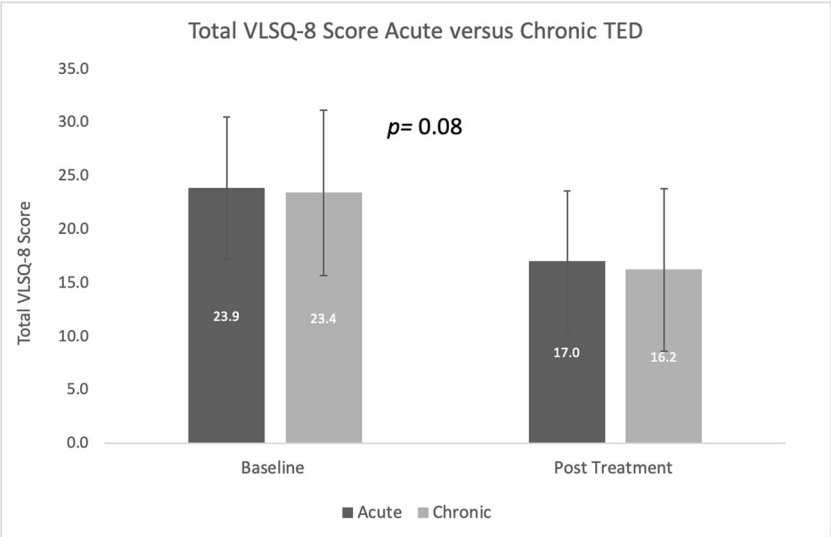

Fig. 4 Changes in VLSQ-8 score following treatment with teprotumumab in patients with acute and chronic TED

Conclusion

Light sensitivity is a common symptom of TED and it impacts QOL in both acute and chronic phases [7, 8]. In this study, we found that teprotumumab can improve light sensitivity and its effects are not limited to either stage of TED. In addition, the data revealed that improvements in light sensitivity were not directly related to the mechanical changes seen in patients following treatment. These findings suggest there may be another underlying mechanism that impacts light sensitivity in TED. Prior research has revealed that TED can affect corneal function [13, 14]. In a more recent study, corneal endothelial function was observed to be poorer in patients with TED than in healthy individuals [15]. The IGF-1R receptor is expressed in corneal epithelial cells in vitro and in human corneal epithelium in situ [16–20]. Therefore, changes to the IGF-1R pathway using medications such as teprotumumab may explain the symptomatic changes seen in the patients included in our study. Finally, improvement in the VLSQ-8 was seen in both acute and chronic TED; therefore, widening the repertoire of teprotumumab therapy in TED.

Author contributions Raymond Douglas and Emanuil Parunakian were involved in the conception and design of the study. Emanuil Parunakian prepared the first manuscript; all authors were involved in drafting of the manuscript. All authors were involved in the data acquisition and analysis.

Funding No funding was received for this research.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the private practice of Dr. Raymond Douglas and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study was approved by the WCG-IRB (WCG, Puyallup, WA, USA) institutional review board (IRB No. 20210376).

Informed consent Informed consent was obtained from all individual participants included in the study.

Financial support None.

Conflict of interest Raymond Douglas is an employee of Sling Therapeutics. All other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Tsui S, Naik V, Hoa N et al (2008) Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in graves' disease. J Immunol 181:4397–4405. https://doi.org/10.4049/jimmunol.181.6.4397
2. Ugradar S, Shi L, Wang Y et al (2021) Teprotumumab for non-inflammatory thyroid eye disease (TED): evidence for increased IGF-1R expression. Eye 35:2607–2612. https://doi.org/10.1038/s41433-020-01297-w
3. Smith TJ, Kahaly GJ, Ezra DG et al (2017) Teprotumumab for thyroid-associated Ophthalmopathy. N Engl J Med 376:1748–1761. https://doi.org/10.1056/NEJMoa1614949
4. Douglas RS, Kahaly GJ, Patel A et al (2020) Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med 382:341–352. https://doi.org/10.1056/NEJMOA1910434
5. Ugradar S, Kang J, Kossler AL et al (2022) Teprotumumab for the treatment of chronic thyroid eye disease. Eye (Lond) 36:1553–1559. https://doi.org/10.1038/s41433-021-01593-z
6. Douglas RS, Couch S, Wester ST et al (2023) Efficacy and safety of teprotumumab in patients with thyroid eye disease of

long duration and low disease activity. J Clin Endocrinol Metab 109:25–35. https://doi.org/10.1210/clinem/dgad637
7. Cockerham KP, Padnick-Silver L, Stuertz N et al (2021) Quality of life in patients with chronic thyroid eye disease in the United States. Ophthalmol Ther 10:975–987. https://doi.org/10.1007/s40123-021-00385-8
8. Ugradar S, Zimmerman E, Parunakian E et al (2023) Change in lacrimal gland volume and aqueous tear production following treatment with teprotumumab. Clin Experiment Ophthalmol 51:339–348. https://doi.org/10.1111/ceo.14208
9. Verriotto JD, Gonzalez A, Aguilar MC et al (2017) New methods for quantification of visual photosensitivity threshold and symptoms. Transl Vis Sci Technol 6:18. https://doi.org/10.1167/tvst.6.4.18
10. Venkateswaran N, Hwang J, Rong AJ et al (2020) Periorbital botulinum toxin a improves photophobia and sensations of dryness in patients without migraine: case series of four patients. Am J Ophthalmol Case Rep 19:100809. https://doi.org/10.1016/j.ajoc.2020.100809
11. Mourits MP, Koornneef L, Wiersinga WM et al (1989) Clinical criteria for the assessment of disease activity in graves' ophthalmopathy: a novel approach. Br J Ophthalmol 73:639–644. https://doi.org/10.1136/bjo.73.8.639
12. Rüfer F, Schröder A, Erb C (2005) White-to-white corneal diameter. Cornea 24:259–261. https://doi.org/10.1097/01.ico.0000148312.01805.53
13. Villani E, Viola F, Sala R et al (2010) Corneal involvement in graves' Orbitopathy: an in vivo confocal study. Investigative Opthalmology & Visual Science 51:4574. https://doi.org/10.1167/iovs.10-5380
14. Wu L-Q, Cheng J-W, Cai J-P et al (2016) Observation of corneal Langerhans cells by in vivo confocal microscopy in thyroid-associated Ophthalmopathy. Curr Eye Res 41:927–932. https://doi.org/10.3109/02713683.2015.1133833
15. Oklar M, Yazicioglu T, Ozen MC et al (2023) Evaluation of corneal endothelium and correlation with disease severity in patients with graves' ophthalmopathy: a specular microscopy-based study. Photodiagn Photodyn Ther 42:103592. https://doi.org/10.1016/j.pdpdt.2023.103592
16. Wu Y-C, Zhu M, Robertson DM (2012) Novel nuclear localization and potential function of insulin-like growth Factor-1 receptor/insulin receptor hybrid in corneal epithelial cells. PLoS One 7:e42483. https://doi.org/10.1371/journal.pone.0042483
17. Nakamura M, Chikama T-I, Nishida T (2000) Characterization of insulin-like growth Factor-1 receptors in rabbit corneal epithelial cells. Exp Eye Res 70:199–204. https://doi.org/10.1006/exer.1999.0775
18. Rocha EM, Cunba DA, Carneiro EM et al (2002) Identification of insulin in the tear film and insulin receptor and IGF-1 receptor on the human ocular surface. Invest Ophthalmol Vis Sci 43
19. Titone R, Zhu M, Robertson DM (2018) Insulin mediates de novo nuclear accumulation of the IGF-1/insulin hybrid receptor in corneal epithelial cells. Sci Rep 8:4378. https://doi.org/10.1038/s41598-018-21031-7
20. Robertson DM, Zhu M, Wu Y-C (2012) Cellular distribution of the IGF-1R in corneal epithelial cells. Exp Eye Res 94:179–186. https://doi.org/10.1016/j.exer.2011.12.006