CJO JCO

Original Article

Orbital decompression following treatment with teprotumumab for thyroid eye disease

Nicole J. Topilow,* Rafaella Cleto Penteado,* Michelle Ting,* Eman Al-Sharif,* George A. Villatoro,* Jin Sook Yoon,† Catherine Y. Liu,* Bobby S. Korn,*,‡ Don O. Kikkawa*,‡

Objective: To quantify the observed decrease in orbital decompressions being performed at one tertiary care institution and to determine the rate and predictive factors of orbital decompression surgery following treatment with teprotumumab for thyroid eye disease.

Methods: Epic's SlicerDicer program was used to analyze recent trends in the overall number of thyroid eye disease (TED) patients evaluated in the oculoplastic surgery department, as well as usage trends of CPT codes 67445 (lateral orbitotomy with bone removal for decompression) and 67414 (orbitotomy with removal of bone for decompression). A retrospective chart review of active moderate-to-severe TED patients treated with teprotumumab was performed at a single tertiary care center. The main outcome measure was whether or not patients underwent bony orbital decompression surgery following treatment with teprotumumab. The SlicerDicer search demonstrated stable usage of CPT codes 67445 and 67414 from 2016 to 2019, followed by a significant decrease from 2020 to 2023, over a background of increasing numbers of TED patients evaluated in clinic. Following teprotumumab therapy, 25% of patients and 18% of orbits underwent bony decompression. Surgically decompressed patients had higher pre- and post-teprotumumab exophthalmometry measurements compared with patients who did not undergo bony decompression. Average time to decompression following conclusion or cessation of teprotumumab therapy was 12.6 months.

Conclusion: While the number of TED patients treated at one tertiary care center has risen over recent years, the number of orbital decompression surgeries has declined. Orbital decompression, however, is still needed in select patients after treatment with teprotumumab.

Objectif: Quantifier la baisse observée du nombre de décompressions orbitaires réalisées dans un établissement de soins tertiaires, calculer le taux de ce type de chirurgie après l'administration de téprotumumab dans le traitement de l'ophtalmopathie thyroïdienne (OT) et faire ressortir les facteurs de prédiction à cet égard.

Méthodes: Le programme SlicerDicer d'Epic a servi à analyser les tendances récentes quant au nombre global de patients présentant une OT qui ont été évalués au service de chirurgie oculoplastique de même que les tendances en matière d'utilisation des codes d'identification 67445 (orbitotomie latérale comprenant une résection osseuse afin de réaliser une décompression) et 67414 (orbitotomie comprenant une résection osseuse afin de réaliser une décompression) selon la *Current Procedural Terminology* (CPT). Un examen rétrospectif des dossiers médicaux de patients présentant une OT évolutive modérée à grave et qui ont reçu le téprotumumab a eu lieu dans un établissement de soins tertiaires unique. Le principal paramètre de mesure reposait sur la réalisation – ou non – d'une chirurgie de décompression orbitaire après un traitement par le téprotumumab. La recherche dans le programme SlicerDicer a mis au jour une utilisation stable des codes 67445 et 67414 selon la CPT de 2016 à 2019, suivie d'une baisse significative de 2020 à 2023, dans un contexte où il se produit une hausse des patients évalués à la clinique en raison d'une OT. Après l'administration de téprotumumab, 25 % des patients et 18 % des orbites ont subi une décompression osseuse. Les mesures obtenues à l'exophtalmométrie chez les patients qui ont subi une chirurgie de décompression étaient plus élevées, tant avant qu'après la prise de téprotumumab, comparativement aux patients qui n'ont pas subi de chirurgie de décompression osseuse. Il s'est écoulé en moyenne 12,6 mois avant la décompression après la fin ou l'interruption de l'administration de téprotumumab.

Conclusion: Si le nombre de patients traités en raison d'une OT dans un centre de soins tertiaires a augmenté au cours des dernières années, le nombre de chirurgies de décompression orbitaire, pour sa part, a diminué. Cela dit, la chirurgie de décompression orbitaire demeure parfois nécessaire chez certains patients après l'administration de téprotumumab.

Teprotumumab is a monoclonal insulin-like growth factor-1 receptor antagonist antibody approved by the U.S. Food and Drug Administration (FDA) for the treatment of thyroid eye disease (TED). Phase II and III clinical trials demonstrated reduced proptosis, diplopia, and Clinical Activity Scores (CAS), in addition to improved quality of life scores in patients with moderate-to-severe active TED.[1,2] Multiple recent studies have also demonstrated teprotumumab's efficacy in treating proptosis and diplopia in chronic TED.[3-5]

Prior to the approval of teprotumumab, surgical decompression was considered a primary treatment for reducing thyroid-related proptosis. While surgical decompression is an established, safe, and efficacious strategy to address proptosis,[6] it can be associated with prolonged recovery periods and possible postoperative side effects, including new or worsened diplopia and other complications.[7-11] Nonsurgical treatment options for symptoms of moderate-to-severe TED were previously limited to intravenous steroids, radiation, and off-label biologic therapy, which demonstrated variable efficacy.[12,13] With the option of teprotumumab infusions for reduction of TED-related proptosis, clinical practice patterns in the United States continue to evolve.

https://doi.org/10.1016/j.jcjo.2024.06.003
ISSN 0008-4182

The goals of this study were to determine: (1) how the overall rate of surgical orbital decompressions performed at one tertiary care institution changed since 2020 when teprotumumab became available; (2) how many patients underwent decompression surgery after teprotumumab treatment; and (3) which factors help us predict which patients will undergo decompression surgery after treatment with teprotumumab.

Methods

Study design

A baseline Epic SlicerDicer search was first performed to assess the trend in number of TED patients evaluated in the oculoplastics clinics from 2018, when the Epic electronic medical record (EMR) system was implemented, until 2023. The base population used for the search was "all patients," and inclusion criteria were any patients of the three faculty oculoplastics providers with medical history of "thyroid eye disease" or "exophthalmos due to thyroid eye disease," or chief complaint of "thyroid eye disease," or diagnosis of "thyroid eye disease."

An Epic SlicerDicer search was then performed to assess usage trends of the CPT codes 67445 (lateral wall decompression with bone removal) and 67414 (orbitotomy with removal of bone for decompression), which are the codes used for orbital decompression. The SlicerDicer program reported patients who underwent either or both of these procedures, stratified by year. One-wall decompression refers to decompression of the deep lateral orbital wall through a lateral lid crease incision using either a diamond-tipped drill or an ultrasonic aspirator. Two-wall decompression refers to a lateral wall decompression, as described above, plus decompression and removal of the medial wall through a transcaruncular incision. Three-wall decompression combines the prior two approaches, plus decompression and removal of the posterior and medial half of the orbital floor through the transcaruncular incision.

The retrospective consecutive case series portion of the study investigated the incidence of surgical decompression, and predictive factors for surgical decompression, in patients with moderate-to-severe active TED,[14,15] who were treated with teprotumumab. The primary outcome measure was whether or not patients underwent orbital decompression.

This study adhered to the tenets of the Declaration of Helsinki, was performed in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and was approved by the site's institutional review board.

Patients

Patients were treated at the University of California, San Diego, in the faculty practice and the multispecialty Thyroid Eye Clinic. All patients who were treated with at least one teprotumumab infusion between February 2020 and January 2023 were included, as some patients did not complete all 8 infusions. Any patient with fewer than 6 months of follow-up from the last infusion and those who had undergone prior orbital decompression surgery were excluded. A secondary analysis was performed of 50 consecutive patients (84 orbits) who underwent bony decompression surgery for TED prior to 2019, excluding any patients who had undergone prior orbital decompression surgery or orbital radiation therapy.

Data collection

Data was collected retrospectively by chart review in EPIC. Data collected for all patients included age, gender,

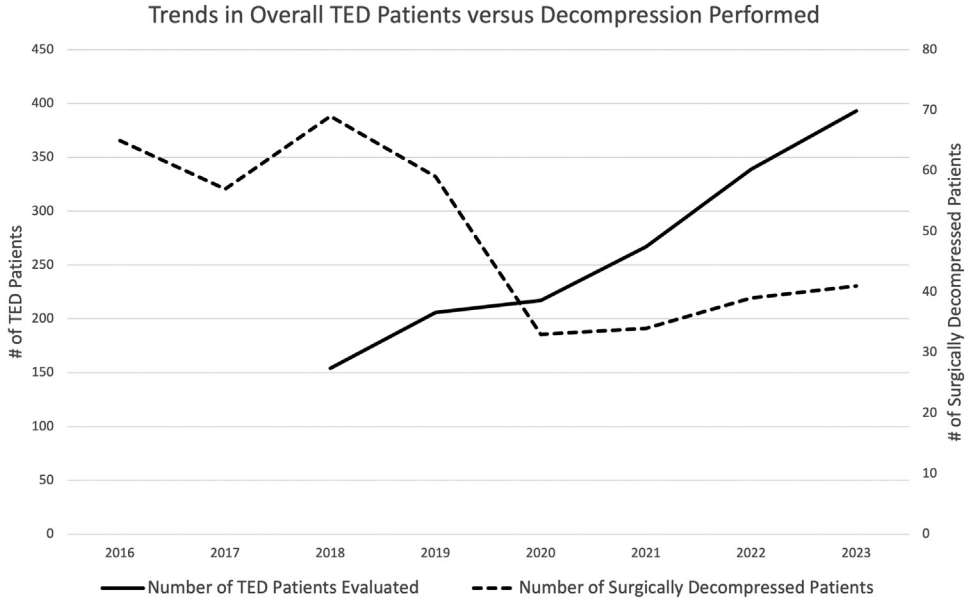

Fig. 1—Epic SlicerDicer trend analysis demonstrating increasing number of TED patients seen in oculoplastics clinics versus a decline in the number of surgical decompressions performed starting in 2020.

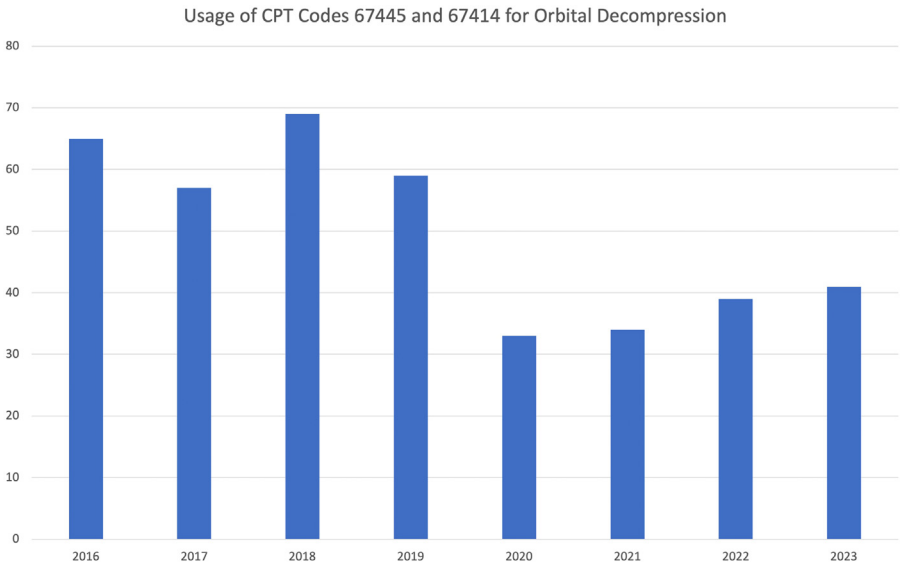

Fig. 2—Usage of CPT Codes 67445 and 67414 at one academic institution decreased after teprotumumab was approved in 2020 for the treatment of thyroid eye disease.

CAS, subjective complaints, and pre- and post-teprotumumab clinical exophthalmometry measurements (performed with a Naugle exophthalmometer). Post-treatment proptosis measurements were obtained within 4 months of the last teprotumumab infusion.

Statistical analysis

Continuous and categorical data are reported as mean (standard deviation) and count (percentage) throughout. Normality was assessed using the Shapiro-Wilk test. Statistical significance of subject level characteristics was determined using Student's *t* test for comparisons involving normally distributed data and Mann—Whitney *U* test for nonparametric data. A p value <0.05 was considered statistically significant. All statistical analyses were performed with Stata software version 14.2 (StataCorp LP, College Station, TX).

Results

EPIC SlicerDicer queries revealed an uptrend in the number of TED patients seen from 2018 through 2023 (Fig. 1).

Table 1—TED relapses after treatment with teprotumumab

Management of TED relapses		Number of patients
Orbital surgery	Decompression after ≥6 mo symptom stability	2
	Currently awaiting ≥6 mo symptom stability for possible decompression	1
	Thyroidectomy followed by decompression after ≥6 mo symptom stability	1
Thyroidectomy	Thyroidectomy only	1
Teprotumumab	2nd treatment course	3
Conservative management	Conservative management	3
	Reactivation after decompression, conservative management	1

TED = thyroid eye disease.

Linear regression analysis demonstrated that, on average, the number of TED patients seen increased by 47 each year ($R^2 = 0.97$). The queries also demonstrated stable usage of CPT codes 67445 and 67414 by 3 faculty oculoplastic surgeons from 2016 to 2019 (mean 62.5), followed by a decrease in usage from 2020 through 2023 (mean 36.8) ($p = 0.0003$, unpaired *t*-test) (Fig. 2).

Patients

Sixty-four patients (128 orbits) were included. Teprotumumab treatment was initiated by 27 patients in 2020 and 27 patients in 2021. Only 10 patients who initiated treatment in 2022 were included to meet follow-up requirements. Forty-seven (73%) of the patients were female, with the mean age being 53 years (range 14—80). The mean pretreatment CAS was 3.7 (SD 1.7). The mean number of completed teprotumumab infusions was 7.5 (SD 1.41), with 9 of 64 patients not completing the full 8-infusion treatment course. The mean follow-up time from the last infusion was 20.4 months (SD 9.0). Twelve of 64 patients (18.8%) experienced reactivation of disease during the study period, with an average time to relapse from last infusion of 10.6 months (SD 7.2, range: 3-24 months) (Table 1).

Sixteen of 64 patients (25%) and 24 of 128 orbits (18.8%) underwent bony decompression following cessation of teprotumumab therapy, with the mean time to surgery from last infusion being 12.6 months (SD 9.4). Of these 16 patients, 3 underwent bony decompression due to reactivation of disease after a period of stable improved symptoms. The remaining 13 patients reported either no (2) or partial (11) subjective improvement of their eye bulging on history-taking during follow-up appointments. These 13 patients all had residual proptosis and desired further treatment to return to their baseline appearance despite some of them reporting improvement in other symptoms such as

Table 2—Bony decompressed vs non-decompressed patients

	Bony decompression	No decompression	*p* Value
Age (y)	50.3 (SD 12.0)	53.7 (SD 15.6)	0.430[b]
Infusions completed	8.0 (SD 0)	7.3 (SD 1.6)	0.065[a]
Initial CAS	3.9 (SD 1.7)	3.7 (SD 1.7)	0.614[a]
Subjective bulging (%)	100	81.3	0.097[c]
Follow-up time (mo)	22.5 (SD 8.5)	19.8 (SD 9.2)	0.212[a]

[a]Mann–Whitney *U* test.
[b]Two-sample *t* test.
[c]Fisher's exact test.

pain and pressure with teprotumumab treatment. No surgical decompression was performed in this group for compressive optic neuropathy.

Six of 64 patients (9.4%) and 12 of 128 orbits (9.4%) underwent fat-only surgical decompression following cessation of teprotumumab therapy, with mean time to surgery from last infusion of 8.4 months (SD 3.7). Fat-only surgical decompression was performed bilaterally for patients with persistent fullness of the lids and anterior orbit following treatment with teprotumumab. This was performed through upper lid crease and lower lid transconjunctival incisions.

Of note, 13 of our 64 patients had their treatment courses interrupted by the suspension of teprotumumab production in December 2020 due to COVID-19 vaccine production prioritization. One patient only completed 7 of 8 infusions due to the stoppage, while the remaining 12 completed all 8 infusions. Four of these patients ultimately underwent bony decompression, and none underwent fat-only decompression.

Thirty-two of 64 patients (50%) noted intermittent or constant diplopia on initial presentation, and 16 of 64 patients (25%) underwent strabismus surgery following cessation of teprotumumab therapy, with mean time to surgery from last infusion being 10.4 months (SD 6.0).

There was no statistically significant difference in mean age at first treatment, initial CAS, number of teprotumumab infusions completed, or follow-up time between patients who did and did not undergo bony decompression surgery following teprotumumab therapy (Table 2). Mean pretreatment exophthalmometry measurements were significantly higher in orbits that underwent bony decompression (23.7 mm, SD 2.6) compared with orbits that did not (20.7 mm, SD 3.1) ($p < 0.001$) (Table 3). The association between a patient's report of subjective bulging or swelling on initial evaluation and eventual bony decompression did not reach statistical significance ($p = 0.100$). The association between report of pain at initial evaluation and eventual bony decompression was also not significant ($p = 0.317$). Posttreatment exophthalmometry measurements were significantly higher in the orbits that underwent bony decompression (20.6 mm, SD 2.7) compared with those that did not (18.6 mm, SD 3.0) ($p = 0.0047$) (Table 2).

Table 3—Bony decompressed vs non-decompressed orbits

	Bony decompression	No decompression	*p* Value
Pre-teprotumumab exophthalmometry, mm (SD)	23.7 (2.6)	20.7 (3.1)	0.000[a]
Post-teprotumumab exophthalmometry, mm (SD)	20.6 (2.7)	18.6 (3.0)	0.0047[a]

[a]Two-sample *t* test.

An analysis was performed comparing presurgery exophthalmometry measurements in 84 orbits that underwent bony decompression surgery for TED prior to the approval of teprotumumab (mean 23.9 mm, SD 3.6) to those 24 that underwent the surgery after treatment with teprotumumab (23.7 SD 2.6). There was no significant difference in presurgery exophthalmometry measurements between these 2 groups ($p = 0.77$).

An analysis was also performed comparing patients who underwent any decompression (bony or fat-only) with those who did not undergo any surgical decompression. There was no statistically significant difference in age, initial CAS, or follow-up time between the two groups. The associations between reported subjective bulging ($p = 0.251$) and reported pain ($p = 0.065$) on initial evaluation and whether a patient underwent surgical decompression were not statistically significant. Pretreatment exophthalmometry measurements were significantly higher in orbits that underwent any decompression (22.6 mm, SD 3.0) compared with those that did not (20.6 mm, SD 3.2) ($p = 0.001$). Post-treatment exophthalmometry measurements were significantly higher in orbits that underwent any decompression (19.9 mm, SD 2.6) compared with those that did not (18.5 mm, SD 3.0) ($p = 0.016$).

Discussion

We found that the number of TED patients seen and treated at a tertiary academic center increased steadily from 2018 through 2023. This may reflect the addition of a new faculty member, as well as an increase in referral volume due to the availability of teprotumumab and increasing awareness among patients themselves. Conversely, the number of surgical decompressions performed decreased significantly starting in 2020.

In studying these trends, we must acknowledge that the approval of teprotumumab in 2020 came just 2 months before the start of the COVID-19 pandemic, which had a significant impact on both routine medical appointments and elective surgeries. The results of Epic SlicerDicer queries demonstrate, however, that despite the pandemic, the number of TED patients seen in the clinic continued to rise through 2020 and 2021, through the height of the pandemic. This suggests that the decline in surgical decompressions performed is likely attributable to factors other than the COVID-19 pandemic, such as the introduction of teprotumumab as an alternative treatment for TED. In fact, the

decline in the decompression rate has persisted through 2021, 2022, and 2023, despite full capacity of elective procedures.

The introduction of teprotumumab likely contributed to the decline of decompression surgery rates for several reasons. Providers may be more likely to prescribe teprotumumab in patients with active disease, who previously might have waited for a 6-month period of disease stability before undergoing decompression surgery. Also, patients with chronic disease now have an option of teprotumumab treatment, who previously might have opted for orbital decompression in the absence of medical options. Patients in various stages of disease, therefore, now have the option to consider medical treatment before surgery. It is likely that over the past several years orbital decompression surgery has become more of a final option for many patients who would prefer the benefits and associated risks of biologic therapy over orbital surgery.

In order to better counsel TED patients, we studied how many patients underwent surgical decompression after teprotumumab treatment and sought to determine whether any predictive factors existed. In 64 teprotumumab-treated patients with over 20 months of average follow-up time, 25% of patients and 18.8% of orbits underwent bony decompression surgery due to reactivation of disease after an initial period of symptomatic improvement or for residual proptosis bothersome to the patient. Reports of subjective bulging or pain on initial evaluation were not statistically significant as predictive factors. Higher pre- and post-treatment exophthalmometry measurements were both statistically significant as predictive factors for any type of surgical decompression. The data suggest that patients with more severe proptosis, while noting meaningful reduction in their proptosis with teprotumumab, may be interested in further intervention for complete return to their baseline appearance.

Moving forward, guidance as to which patients will have the best response to teprotumumab may assist with treatment strategies. A recent study found that patients with lower pre-treatment fat-to-muscle ratios (FMR) on CT and MR imaging (historically deemed "type 2" TED patients) had a greater clinical response to teprotumumab.[16,17] A subsequent study found that in patients with FMR $\geq$1.80, surgical decompression led to significantly more proptosis reduction than teprotumumab, while in patients with FMR $<$1.80, teprotumumab and surgical decompression led to similar amounts of proptosis reduction.[17] As the authors concluded, pretreatment FMR may help physicians counsel patients regarding treatment response and the possibility of needing further intervention.

In conclusion, 25% of patients who received teprotumumab treatment ultimately underwent bony orbital decompression over the course of this study. Higher pre- and post-treatment exophthalmometry measurements may help predict this cohort of patients. Treatment with teprotumumab likely reduces the need for orbital decompression and its associated morbidity in many patients. Further studies with larger patient populations will enable investigators to confirm the applicability of these findings, to determine how treatment with teprotumumab affects rates of eyelid surgeries, and to examine which TED patients, if any, may do better with one treatment modality.

Study limitations and potential bias

Limitations of the consecutive case series include the small sample size, its retrospective nature, and inclusion of a single tertiary center. The inclusion of patients who did not complete the full course of teprotumumab was intentional, as this was a study of "real-life" clinical practice patterns, and patients may not complete all 8 infusions for various reasons. While 8 infusions remain the standard treatment regimen, some studies have demonstrated early treatment efficacy within the first few doses.[18,19] This could have theoretically increased the observed rate of post-treatment decompression surgery in our study, but on review of the post-treatment patients who required orbital decompression, all had completed the full teprotumumab treatment course. Finally, one limitation of the Epic SlicerDicer trend analysis is that while there was clearly an increase in overall number of TED patients being seen, this reflected overall patients and was not detailed for any specific TED phenotype.

Summary

Although the number of orbital decompression surgeries performed is declining, the surgery is still needed in a select group of patients following teprotumumab treatment for thyroid eye disease.

References

1. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med 2020;382:341–52.
2. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. New England Journal of Medicine 2017;376:1748–61.
3. Ugradar S, Kang J, Kossler AL, et al. Teprotumumab for the treatment of chronic thyroid eye disease. Eye (Lond) 2022;36:1553–9.
4. Ozzello DJ, Dallalzadeh LO, Liu CY. Teprotumumab for chronic thyroid eye disease. Orbit 2022;41:539–46.
5. Ozzello DJ, Kikkawa DO, Korn BS. Early experience with teprotumumab for chronic thyroid eye disease. Am J Ophthalmol Case Rep 2020;19:100744.
6. Ediriwickrema LS, Korn BS, Kikkawa DO. Orbital decompression for thyroid-related orbitopathy during the quiescent phase. Ophthalmic Plast Reconstr Surg 2018;34:S90–7.
7. Jefferis JM, Jones RK, Currie ZI, Tan JH, Salvi SM. Orbital decompression for thyroid eye disease: methods, outcomes, and complications. Eye (Lond) 2018;32:626–36.

8. Cheng AMS, Wei YH, Liao SL. Strategies in surgical decompression for thyroid eye disease. Oxid Med Cell Longev 2020;2020:3537675.
9. Graham SM, Brown CL, Carter KD, Song A, Nerad JA. Medial and lateral orbital wall surgery for balanced decompression in thyroid eye disease. Laryngoscope 2003;113:1206–9.
10. Sellari-Franceschini S, Berrettini S, Santoro A, et al. Orbital decompression in graves' ophthalmopathy by medial and lateral wall removal. Otolaryngol Head Neck Surg 2005;133:185–9.
11. Mourits MP, Bijl H, Altea MA, et al. Outcome of orbital decompression for disfiguring proptosis in patients with Graves' orbitopathy using various surgical procedures. Br J Ophthalmol 2009;93:1518–23.
12. Taylor PN, Zhang L, Lee RWJ, et al. New insights into the pathogenesis and nonsurgical management of Graves orbitopathy. Nat Rev Endocrinol 2020;16:104–16.
13. Khong JJ, McNab A. Medical treatment in thyroid eye disease in 2020. Br J Ophthalmol 2021;105:299–305.
14. Burch HB, Perros P, Bednarczuk T, et al. Management of thyroid eye disease: a Consensus Statement by the American Thyroid Association and the European Thyroid Association. Eur Thyroid J 2022;11:e220189.
15. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid 2016;26:1343–421.
16. Ting MA, Ozzello DJ, Topilow NJ, et al. Differential effects of teprotumumab treatment based on fat-to-muscle ratio in patients with thyroid eye disease. Orbit 2023;42:418–25.
17. Ting MAJ, Topilow NJ, Ediriwickrema LS, Yoon JS, Liu CY, Korn BS, Kikkawa DO. A comparison of proptosis reduction with teprotumumab versus surgical decompression based on fat-to-muscle ratio in thyroid eye disease. Orbit 2024;43:222–30.
18. Sears CM, Wang Y, Bailey LA, et al. Early efficacy of teprotumumab for the treatment of dysthyroid optic neuropathy: A multicenter study. Am J Ophthalmol Case Rep 2021;23:101111.
19. Slentz DH, Smith TJ, Kim DS, Joseph SS. Teprotumumab for optic neuropathy in thyroid eye disease. JAMA Ophthalmol 2021;139:244–7.

Footnotes and Disclosure

Don O. Kikkawa is a consultant with Horizon Therapeutics, Thyroscope, and Immunovant. Bobby S. Korn was a consultant with Horizon Therapeutics until May 2021. Bobby S. Korn and Don O. Kikkawa receive book royalties from Elsevier Publishing. Catherine Y Liu receives grant support from Horizon Therapeutics and receives royalties from Wolters Kluwer Health. The authors have no proprietary or commercial interest in any materials discussed in this article.

From the *Division of Oculofacial Plastic and Reconstructive Surgery, University of California San Diego Viterbi Family Department of Ophthalmology, Shiley Eye Institute, La Jolla, CA; †Department of Ophthalmology, Severance Hospital, Institute of Vision Research, Yonsei University College of Medicine, Yonsei, Korea; ‡Division of Plastic Surgery, Department of Surgery, University of California San Diego Department of Surgery, La Jolla, CA.

Originally received Oct. 1, 2023. Final revision Mar. 17, 2024. Accepted Jun. 3, 2024.

Correspondence to Nicole J Topilow, MD, 9350 Campus Point Drive, Suite 1A, San Diego, CA 92037; ntopilow@gmail.com.