

Expert Consensus on the Use of Teprotumumab for the Management of Thyroid Eye Disease Using a Modified-Delphi Approach

Raymond S. Douglas, MD, PhD, Andrea L. Kossler, MD, Jody Abrams, MD, Cesar A. Briceño, MD, David Gay, MD, Andrew Harrison, MD, Michael Lee, MD, John Nguyen, MD, Shannon S. Joseph, MD, Dianne Schlachter, MD, Jeremy Tan, MD, Judah Lynch, MScRes, Louisa Oliver, BSc, Richard Perry, BSc, Shoab Ugradar, MD,

Background: Teprotumumab is the first treatment for thyroid eye disease (TED), a debilitating autoinflammatory condition, approved by the Food and Drug Administration in the United States, which reduces proptosis and improves quality of life. In the absence of guidelines, clinical

Division of Oculoplastics (RSD), Cedars Sinai Medical Center, Los Angeles, California; Byers Eye Institute (ALK), Stanford University School of Medicine, Palo Alto, California; Sarasota Retina Institute (JA), Sarasota, Florida; Scheie Eye Institute (CAB), University of Pennsylvania, Philadelphia, Pennsylvania; Austin Face and Body (DG), Austin, Texas; Department of Ophthalmology (AH, ML), University of Minnesota, Minneapolis, Minnesota; West Virginia University (JN), Morgantown, West Virginia; Division of Oculoplastic Surgery (SSJ), Kellogg Eye Center, Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, Michigan; Consultants in Ophthalmic and Facial Plastic Surgery (DS), Southfield, Ann Arbor, Michigan; Dean McGee Eye Institute (JT), Oklahoma University, Norman, Oklahoma; Adelphi Values (JL, LO, RP), Manchester, United Kingdom; and The Jules Stein Eye Institute (SU), UCLA, Los Angeles, California.

R. S Douglas: Consultant Horizon Therapeutics, Immunovant Corporation, and Veridian Corporation. A. L. Kossler: Consultant Horizon Therapeutics, Osmotica Pharmaceuticals, Immunovant Corporation, and Axogen Corporation. J. Abrams: Speaker for Horizon Therapeutics. C. A. Briceño: Consultant for Horizon Therapeutics. A. Harrison: Consultant for Horizon Therapeutics and Osmotica. M. Lee: Equity ownership, Horizon Therapeutics. J. Nguyen: Consultant for Horizon Therapeutics. S. S. Joseph: Consultant for Horizon Therapeutics. J. Tan: Consultant for Horizon Therapeutics. The remaining authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the full text and PDF versions of this article on the journal's Web site (www.jneuro-ophthalmology.com).

Address correspondence to Shoab Ugradar, MD, The Jules Stein Eye Institute, University of California, Los Angeles, Los Angeles, CA; E-mail: Shoab.ugradar@gmail.com

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

recommendations were developed for using teprotumumab in patients with TED in the United States.

Methods: A 3-round modified-Delphi panel was conducted between October 2020 and February 2021 with experts in the management of patients with TED. Key areas regarding the use of teprotumumab were investigated, including eligible patient populations, concomitant treatments, and assessment of response and adverse events. This used 2 survey rounds via an online questionnaire, where statements were scored using 9-point Likert scales. Statements with conflict were included in the third round, involving a consensus meeting via videoconference.

Results: Consensus was obtained for all statements ($n = 75$); of which, 56% were revised to enable agreement of the group. The consensus meeting provided agreement regarding which populations should receive teprotumumab therapy, including all adult patients with TED with a clinical activity score of ≥ 4 . Treatment with teprotumumab can also be considered for TED patients displaying the following characteristics: a CAS of < 3 , lid retraction of ≥ 2 , and mild or early optic neuropathy with close clinical observation. Further recommendations included suitability of treatment for those beyond 16 months following the initial diagnosis of TED, low CAS concomitant treatment with steroids in some cases, retreatment for those who have relapses, and finally a recommendation to continue therapy for all 8 infusions despite the lack of response by the fourth infusion.

Conclusions: This work constitutes the first consensus on guidelines for the use of teprotumumab. The modified Delphi approach involved physicians with significant experience with the clinical use of teprotumumab, and recommendations were based on current evidence.

Journal of Neuro-Ophthalmology 2022;42:334–339

doi: 10.1097/WNO.0000000000001560

© 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the North American Neuro-Ophthalmology Society.

Thyroid eye disease (TED) is a complex autoimmune condition that may be associated with thyroid dysfunction.

tion. The acute phase is typically associated with inflammation of the orbital and periorbital tissues, with resulting tissue expansion, diplopia, and proptosis (1). In most cases, TED begins with an inflammatory phase that typically lasts up to 3 years; however, it can be longer in rare cases. Once inflammation subsides, patients progress into a chronic TED phase where tissue changes can result in persistent proptosis and diplopia (2). Approximately 5% of patients with TED develop optic neuropathy, which may require more urgent therapy (3).

Teprotumumab

In early 2020, teprotumumab (TEPEZZA; Horizon Therapeutics, Dublin, Ireland), a first-in-class monoclonal antibody and a targeted inhibitor of the insulin-like growth factor-1 receptor (IGF-1R), became the first treatment approved for TED by the Food and Drug Administration in the United States (4). The approval was based on findings from the OPTIC study showing superiority of teprotumumab to placebo in respect to proptosis, diplopia, and quality of life (5). Prior to the approval of teprotumumab, treatment options were restricted to the off-label use of a range of treatments (e.g., corticosteroids) to manage inflammation. Evidence supporting the use of these therapies is conflicting, does not consistently demonstrate improvements in proptosis and diplopia, and is associated with adverse events (6,7).

There are no specific US guidelines for the treatment of TED. In 2016, the American Thyroid Association published guidelines for the diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis (8). Treatment options for TED included local measures, corticosteroids, orbital radiation, and surgery. In Europe, the European Thyroid Association commissioned the European Group On Graves' Orbitopathy to provide guidelines for the clinical management of TED based on previous randomized, nonplacebo-controlled, clinical trials (9). However, the treatment options described in the European guidelines vary from the current clinical practice and do not consider new biologic medications used for the treatment of TED. Therefore, the utility of these guidelines is limited in the United States.

The aim of this modified-Delphi panel was to reach consensus on the use of teprotumumab and how this use can be optimized within the overall management of patients with TED in the United States.

METHODS

A modified-Delphi study was conducted between October 2020 and February 2021 to determine the use of teprotumumab in TED. This study involved 2 rounds of anonymized online questionnaires and an online consensus meeting, with controlled feedback at each stage (by displaying the median group response) to encourage a

reduction in the variation of responses, moving toward consensus (Fig. 1) (10).

The panelists recruited were experts in treating patients with TED from various practices and geographical locations in the United States to ensure that results from the panel were generalizable to the US health care system. A recruitment screener was designed to ensure that all experts recruited had sufficient knowledge and experience to respond to statements on the use of teprotumumab and contribute fully to discussions (Table 1). Potential experts were identified based on membership of the American Academy of Ophthalmology and the American Society of Ophthalmic Plastic and Reconstructive Surgeons to ensure a balanced representation of insight and minimize bias in selecting experts. A detailed description of the Delphi process and restriction of bias is provided in Supplement 1 (see **Supplemental Digital Content 1**, <http://links.lww.com/WNO/A566>).

RESULTS

Eighteen experts agreed to participate in the Delphi panel and completed the first-round questionnaire. Following this questionnaire, 15 experts participated in the second-round survey. Finally, 8 experts were available to participate in the consensus meeting and therefore completed the full Delphi process discussing those statements that were not settled in the first 2 rounds. Additionally, the outputs of the consensus meeting were agreed by all experts who completed the second-round survey ($n = 15$). For consistency and to ensure that all viewpoints were considered, input from all experts were included in the analyses used to develop the materials presented in the later stages of the Delphi panel.

Following completion of the Delphi panel, consensus was obtained for all statements related to the use of teprotumumab including the following categories: indications, eligible patient populations, dosing, concomitant treatments, medical history, assessment of monitoring, assessment of response, and adverse effects (Table 2). Fifty-six percent of statements (42 of 75) were revised to enable agreement of the group. Notably, in the consensus meeting, most areas of conflict discussed were due to terminology used in the statements and could be resolved by editing statements in the meeting to reach consensus.

Consensus Statements and Rationale

The following statements reached agreement:

Indications in Thyroid Eye Disease

Teprotumumab should be considered as the first-line therapy for patients with significant TED defined as any of the following:

TABLE 1. Key criteria for expert participation

Oculoplastic surgeon, ophthalmologist, or neuro-ophthalmologist
Working in their chosen medical specialty for ≥ 24 mo
Personally responsible for the management of patients with TED
Personally prescribed teprotumumab to at least 3 patients
Actively treating patients with TED

TED, thyroid eye disease.

- Clinical activity score (CAS) of ≥ 4 , moderate or severe soft tissue involvement, exophthalmos of ≥ 3 mm above normal for race and gender, intermittent or constant diplopia, and orbital pain and/or pressure.
- Treatment with teprotumumab can also be considered for TED patients displaying the following characteristics: a CAS of < 3 , lid retraction of ≥ 2 , and mild or early optic neuropathy with close clinical observation.
- Overlapping the use of steroids and teprotumumab can be considered in specific instances.
- Teprotumumab may be considered after treatment with rituximab or tocilizumab, as contraindication has not been established.
- The appropriate washout period between stopping treatments with biologics and starting treatment with teprotumumab varies from treatment to treatment.
- Teprotumumab is suitable for the treatment of patients with TED beyond 16 months of their initial diagnosis.
- Teprotumumab may be appropriate for use as a single therapy for the primary treatment of patients with mild compressive orbital neuropathy (CON) depending on timely initiation, but close clinical observation is needed. Teprotumumab is not appropriate for the primary treatment of patients with severe CON.
- High-dose steroids or orbital decompression could be considered for some patients with CON ahead of treatment with teprotumumab.
- Teprotumumab could be used in conjunction with steroid therapy as the primary treatment of CON.

Rationale

Teprotumumab is indicated for the treatment of TED (4). Although a CAS of ≥ 4 may be an indicative factor for deciding whether to prescribe teprotumumab as a first-line treatment for TED, it should not be used as a sole indicative factor because there may be variation between patients. Patients with debilitating diplopia, extreme proptosis, and compressive optic neuropathy may score low on the CAS but may also benefit significantly from teprotumumab treatment (11).

Rituximab-treated patients have depleted B-cell counts for 6 months following their last treatment; therefore, a 6-month washout period is required before teprotumumab treatment (12). However, the washout period for other treatments may vary.

Teprotumumab may be appropriate for the primary treatment of patients with mild CON but not severe CON. This distinction is because teprotumumab's therapeutic effects take time to manifest and patients with severe CON would have a significant risk of permanent loss of vision. The 2 main forms of treatment for CON, orbital decompression and steroid therapy (13), may be used ahead of treatment with teprotumumab, or concurrently, because contraindication has not been established between the therapies.

Inclusion Criteria

Teprotumumab can be prescribed to

- all adults ≥ 18 years of age, including healthy elderly patients > 80 years of age,
- patients irrespective of thyroid status,
- patients with diabetes with blood sugar monitoring,
- patients with stable inflammatory bowel disease (IBD) with close clinical monitoring,
- commencement of treatment with teprotumumab can occur concomitantly with attempts to achieve euthyroid status, and
- preexisting diabetes, glucose intolerance, or history of gestational diabetes can be used as an indicator for close glycemic monitoring during treatment with teprotumumab.

Rationale

Teprotumumab can be administered concomitantly with the initiation of antithyroid medication, without having to wait for a euthyroid state to be achieved, as thyroid status has not been shown to impact the efficiency or safety of teprotumumab. Teprotumumab can be prescribed to patients with TED who have concomitant diabetes while monitoring blood sugar (4).

The IGF-I pathway coregulates glucose homeostasis with insulin (12). Therefore, the introduction of teprotumumab can trigger hyperglycemia in some diabetic patients with TED, and preexisting diabetes in patients with TED should be an indicator for close glycemic monitoring during treatment with teprotumumab. Hemoglobin A1C and blood glucose should be closely monitored following treatment.

Teprotumumab can be cautiously prescribed to patients with TED with stable IBD. Close clinical monitoring and comanagement with a gastroenterologist is strongly recommended as treatment with teprotumumab may exacerbate stable IBD (4).

Exclusion Criteria

Teprotumumab should not be prescribed to

- prepubertal children until evidence of safety in this population has been investigated and established,
- patients experiencing thyroid storm, and
- female patients who are attempting to become pregnant or not using contraception.

TABLE 2. Statements reaching consensus in each Delphi round

Area of Survey	Consensus Achieved			
	Round 1	Round 2	Consensus Meeting	
			Statements That Achieved Consensus	Statements Revised to Achieve Consensus
Indications in TED	41% (7/17)	9% (1/11)	100% (9/9)	100% (9/9)
Eligible patient populations	60% (6/10)	0% (0/3)	100% (4/4)	50% (2/4)
Dosing	20% (1/5)	17% (1/6)	100% (6/6)	83% (5/6)
Concomitant treatments, medical history, and assessment and monitoring	25% (9/36)	29% (8/28)	100% (26/26)	55% (11/20)
Assessment of response	30% (3/10)	33% (3/9)	100% (6/6)	86% (5/6)
Adverse events	21% (4/19)	22% (8/37)	100% (30/30)	33% (10/30)

The number of statements increased from round 1 to round 2 due to the incorporation of expert feedback. TED, thyroid eye disease.

Rationale

Due to teprotumumab's potential for triggering growth retardation, it should not be prescribed to prepubertal children until evidence of safety in this population has been investigated and established. Similarly, due to teprotumumab's potential for triggering growth retardation and developmental abnormalities, teprotumumab should not be used to treat female patients with TED who are attempting to become pregnant or are not using contraception (4).

Teprotumumab should not be prescribed to a patient experiencing thyroid storm because this condition is potentially life threatening (14). Good medical practice would dictate that the thyroid storm is adequately treated and the patient's thyroid status is well controlled before administering systemic therapy to reduce signs and symptoms of orbitopathy.

Medical History

- The following initial assessments of a patient's medical or surgical history *must be completed* before the initiation of treatment with teprotumumab: weight and blood pressure, history of diabetes, history of IBD, Graves disease history, history of hearing loss, review of patient medications, and use of steroids for treatment of TED.
- The following initial assessments of a patient's medical or surgical history *may be completed* before the initiation of treatment with teprotumumab: orbital irradiation for TED history, issues with hearing other than loss, and history of eye surgery for TED.

Rationale

Assessment of history for diabetes, IBD, and hearing loss must be carried out before teprotumumab treatment because these conditions may worsen during treatment (4).

Assessment and Management

- The following examinations must be conducted before the initiation of treatment with teprotumumab: fasting

blood glucose, hemoglobin A1C, baseline vision, and pregnancy test (premenopausal females only).

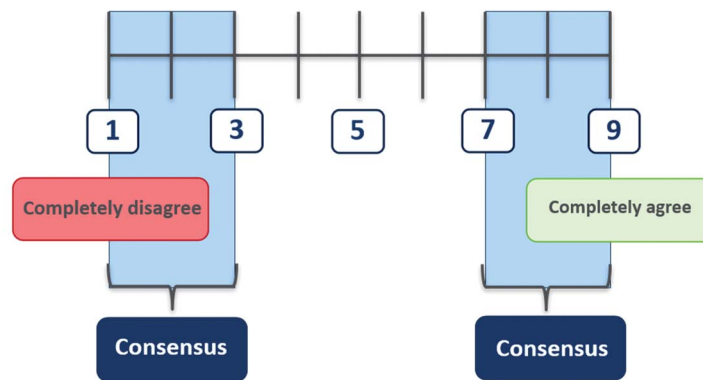
- An ophthalmologist, neuro-ophthalmologist or endocrinologist should be responsible for the primary management of patients treated with teprotumumab.
- The following examinations may be conducted before the initiation of treatment with teprotumumab but are not necessary to direct treatment: baseline audiogram, patulous eustachian tube testing, and metabolic panel with liver function test and complete blood count.
- Diabetic or prediabetic patients should have fasting blood glucose measured after each of the first 2 infusions with teprotumumab and should measure their blood glucose levels at a frequency recommended by their endocrinologist or diabetes physician.
- Patients treated with teprotumumab should be reviewed by an ophthalmologist and/or endocrinologist every 6–12 weeks depending on the severity of the disease. However, patients with CON should be reviewed more regularly at the discretion of the physician to assess response to therapy.

Rationale

Appropriate examinations, should be carried out before the initiation of teprotumumab treatment, and regular monitoring should also be completed, as described to ensure that patients with TED are appropriately responding to the treatment with minimal adverse events. Recommendations on dosing, concomitant treatments, and measurements of outcomes is included in Supplement 2 (see **Supplemental Digital Content 2**, <http://links.lww.com/WNO/A567>).

Adverse Events

Prior to the commencement of treatment with teprotumumab, the following potential adverse events *should* be discussed with patients: muscle spasms, nausea, alopecia, fatigue, hyperglycemia, diarrhea, and hearing impairment.



$\geq 80\%$ rate their “disagreement” as 1–3 or “agreement” as 7–9 (on a 9-point scale) = consensus

FIG. 1. The scale used to define consensus.

The following management strategies to combat these adverse effects induced by teprotumumab treatment *may* be recommended at the practitioner’s discretion:

- for the management of muscle spasms: hydration and magnesium supplements,
- for the management of nausea: hydration and antiemetics,
- for the management of alopecia: referral to a hair care specialist or dermatologist,
- for the management of diarrhea: hydration and referral to gastroenterologist or primary care physician if continuous or bloody,
- for the management of fatigue: rest and hydration; follow oncology guidance on chemotherapy-induced fatigue,
- for the management of hyperglycemia: referral to endocrinologist, and
- for the management of hearing impairment: referral to ear, nose, and throat specialist/audiologist or discuss discontinuation of therapy.

Prior to the commencement of treatment with teprotumumab, the following potential adverse events *may* be discussed with patients: manageable headaches, manageable dry skin, and reversible dysgeusia.

Rationale

Adverse events including muscle spasms and nausea, should be discussed with patients before the commencement of teprotumumab therapy and management strategies may be considered.

CONCLUSIONS

This modified-Delphi study elicited expert consensus to develop clinical guideline recommendations for the use of teprotumumab in patients with TED within the United States. From 2 rounds of survey and 1 consensus meeting, expert consensus statements were derived in all key areas (indications in TED, eligible patient populations, dosing,

concomitant treatments, medical history, assessment and monitoring, assessment of response and adverse events), which can be used to support the appropriate use of teprotumumab.

Several statements did not reach consensus in the survey rounds owing to a current lack of supporting evidence. For example, research demonstrating the safety of prescribing teprotumumab therapy to patients who have previously received orbital radiation to treat their TED is lacking. However, wording for these statements was adjusted to achieve consensus. For some statements, experts also noted that, without supporting evidence, teprotumumab should not be recommended, such as treatment in prepubescent children.

Most (42 of 75) statements that did not reach consensus in the survey rounds were revised during discussion in the consensus meeting, so the consensus threshold could be reached. The majority of statements that had conflict were due to disagreements in wording. To overcome this problem, the moderators adjusted the wording of different statements until the threshold for consensus was reached. In some cases, statements were excluded (27 of 75), but consensus was still achieved to exclude the statements from the list of recommendations. The remaining statements (6 of 75) achieved consensus without any revisions.

The expert panel for this modified-Delphi process involved representatives from multiple disciplines ranging from endocrinology to ophthalmology from across the United States, which were recruited using a predefined screener to minimize bias, and 49 experts were contacted who met the initial criteria. Through considering all panel viewpoints and experiences during the Delphi process, statements were developed and agreed that reflected US clinical practice. No honoraria were provided to experts contributing to this Delphi panel in order to minimize bias.

Limitations

As described above, this modified-Delphi process was conducted in a robust and reliable manner; however, there were limitations due to attrition between the panel rounds.

First, 3 experts dropped out after the first Delphi round, which meant viewpoints were lost from the second-round onwards. It is best practice to carry the results forward to the next round to allow all perceptions reported to be considered; however, this practice meant the experts were not able to put forward their rationale or justify their reasoning for areas of disagreement in the consensus meeting. To further understand this issue, individual analysis of the results was conducted to assess for outliers and their potential impact. For all areas in which the expert input was an outlier, statements were reported as being outside of their specific expertise, for example, diagnosis and initiation of treatment. Additionally, for all areas of conflict, the statements were modified according to expert feedback in the consensus meeting, with all 8 experts who attended in agreement. Therefore, even if the dropout remained an outlier for these statements, consensus would have been reached, as the dropout had minimal impact on the overall results.

Second, the number of experts who participated in the consensus meeting was significantly lower than the first-round survey (8 vs. 18 participants), also acting as a limitation because vital contributing expert opinions could be missed. However, the 7 experts who participated in the second round, but could not attend the final meeting, were given the chance to review the final statements from the consensus meeting and provide feedback, contributing to achieving consensus. The results included in this article were therefore approved by a total of 15 experts.

In order to provide expert opinion on teprotumumab, all panel members were required to have a level of knowledge regarding the product, and several of the authors are acknowledged to have provided paid consultancy relating to this medication. It must be stressed, however, that the panel was conducted completely independently from the pharmaceutical company developing teprotumumab and that the pharmaceutical company had no involvement in the materials used in the study nor the analysis and interpretation of the results contained within this article.

Overall, the achievement of consensus on all statements in this study has significantly contributed to the understanding of the use and value of teprotumumab, specifically how this medication can be optimized within the overall management of patients with TED. This issue highlights the need for further research in this area because teprotumumab may be a viable treatment for patients with TED who are currently receiving therapies such as steroids,

nonsteroidal immunosuppressive agents (apart from rituximab or tocilizumab), and orbital radiation.

STATEMENT OF AUTHORSHIP

Category 1: a. Conception and design: S. Ugradar and R. S. Douglas; b. Acquisition of data: All authors; c. Analysis and interpretation of data: All authors. Category 2: a. Drafting the manuscript: All authors; b. Revising it for intellectual content: All authors. Category 3: a. Final approval of the completed manuscript: All authors.

REFERENCES

1. **Lazarus JH.** Epidemiology of Graves' orbitopathy (GO) and relationship with thyroid disease. *Best Pract Res Clin Endocrinol Metab.* 2012;26:273–279.
2. **Bartley GB, Fatourehchi V, Kadmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, Gorman CA.** Clinical features of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol.* 1996;121:284–290.
3. **Kauh CY, Gupta S, Douglas RS, Elner VM, Nelson CC, Niziol LM, Kahana A.** Compressive optic neuropathy and repeat orbital decompression: a case series. *Ophthalmic Plast Reconstr Surg.* 2015;31:385–390.
4. **FDA.** Teprotumumab FDA label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761143s000lbl.pdf. Published 2020. Accessed February 22, 2021.
5. **Yeatts RP.** Quality of life in patients with Graves ophthalmopathy. *Trans Am Ophthalmol Soc.* 2005;103:368–411.
6. **Mallika P, Tan A, Aziz S, Alwi SS, Chong M, Vanitha R, Intan G.** Thyroid associated ophthalmopathy—a review. *Malays Fam Physician.* 2009;4:8–14.
7. **Smith TJ.** Challenges in orphan drug development: identification of effective therapy for thyroid-associated ophthalmopathy. *Annu Rev Pharmacol Toxicol.* 2019;59:129–148.
8. **Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA.** 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid.* 2016;26:1343–1421.
9. **Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, Perros P, Salvi M, Wiersinga WM.** The 2016 European Thyroid Association/European Group on Graves' Orbitopathy guidelines for the management of Graves' orbitopathy. *Eur Thyroid J.* 2016;5:9–26.
10. **Clayton MJ.** Delphi: a technique to harness expert opinion for critical decision-making tasks in education. *Educ Psychol.* 1997;17:373–386.
11. **Sears CM, Wang Y, Bailey LA, Turbin R, Subramanian PS, Douglas R, Cockerham K, Kossler AL.** Early efficacy of teprotumumab for the treatment of dysthyroid optic neuropathy: a multicenter study. *Am J Ophthalmol Case Rep.* 2021;23:101111.
12. **Douglas RS, Wang Y, Dailey RA, Harris GJ, Wester ST, Schiffman JS, Tang RA, Fowler B, Fleming J, Smith TJ.** Teprotumumab in clinical practice: recommendations and considerations from the OPTIC Trial Investigators. *J Neuroophthalmol.* 2021;41:461–468.
13. **Perumal B, Meyer DR.** Treatment of severe thyroid eye disease: a survey of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS). *Ophthalmic Plast Reconstr Surg.* 2015;31:127–131.
14. **Carroll R, Matfin G.** Endocrine and metabolic emergencies: thyroid storm. *Ther Adv Endocrinol Metab.* 2010;1:139–145.