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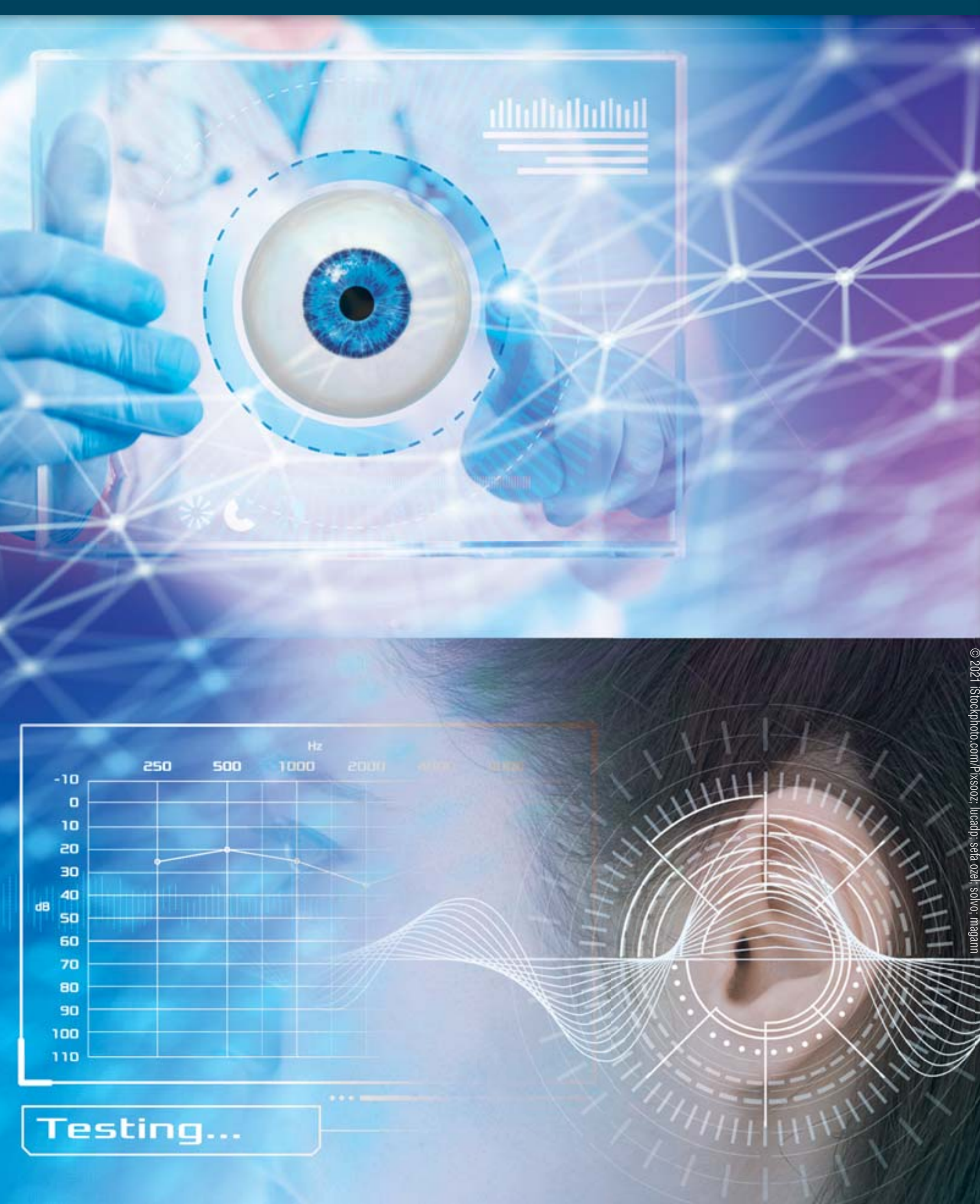
Insulin-like Growth Factor-1–Receptor Inhibitors in Thyroid Eye Disease:

Developing a Consensus to Address and Manage Hearing-related Impairment



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The articles in this monograph were composed by medical writer Valerie Zimmerman, PhD, based on the presentations of Drs. Cockerham, Douglas, Hansen, Kossler, Michaelides, and Shriver during a virtual expert panel held on October 23, 2021. The monograph has been approved by each of the faculty individually as an accurate representation of their presentations. The expert panel can be viewed at: https://cme.healio.com/ophthalmology/20211104/insulin-like-growth-factor-1-receptor-inhibitors-in-thyroid-eye-disease/overview.

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Overview

Thyroid eye disease (TED) is an autoimmune disorder that is believed to result from the stimulation of several receptors located in the orbital fibroblasts. It is frequently misdiagnosed, due to both the heterogeneity of clinical presentation and lack of understanding of the relationship between TED and hyperthyroidism. Misdiagnosis can place patients at risk, as management is most effective during the initial active phase of the disease. However, differential diagnoses can be achieved with the assistance of imaging, and early treatment may limit disfigurement and reduce vision loss. Ophthalmologists, endocrinologists, and other clinicians who care for patients with TED should be knowledgeable about conventional and new treatments as well as how to apply this information to practice. In this CME activity, experts in the field will explore conventional and new treatment options, including teprotumumab, the first and only medical agent approved by the US Food and Drug Administration for the treatment of TED. This monograph will explore the potential adverse effects associated with teprotumumab treatment, particularly hearing impairment, and will specifically address appropriate auditory testing and monitoring of patients being treatment with teprotumumab.

Target Audience

The intended audience for this activity is endocrinologists, ophthalmologists, and other health care professionals involved in the management of patients with TED.

Learning Objectives

Upon successful completion of this activity, participants should be better able to:

- Review the efficacy and safety of conventional and new treatments for TED.
- Assess the evidence on physiological mechanisms that may lead to adverse events in patients receiving insulin-like growth factor-1–receptor (IGF-1R) inhibitor therapy for the treatment of TED.
- Describe best practices that can be incorporated to improve the testing and monitoring of patients prescribed IGF-1R inhibitor therapy to proactively address potential safety concerns.
- Outline practices and procedures that can improve the multidisciplinary management of hearing-related adverse effects associated with IGF-1R inhibitor therapy for TED.

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Introduction and Overview of Thyroid Eye Disease

Andrea Lora Kossler, MD, FACS

Graves' disease (GD) is a systemic, autoimmune condition that has a prevalence in the United States of 0.5% to 1%.[1] Approximately 90% of patients with GD have hyperthyroidism, whereas 10% are euthyroid or have hypothyroidism.[2] Thyroid eye disease (TED), also known as Graves' orbitopathy and thyroid-associated orbitopathy, is the most common extrathyroidal manifestation of GD and occurs in about 50% of patients with GD.[3-6] Patients with TED can present with other systemic findings, such as pretibial myxedema, dermopathy, and periosteal deposition of the joints (known as acropachy).[2,3]

Thyroid eye disease is an unpredictable, autoimmune, inflammatory disorder. It has a biphasic course, starting with an active inflammatory stage that is characterized by pain, swelling, and inflammation.[5,7] Symptoms are mild in 70% of patients and moderate to severe in 25% to 30%.[5,7] Between 5% and 9% of patients develop sight-threatening disease.[5,7] The active phase can range from 6 months to 3 years if untreated and averages approximately 18 months.[5,7] Patients can develop proptosis, diplopia, eyelid retraction, and worsening vision. When they enter the more stable, chronic phase, the inflammatory signs and symptoms typically resolve. However, ocular sequelae can persist and are characterized by fibrosis and scarring.

Pathogenesis

Graves' disease and TED occur when immune cells misrecognize the thyrotropin receptor, found on thyroid gland cells and orbital fibroblasts, as antigen (Figure).[8] The insulin-like growth factor-1 receptor (IGF-1R) colocalizes with the thyrotropin receptor on orbital fibroblasts. The antibodies that develop to these receptor antigens initiate the pathophysiology of thyroid dysfunction and TED.

Activation of the IGF-1R–thyroid-stimulating hormone receptor (TSH-R) complex on orbital fibroblasts triggers an inflammatory response, accompanied by tissue expansion and remodeling.[7,9,10] The fibroblasts can differentiate into adipocytes, resulting in fat proliferation. Inflammatory cells release hyaluronan, cytokines, and other inflammatory products that are responsible for the orbital swelling.[7,9,10] The dysfunctional ocular fibroblasts can also differentiate into myofibroblasts, causing extraocular muscle enlargement and scarring.[7,9,10]

Epidemiology

Few data are available on the incidence of TED.[11] The annual incidence was estimated from a 15-year study in Olmsted County, Minnesota, between 1976 and 1990 at 16/100,000 population/year for women and 3/100,000 for men.[12] More recent data suggest a lower incidence of 3.3/100,000 population/year for women and 0.9/100,000 for men.[11] Diagnosis is challenging, with approximately 20% of patients presenting before the diagnosis of thyroid pathology, 40% concurrently, and 40% after diagnosis.[12]

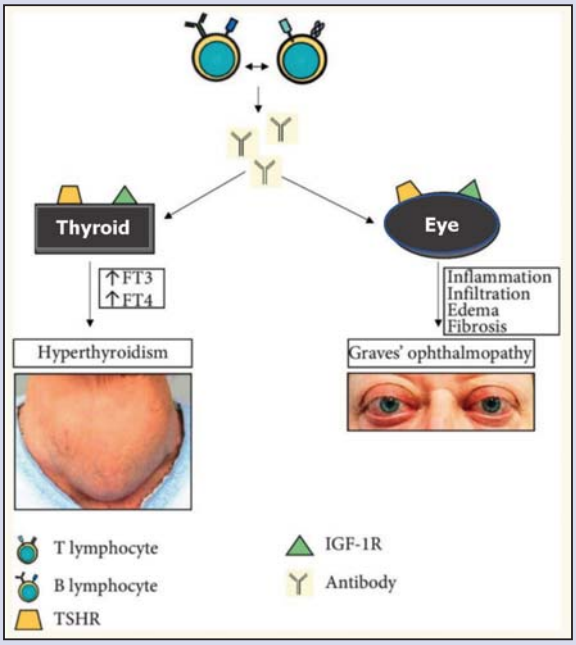
The Minnesota study noted 2 age-related peaks; the first was at 40 to 49 years and the second at 60 to 69 years, with peaks in women occurring about 5 years earlier than those in men.[12] However, the risk for TED generally increases 17% with each advancing decade.[13] Although women are at higher risk for TED, it is more severe in men.[11] Other risk factors include smoking, which increases the risk for worsening TED approximately 8-fold.[13-15] Radioactive iodine therapy for GD can increase the risk for new or worsening TED by 15% to 20%.[16] Low levels of vitamin D and selenium have been associated with TED.[17,18] In a cross-sectional study, sleep apnea was significantly more prevalent in patients with TED who had compressive optic neuropathy than in those without neuropathy complications.[19]

Signs and Symptoms

Many of the signs and symptoms of TED can affect patients' vision and daily activities. Of note, clinicians should be diligent about identifying and addressing dry eye disease, which affects approximately two-thirds of patients.[12,20-27]

Quality of life is profoundly affected by TED, and even mild disease can have a substantial impact. Studies have reported worse quality-of-life scores in patients with TED than in those with diabetes mellitus, emphysema, heart failure, and inflammatory bowel disease.[28] After conventional therapies, almost two-thirds (61%) of patients believed that their appearance has not returned to baseline, and more than half (51%) believed that their eyes continue to look abnormal.[2] Further, almost half of patients with TED have symptoms of anxiety and/or depression.[29]

Figure. Autoimmune Pathogenesis: Graves' Disease and Thyroid Eye Disease



IGF-1R = insulin-like growth factor-1 receptor; TSHR = thyroid-stimulating hormone receptor.

Source: Lacheta D, et al.[8] Open Access.

Importance of Early Diagnosis

Early diagnosis of TED is essential to timely intervention. The active phase can be described by the Clinical Activity Score, which ranges from 0 to 10 based on the presence of defined elements (Table 1).[1] A 7-point scale, without the last 3 elements, is used when previous assessments are not available—for example, at a patient's first visit.[1] Each element contributes 1 point to the total score, and a score ⩾3 indicates active TED.

Accurately assessing disease activity and severity are important parts of each clinical evaluation.[30] Immunomodulatory therapies are recommended only in cases of active inflammation. Unless urgently indicated, surgical interventions should only be done during periods of inactive disease.[30]

Classifications that divide TED among mild, moderate, severe, and sight-threatening have been validated in several studies, although some classifications include "moderate-to-severe" as a single classification.[1,5] These criteria are related to the impact of the clinical features of TED on the patient's daily life. Features of mild TED have only a minor impact on daily life and are not sufficient to warrant immunosuppressive or surgical treatment (Table 2).[1] Moderate-to-severe TED includes patients without sight-threatening disease. However, its impact on daily life is sufficient to justify the risk for immunosuppression if active or surgical intervention if inactive. Sight-threatening TED with dysthyroid optic neuropathy and/or corneal breakdown warrants immediate intervention.

The treatment window for TED is limited.[30-32] Once it becomes fibrotic, damage from the inflammatory processes may be irreversible, even with surgical intervention.[30-34]

Treatment Guidelines

The European Group On Graves' Orbitopathy (EUGOGO) published clinical practice guidelines in 2021 for the medical management of TED.[5] Treatment decisions were based on severity, activity, and duration. For active moderate-to-severe TED, general recommendations include referral to a thyroid eye clinic for counseling and shared patient–provider development of a treatment plan. As applicable, patients should be encouraged to stop smoking. Thyroid dysfunction should be appropriately treated, and iatrogenic hypothyroidism should be avoided. Recommendations for first-line medical treatment in the EUGOGO guidelines include intravenous methylprednisolone (IVMP) (0.5 g/week for 6 weeks) plus mycophenolate sodium (0.72 g/day for 6 weeks), or high-dose IVMP (0.75 g/week for 6 weeks) as first-line therapy.[5] Second-line treatment recommendations include a second course of IVMP, starting with high doses (7.5 g/course).[5] Other options include oral steroids plus cyclosporine or azathioprine, orbital radiotherapy plus oral or intravenous MP, rituximab, tocilizumab, or teprotumumab. For sight-threatening TED, high-dose IVMP (0.5-1.0 g/dose) for 3 consecutive or alternative days is recommended.[5] Urgent orbital decompression is recommended if the patient has either no or a poor response to therapy within 1 to 2 weeks.[5]

Limitations of the EUGOGO guidelines are that they are not supported by high-quality evidence.[5] In addition, teprotumumab has regulatory approval in the United States but not in the European Union, where the guidelines originated.[5,35] Therefore, they do not reflect practice in the United States, where an expert panel that convened in late 2019 recommended considering teprotumumab as first-line therapy for patients with clinically significant ophthalmopathy, including those with a duration of disease >9 months.[36]

Guidelines specific for practitioners in the United States are needed to more accurately define the role of teprotumumab and other biologics for treating patients with TED. Preliminary results of a recent survey of American Thyroid Association/European Thyroid Association members on TED were presented at the 2021 meetings.[37] However, the survey only received a 15% response.[37] Geographic variation in treatment

Table 1. Thyroid Eye Disease: Clinical Activity Score Elements

Element	Each visit	Compared with previous visit	Score
Pain behind the globe over the past 4 weeks	X		1
Pain with eye movement over the past 4 weeks	X		1
Eyelid redness	X		1
Conjunctiva redness	X		1
Eyelid swelling	X		1
Chemosis (edema of the conjunctiva)	X		1
Swollen caruncle (flesh body at medial angle of eye)	X		1
Increased proptosis ⩾2 mm		X	1
Decreased eye movement ⩾5 degrees in any direction		X	1
Decreased visual acuity ⩾1 line on the Snellen chart		X	1

Source: Data from Ross DS, et al.[1]

Table 2. Thyroid Eye Disease: Severity Assessment

Grade[a]	Lid retraction	Soft tissues	Proptosis[b]	Diplopia	Corneal exposure	Optic nerve status
Mild	<2 mm	Mild involvement	<3 mm	Transient or absent	Absent	Normal
Moderate	⩾2 mm	Moderate involvement	⩾3 mm	Inconstant	Mild	Normal
Severe	⩾2 mm	Severe involvement	⩾3 mm	Constant	Mild	Normal
Sight threatening	—	—	—	—	Severe	Compressed

[a]Mild: minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment. Moderate to severe: non–sight-threatening disease but sufficient to impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Sight-threatening: dysthyroid optic neuropathy and/or corneal breakdown; these patients warrant immediate intervention. [b]Variation compared with the upper limit of normal according to race/ethnicity and sex, or the patient's baseline measurement, if available.

Source: Data from Ross DS, et al.[1]

practices was evident. Teprotumumab was the treatment of choice for active moderate-to-severe TED in North America and was the second choice after intravenous steroids for treating dysthyroid optic neuropathy.[37] Intravenous steroids remained the TED treatment of choice in Europe and other regions.[37]

Summary

Thyroid eye disease is a complicated, unpredictable autoimmune disorder that is driven by the IGF-1R/TSH-R complex. Management is guided by disease activity and severity, with teprotumumab providing an approved first-line treatment option in the United States. Management guidelines reflecting a US treatment consensus are needed.

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Efficacy and Safety of Conventional Treatments for Thyroid Eye Disease

Erin M. Shriver, MD, FACS

Historically, treatments for patients with thyroid eye disease (TED) have targeted the inflammatory component of TED, have not significantly altered the orbital disease process, and have been used off-label. Rundle's curve, described in 1945 to depict the natural history of TED divided into active and stable phases, has been the traditional model for disease progression. The model has historically been used to demonstrate the potential of early therapy initiation to mitigate the severity of later disease manifestations (Figure 1).[1,2]

Goals of Therapy

The active phase of TED typically lasts 1 to 3 years. It has a recurrence rate of 5% to 10% and is less likely to return after 18 months of quiescence.[2] Disease activity more than severity has been believed to determine the outcome of immunosuppressive therapy.[3] When considering the goals of therapy, first and foremost, patients must maintain their general health and a euthyroid state. They must also stop smoking and avoid second-hand smoke. From an ophthalmic perspective, the goals of therapy are to preserve vision; prevent corneal exposure; correct diplopia; and improve ocular and orbital comfort, cosmesis, and mental well-being.[4,5]

Approximately 75% of patients need only supportive measures, including lubrication and monitoring with ophthalmic examinations.[4,5] When TED becomes more inflamed and active, medication is often initiated. Surgery should be reserved for patients with disease in the stable phase unless they also have dysthyroid optic neuropathy.[4,5] However, how and when to treat patients with TED is evolving as new options and medications become available. Management strategy changes can be considered in relation to the status of conventional treatments for patients with TED.

Smoking Cessation

The cyanide contained in cigarettes is converted to thiocyanate in the body, which is an antithyroid agent.[6] Patients with Graves' disease who smoke are 7.7 times more likely to develop TED.[6] Smoking increases the severity of disease, extends the average duration of the active phase (from 1 year in nonsmokers to 2 to 3 years in smokers), and decreases treatment effectiveness.[6]

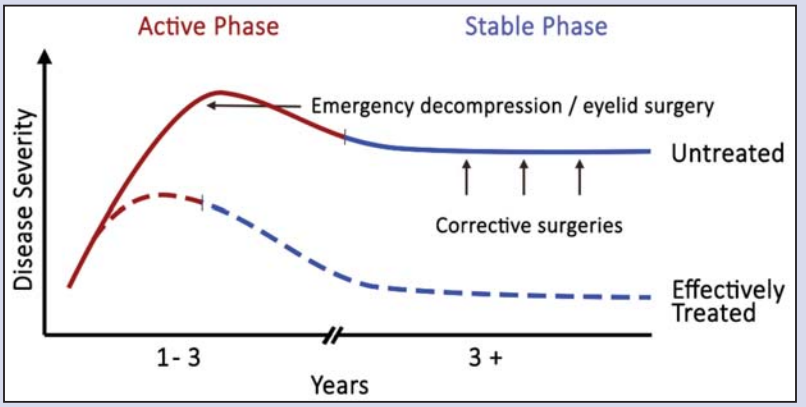
Selenium Supplementation

Selenium, an antioxidant enzyme component, was shown in a European Group On Graves' Orbitopathy study to be beneficial in cases of mild noninflammatory TED.[7] However, Europe has endemic selenium deficiencies, and there is little information for the United States, restricting the generalizability of this observation.

Trends in Treatment

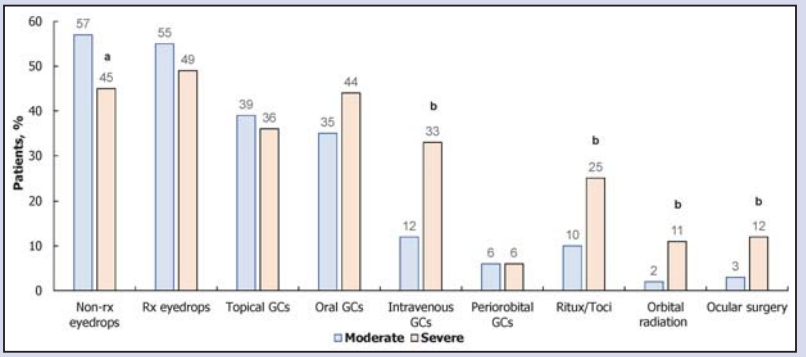
In 2018, a cross-sectional study evaluated the treatment strategies used by 181 US ophthalmologists and endocrinologists for 714 patients.[8] Eye drops were the predominant therapy provided, followed by topical and oral glucocorticoids (GCs) (Figure 2).[8] Approximately one-third and one-fourth of patients with severe TED were treated with intravenous GCs and targeted biologic therapies, respectively.[8] This study highlights the lack of consensus on treatment algorithms because no therapies were clearly extremely effective or approved by the US Food and Drug Administration (FDA).

Figure 1. Rundle's Curve



Source: Data from Dickinson AJ, et al[1]; Liaboe C, et al.[2]

Figure 2. Treatments for Active Moderate and Severe Thyroid Eye Disease, Late 2018



Treatments shown represent therapies being used at the time of data collection. [a]*P*=.03; [b]*P*=.001. GC = glucocorticoid; Non-rx = nonprescription; Ritux/Toci = rituximab and/or tocilizumab; Rx = prescription.

Source: Data from Wang Y, et al.[8]

Glucocorticoids

The potent anti-inflammatory and immunosuppressive effects of GCs at high doses have made them the mainstay of first-line treatment for active TED since their introduction in the 1950s.[4,9-12] The efficacy of GCs in TED ranges between 50% and 88%.[13-15] Intravenous administration is more effective than oral dosing for moderate-to-severe disease.[13-15] Intravenous GCs are approximately 70% to 80% effective in reducing inflammatory signs in TED, compared with an approximate 60% short-term benefit with oral prednisone.[13-15] Steroids are relatively ineffective for treating patients with strabismus and eyelid retraction and have only a mild effect on proptosis.[13-15]

Glucocorticoid treatment is associated with several cumulative dose-dependent adverse effects.[16] Cumulative doses of 8.0 g methylprednisolone per cycle and consecutive-day administration are associated with a higher rate of adverse effects, including liver toxicity and serious cardiovascular events.[16]

Several studies have compared GCs alone with other nonsurgical therapies, including radiotherapy, rituximab, cyclosporine, colchicine, immunoglobulin, mycophenolate mofetil (MMF), and somatostatin.[17,18] A study that compared methylprednisolone with MMF noted an increased I^2 value of heterogeneity in the MMF group from 8% to 69%.[18] Mycophenolate mofetil was associated with a better response rate (RR = 0.74; 95% CI, 0.63-0.88, *P*=.0005) and a greater reduction of the clinical activity score and proptosis than GCs.[18] The response rate in the GC group was similar to that of the immunoglobulin, colchicine, somatostatin, and radiotherapy groups and better than that in the cyclosporine group.[18] However, GCs did not have better proptosis reduction (mean difference = 0.42; 95% CI, 0.00-0.85; *P*=.05).[18]

Absolute contraindications to GCs include recent viral hepatitis, significant hepatic dysfunction, severe

cardiovascular morbidity, and psychiatric disorders.[16] Diabetes and hypertension must be well controlled, and patients with these disorders must be closely monitored. Weight gain and cushingoid features, including truncal obesity, buffalo hump, and moon face, can develop during treatment.[16] Prophylaxis for osteoporosis and ulcers is warranted.

Orbital Radiotherapy

Orbital radiotherapy decreases inflammation in approximately 60% of patients.[7,17,19-22] A typical treatment course comprises a total of 20 Gray doses fractionated over 10 treatments. Initial postradiation transient inflammation usually responds to steroid treatment.[19-22] Radiotherapy is effective in improving diplopia and ductions, with demonstrated benefit in compressive optic neuropathy.[19-22] However, it has little benefit in reducing proptosis or lid retraction.[19-22] Complications of radiotherapy include tumorigenesis, radiation retinopathy, and cataracts. Therefore, it should not be used in patients aged <35 years.[19-22]

Surgical Intervention/Rehabilitation

Orbital decompression is typically used urgently for dysthyroids optic neuropathy and in stable, inactive patients with exophthalmos.[2] Surgical intervention may be appropriate for inactive, stable cases with strabismus or eyelid retraction.[2]

Mycophenolate Mofetil

Mycophenolate mofetil therapy is associated with decreased antibody production by B cells and has a dual antiproliferative effect on both B and T cells.[17,19] In a study of 174 patients with moderate-to-severe TED who were randomly assigned to treatment with MMF or GCs, a greater overall response at 24 weeks, according to the Clinical Activity Score and several TED-related signs and symptoms, was observed in the MMF group compared with the GC group (92.5% vs 70.5%; $P<.05$).[17] Another study randomly assigned 164 patients with active moderate-to-severe TED to intravenous GC monotherapy or to GCs combined with MMF.[22] The response rate at 12 weeks and relapse rates at 24 and 36 weeks were not significantly different between groups.[22] However, a post hoc analysis suggested that an improved response rate was achieved in the combination therapy group at 24 and 36 weeks.[17,22] Mild and moderate drug-related adverse effects occurred in 20% and 25% of patients receiving monotherapy and combination therapy, respectively.[17,22]

Cyclosporine

Cyclosporine is a potent immunosuppressive agent that inhibits the calcineurin pathway, reducing T-cell proliferation and interleukin-2 secretion.[23,24] Two small trials reported superior outcomes in patients who were treated with cyclosporine combined with oral GCs compared with either treatment given as monotherapy.[23,24]

Azathioprine

Azathioprine inhibits DNA synthesis and acts as an immunosuppressant.[25] Although it is not effective as monotherapy, it may allow weaning of corticosteroids for long-term treatment. Side effects include nausea, fatigue, hair loss, rash, bone marrow suppression, and secondary infections.

Rituximab

Rituximab is a chimeric human and mouse monoclonal antibody against the cluster of differentiation–20 surface antigen expressed on B cells, with treatment leading to immunosuppression and B-cell depletion.[26-28] Rituximab has several indications approved by the FDA for treating patients with lymphoproliferative cancers and autoimmune disorders. However, studies in patients with TED have produced contradictory results.[12,29] A small study from Italy compared rituximab (500 or 2000 mg) with intravenous GCs (7.5 g) in 32 patients with active moderate-to-severe TED and reported superior ophthalmic and quality-of-life outcomes in the rituximab groups at 16, 20, and 24 weeks.[26] A subsequent study of a single 100-mg dose of rituximab done in Italy also reported positive outcomes.[28] However, a placebo-controlled US study of 25 patients reported no significant benefits with rituximab compared with placebo treatment, with 5 of the 6 moderate or severe adverse effects occurring in the rituximab group.[27]

Tocilizumab

Interleukin-6 is involved with T- and B-cell activation as a proinflammatory cytokine, acting directly on orbital preadipocytes to promote volume expansion.[30] Tocilizumab is a humanized anti–interleukin-6 receptor monoclonal antibody that is FDA-approved for treating patients with rheumatoid arthritis.[30] Promising results were reported in several small studies of tocilizumab in patients with active TED that was refractory to steroid treatment.[10] In a small randomized controlled trial, 32 patients with moderate-to-severe GC-resistant TED received tocilizumab or placebo intravenously at weeks 0, 4, 8, and 12, with follow-up for an additional 28 weeks.[30] The primary outcome of a $\geqslant$2-point decrease in Clinical Activity Score from baseline to week 16 was met by 93.3% of patients in the tocilizumab group and by 58.8% of patients in the placebo group ($P=.04$)[30] In addition, exophthalmos decreased by a mean of 1.5 mm in the tocilizumab group compared with no decrease in the placebo group ($P=.01$).[30]

Anti–Tumor Necrosis Factor

Although the rationale for exploring inhibition of tumor necrosis factor-α was supported by observations of elevated levels in serum, tears, and orbital tissues of patients with TED compared with controls, several small, open-label studies showed only limited treatment efficacy of tumor necrosis factor-α inhibitors.[12] A case series of 10 patients treated with adalimumab reported a decreased inflammatory score in 6 patients, an increased score in 3 patients, and a stable score in 1 patient.[31] The 5 patients with a high baseline inflammatory index (>4) had significant improvement.[31] A few case reports described clinical and radiological improvement with infliximab treatment.[32,33] A pilot study of 10 patients treated with etanercept reported improvement in 6, with rebound in 3 patients after treatment discontinuation.[34] Exophthalmos was not improved.[33]

Summary

Glucocorticoids have traditionally been the mainstay of TED treatment despite associated complication risks, unpredictable durability, and lack of resolution of associated periorbital changes and orbitopathy. Advances have been made with the use of biologics, and further studies are needed to determine the optimal use for targeted therapies such as teprotumumab.

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Efficacy and Safety of Teprotumumab for Thyroid Eye Disease

Kimberly Cockerham, MD, FACS

Recent research has provided considerable evidence to support a comprehensive role of orbital fibroblasts in the pathogenesis of thyroid eye disease (TED).[1-4] However, many details remain uncertain.[1-4] The physical and functional interactions between thyroid-stimulating hormone receptors (TSH-Rs) and insulin-like growth factor-1 receptors (IGF-1Rs) in the orbital fibroblasts and fat of patients with TED include fibroblast activation and synthesis of T-cell chemo-attractants and hyalurons.[5] What we do know is that the 2 receptors are colocated, coacting, and directly involved in the pathogenesis of TED. These changes contribute to the characteristic signs and symptoms of TED.[5] Early studies of the therapeutic potential of the monoclonal antibody teprotumumab's ability to inhibit IGF-1R gave further support for the role of IGF-1Rs in TED pathogenesis.[5]

The classic description is that the TED course of disease progresses from an active phase, which may persist for up to 2 years, to an inactive phase, which can last from 3 to 6 years and has the potential to reactivate the inflammatory phase.[1,4,6] However, fluctuations in the active phase are common, and the duration of disease can be much longer. Reactivation is possible after years of chronic, stable disease,[1,4,6] and patients with chronic, stable TED report a significant impact on their quality of life.[7] Accumulating evidence on TSH-Rs, IGF-1Rs, T and B cells, lymphocyte-derived antibodies, and upregulated inflammatory cytokines suggests several potential targets for immunotherapeutic agents for TED treatment.[1,8,9] Several targeted treatments have been examined for their potential to achieve this objective (Figure 1), although inconsistent outcomes and lack of robust efficacy have restricted the development of many of these agents.[1] In 2020, the IGF-1R inhibitor teprotumumab became the first treatment to receive approval from the US Food and Drug Administration (FDA) for TED treatment.[10,11] The availability of a disease-modifying therapy that can provide long-term benefits independent of activity and duration of TED and has an optimal safety profile is leading to a paradigm shift in management.

Teprotumumab is a fully humanized IGF-1R inhibitory monoclonal antibody, with targeted binding to the IGF-1R/TSH-R signaling complex.[1,4,11] Initial studies of IGF-1R inhibition supported several potential therapeutic mechanisms in patients with TED.[9] The induction of T-cell chemoattractants by Graves' disease–immunoglobulin G/IGF-1 in orbital fibroblasts was inhibited; IGF-1R and TSH-R surface display on fibroblasts was reduced; and fibrocyte expression of monoclonal antibody–induced proinflammatory cytokines, including interleukin (IL)–6, IL-8, and tumor necrosis factor–α, was inhibited.[9]

By blocking autoantibodies from attacking orbital cells and activating fibroblasts, teprotumumab turns off IGF-1R/TSH-R signaling at the source of disease.[1,4,11] Downstream effects on T and B cells, adipocytes, and myofibroblasts promote inflammation resolution and minimize tissue expansion, promoting resumption of homeostasis in the orbital environment.[1,4,11]

Phase 2 Clinical Trial

The efficacy and safety of teprotumumab were explored in a phase 2 clinical trial that enrolled 88 patients with active moderate-to-severe TED, producing data that also contributed to the FDA's approval of teprotumumab for TED treatment.[11,12] The primary outcome was response in the study eye at week 24, defined as a ⩾2-mm reduction in proptosis.[11,12] Significant differences in response between the teprotumumab and placebo groups were observed at the 6-, 12-, 18-, and 24-week timepoints, with 69% and 20% of teprotumumab and placebo group patients, respectively, achieving a response at week 24 ($P<.001$ for all comparisons).[11,12] Response to teprotumumab was rapid, with 43% and 4% of teprotumumab and placebo group patients, respectively, achieving a response by week 6 ($P<.001$).[12,13] The mean change from baseline in proptosis was –2.46 and –0.15 mm in the teprotumumab and placebo groups, respectively ($P<.001$) (Figure 2).[12,13] There was also a reduction of ⩾2 points in the Clinical Activity Score (CAS), which ranges from 0 to 7, with a score of ⩾3 indicating active TED.[12,13]

OPTIC: Pivotal Phase 3 Trial

Eligibility criteria for the phase 3 OPTIC trial were similar to those for the phase 2 study.[14] The OPTIC trial enrolled 83 treatment-naive patients aged 18 to 80 years with onset of

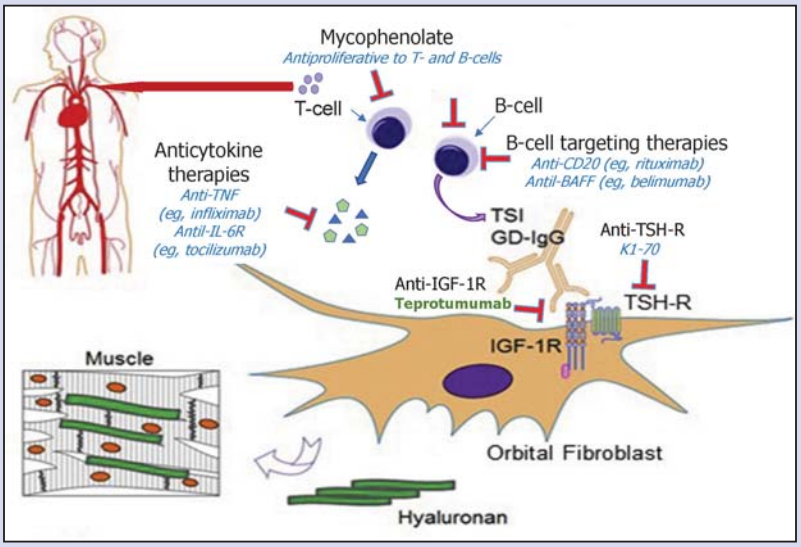
active TED <9 months previously.[14] Eligible patients were euthyroid and had a CAS of ⩾4.[14] Participants were randomly assigned to 8 intravenous infusions of teprotumumab or placebo at 3-week intervals, with the last dose administered at week 21.[14] The primary endpoint was a ⩾2-mm improvement in proptosis at week 24.[14] After 24 weeks, patients without a proptosis response were eligible to enter the OPTIC-X open-label extension study and receive an additional 8 infusions.[14] Patients who were not enrolled in the extension study were followed for 48 weeks, and those whose condition relapsed during the extension period could enroll in the study.[14]

The primary outcome was met, with 83% and 10% of teprotumumab and placebo group patients, respectively, achieving a proptosis response at week 24 (P<.001).[14] At the initial 6-week follow-up, more than half (56%) of the patients receiving teprotumumab achieved a response compared with 7% of the patients receiving placebo.[14] The change in proptosis from baseline to week 24 in the teprotumumab group was –3.32 mm, with a between-group difference of –2.79 mm (95% CI, –3.40 to –2.17), which was equivalent to a 73.45% (95% CI, 58.89-88.01) treatment difference compared with placebo.[14] All patients in the teprotumumab group achieved at least some reduction in proptosis at week 24.[14]

The secondary outcomes were also significantly better in the teprotumumab group than in the placebo group.[14] By week 6, the difference in these outcomes between the teprotumumab and the placebo groups was robust.[14] Among the 8 patients in both groups who had diplopia at baseline, improvement—defined as a reduction in diplopia score ⩾1 grade—was achieved by 68% of teprotumumab and 29% of placebo group patients at week 24 (P=.001). A CAS of 0 or 1 was achieved by 59% and 21% of patients, respectively (P<.001) (Figure 3).[14]

Several TED manifestations can decrease quality of life, including ocular pain, proptosis, diplopia, and blurred vision.[15,16] A change in quality-of-life scores of ⩾6 points is considered clinically important when assessing a noninvasive therapy.[14] The overall Graves' orbitopathy quality-of-life score changed by a mean 17.28 points from baseline in the teprotumumab group compared with 1.80 points in the placebo group (P<.001) (Figure 4).[13,14] Vision and appearance subscale scores decreased by 15 and 19 points, respectively, at 24 weeks in the teprotumumab group compared with 3 points and <1 point, respectively, in the placebo group.[14]

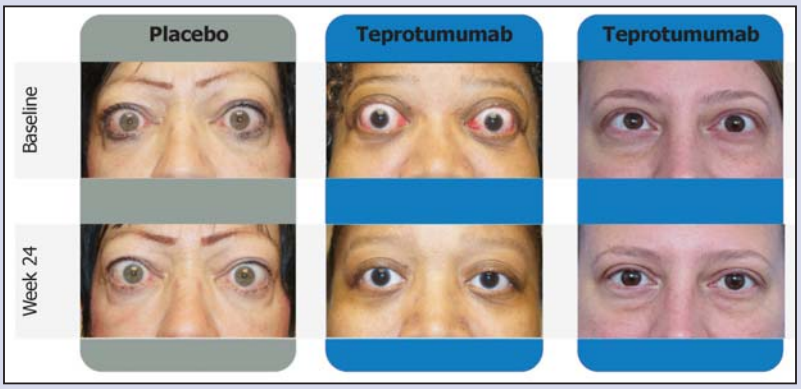
Figure 1. Thyroid Eye Disease: Targeted Treatments



Blue italics = Not approved by the US Food and Drug Administration for thyroid eye disease. Green font = approved by the US Food and Drug Administration. BAFF = B-cell–activating factor; CD = cluster of differentiation; GD-IgG = Graves' disease immunoglobulin G; IGF-1R = insulin-like growth factor-1 receptor; IL-6R = interleukin-6 receptor; TNF = tumor necrosis factor; TSH-R = thyroid-stimulating hormone receptor; TSI = thyroid-stimulating immunoglobulin.

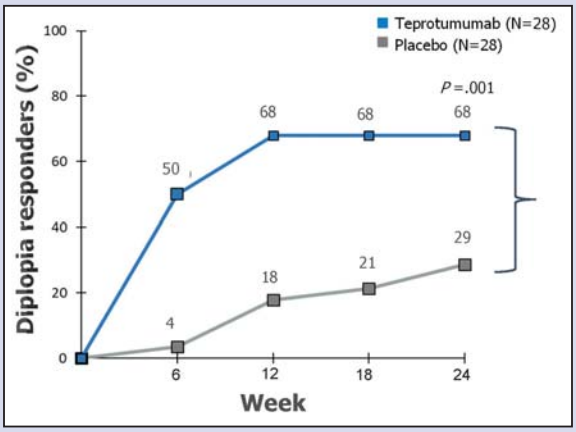
Source: Douglas RS.[1] Open Access.

Figure 2. Phase 2 Trial: Teprotumumab Proptosis Response



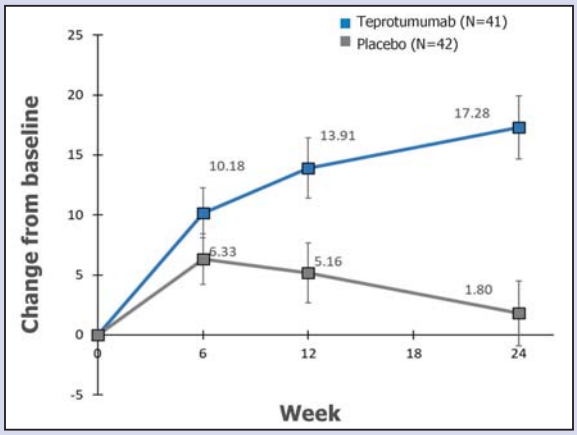
Source: Kahaly GJ, et al.[13] Reprinted with permission from the authors.

Figure 3. Diplopia Responders: ⩾1 Grade Improvement in Patients With Baseline Diplopia



Source: Douglas RS, et al.[14] *N Engl J Med.* 2020;382(4):341-352. Copyright 2020. Reprinted with permission from Massachusetts Medical Society.

Figure 4. Overall Improvements in Quality of Life in Patients Receiving Teprotumumab



Source: Douglas RS, et al.[14] *N Engl J Med.* 2020;382(4):341-352. Copyright 2020. Reprinted with permission from Massachusetts Medical Society.

OPTIC 72-Week Follow-up and OPTIC-X Extension Study

The overall response of placebo group patients who switched to teprotumumab during OPTIC-X closely paralleled the 24-week responses of teprotumumab group patients in the core OPTIC study, with 82.9% and 89.2% responders, respectively, at 24 weeks in both trials.[17] Similarly, at 24 weeks, 60.9% of OPTIC-X crossover patients with diplopia at baseline responded compared with 67.9% in the OPTIC trial teprotumumab group.[17] In the OPTIC-X and OPTIC trials, there was an overall response in 78.0% and 78.1% of patients, respectively.[17] These data showed that patients receiving placebo who switched to teprotumumab after 6 additional months of active TED responded similarly to those treated earlier in the active phase.[17]

Ten of 34 (29.4%) responders in the OPTIC trial had a flare during weeks 48 to 72, of whom 8 contributed data after enrolling in OPTIC-X.[16] Five (62.5%) patients had a proptosis response during their second teprotumumab treatment course.[17] These data suggested that patients who have a flare after a treatment response may respond to a second treatment course.

Pooled date from the 2 clinical trials indicated durability of teprotumumab benefits.[18] An integrated 72-week proptosis response was achieved by 67% of 52 patients with available data, and a diplopia response was achieved by 69% of 48 patients.[18] A post hoc composite outcome, defined as the proportion of patients with improvement in at least 1 eye from baseline without deterioration in any of the same measures in either eye in ⩾2 of the common TED manifestations, was achieved by 83% of 58 patients at week 72.[18]

Emerging data from 20 patients in the OPTIC trial who had a proptosis response revealed that 18 (90%) received no other therapy through week 120.[19] One patient received teprotumumab 16 months after the last dose in the OPTIC trial, and 1 had eyelid surgery 1 year after the last dose.[19]

Teprotumumab for Chronic TED

A retrospective study examined proptosis outcomes in 31 patients with chronic stable TED for >2 years who received ⩾3 teprotumumab infusions.[20] The mean duration of TED was 81 ± 56 months, and the mean number of infusions was 7 ± 2.[19] The mean proptosis reduction was 3.5 ± 0.4 mm, with a 90% CAS response.[20] Two-thirds of patients with diplopia at baseline had a clinically significant response, and 47% had complete resolution after teprotumumab treatment.[20] Strabismus and orbital soft tissue volumes were also significantly reduced in patients with chronic TED.[20]

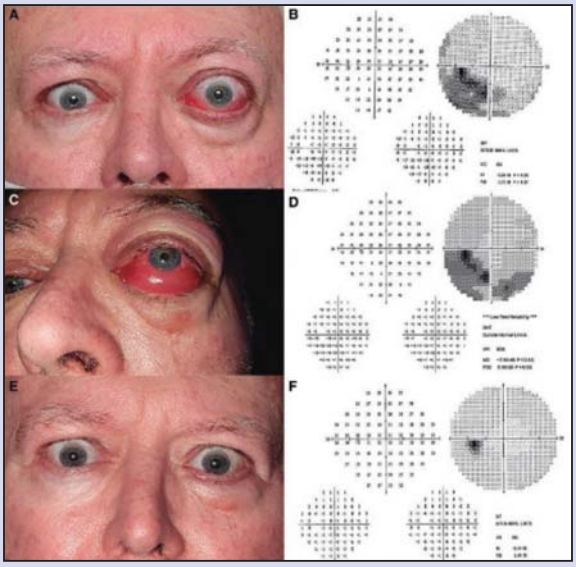
Other reports included positive outcomes in patients whose duration of TED ranged over >10 years and in patients with compressive optic neuropathy (Figure 5).[21,22] The emerging data support treatment effectiveness in a heterogeneous population that includes patients who were ineligible for enrollment in clinical trials, including those with stable, mildly severe, and vision-threatening TED.

Safety Profile

Pooled data from the 2 clinical trials revealed an increased incidence of several adverse events in patients treated with teprotumumab compared with placebo (Table).[11] A 3- to 10-fold increase was observed for muscle spasms, hyperglycemia, dysgeusia, dry skin, and hearing impairment.[11]

In addition to standard precautions for infusion reactions, patients with inflammatory bowel disease should

Figure 5. Early Clinical Experience With Teprotumumab



External photograph (**A**) and Humphrey visual field (**B**) of a 65-year-old man with thyroid eye disease and dysthyroid optic neuropathy at the time of presentation. After high-dose, pulsed methylprednisolone 1 g and optic canal decompression, the patient had increased chemosis (**C**) and worsening of the visual field (**D**). After 3 infusions of teprotumumab (**E**), the patient had a remarkable improvement of the visual field (**F**) as well as visual acuity and color vision.

Source: Diniz SB, et al.[21] Copyright 2021. Reprinted with permission from Wolters Kluwer Health, Inc.

be monitored for flares. Glucose levels should be checked, and treatment provided as warranted. Women of childbearing potential should use effective contraception before and during treatment and for 6 months after the last dose.

Summary

Teprotumumab has a unique disease-modifying activity that remodels the retro-orbital fat and muscles back toward their normal architecture. Patients who received a series of 8 intravenous infusions of teprotumumab over 21 weeks achieved a significant reduction in proptosis, diplopia, and CAS in phase 2 and 3 clinical trials and postmarket publications. Significant improvements were often achieved early in the treatment course, often after the second or third infusion. Treatment durability was supported in the OPTIC-X extension trial and in emerging postmarketing reports.

Table. Adverse Events Noted in Phase 2 and Phase 3 Teprotumumab Trials

Adverse event	Teprotumumab % (n=84)	Placebo % (n=86)
Muscle spasms	21 (25)	6 (7%)
Nausea	14 (17)	8 (9%)
Alopecia	11 (13)	7 (8)
Diarrhea	10 (12)	7 (8)
Fatigue[a]	10 (12)	6 (7)
Hyperglycemia[b]	8 (10)	1 (1)
Hearing impairment[c]	8 (10)	0
Dysgeusia	7 (8)	0
Headache	7 (8)	6 (7)
Dry skin	7 (8)	0

[a]Includes asthenia. [b]Includes an increase in blood glucose levels. [c]Includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis, and autophony.

Source: Data from package insert.[11]

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Physiological Functions of the Ear Regulated by Insulin-like Growth Factor-1

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As the use of targeted biologics becomes more widespread, unintended effects on the targeted pathway in other organ systems can manifest as treatment adverse effects and toxicity. The insulin-like growth factor-1 receptor (IGF-1R) is ubiquitous in normal tissues.[1] With its ligand, IGF-1, IGF-1R is an important modulator of inner ear development, and it also protects and maintains hearing.[2-4] A review of physiological functions of the ear that are regulated by IGF-1 can facilitate an understanding of the audiological adverse events that can accompany IGF-1–targeted therapies.

Inner Ear Structure and Physiology

The anatomy of the inner is shown in the Figure.[5,6] The cochlea is responsible for hearing, and the vestibular organs provide information regarding the movements and position of the head and body.[6,7] Sound is encoded in the cochlea, proceeding down its length as a traveling wave.[7] Highly specialized inner hair cells (IHCs) and outer hair cells (OHCs) in the organ of Corti transform mechanical sounds into electrochemical signals that are conveyed to the brain through the vestibulocochlear nerve (VIII cranial nerve).[6,7] The organ of Corti contains a single row of IHCs and 3 parallel rows of OHCs that sit on the basilar membrane.[8] Depolarization of IHCs results in glutamate release and neuron stimulation, whereas the OHCs amplify incoming sound and enhance frequency selectivity.[7] Connection to the brain from the organ of Corti is completed by 2 types of spiral ganglion neurons (SGNs).[7] Type I neurons innervate the IHCs and are most abundant, comprising 95% of the SGNs.[7] Each of the approximate 3500 IHCs are innervated by approximately 10 to 20 auditory nerve fibers.[9-11] Each type II neuron innervates several of the 12,000 OHCs.[12] Different sound frequencies are coded by different nerve fibers, so that the auditory nerve is tonotopically organized as each nerve fiber relays information related to a narrow frequency range.[12]

The stria vascularis is part of the lateral wall of the cochlear duct. It contains 3 types of cells: marginal cells, which maintain the K+ concentration; intermediate cells, which are pigment-containing cells scattered among capillaries; and basal cells, which separate the stria vascularis from the underlying spiral ligament and endocochlear potential.[5,13]

The cochlear amplifier is a positive feedback loop that amplifies the vibratory pattern, or traveling wave.[8,12] When sound-induced vibrations arrive in the cochlea, they cause the basilar membrane to move up and down, creating a shearing force along the organ of Corti that deflects the hair cell stereocilia.[8] A synchronous force is generated in the cochlea through OHC electromotility and active bundle movements to increase the vibrations. Without the contribution of OHCs, a pure tone produces a passive mechanism vibration pattern.[8,14] An active mechanism, with the electromotility contribution of the OHCs, produces a vibration pattern that is dramatically more sensitive and more sharply tuned.[14]

IGF-1 and Inner Ear Development

The pleiotropic effects of IGF-1 depend on its cellular context, where it can serve as a critical regulator of a variety of essential functions.[5,15] In a mouse model, robust deviations from normal concentrations of circulating IGF-1 throughout the lifespan were shown to cause substantial changes in several tissues.[15] Critical process modulation by IGF-1 includes gene expression in chondrocytes, protein synthesis in osteoblasts, cell cycle in enterocytes, and metabolism in adipocytes.[5] Several otic functions are also known to be modulated by IGF-1, and a deficiency in IGF-1 is associated with severe cochlear defects and sensorineural deafness.[5,16]

Development of the inner ear is supported by IGF-1, which promotes proliferation and survival of otic progenitor cells and supports neurogenesis, facilitating late differentiation and maturation of innervation patterns.[5,17,18] Mutations in IGF-1 and, to a lesser extent, IGF-1R are reported to cause hearing loss, which is usually profound and most common in children.[5,17,18]

In the mouse cochlea, IGF-1 has been detected in SGNs and the stria vascularis, where expression is modulated with age.[5] In human cohorts, age-related decreases in IGF-1 bioavailability have been associated with hearing impairment.[5]

The potential of IGF-1 as a therapeutic agent for inner ear diseases has undergone limited preclinical and clinical investigation.[3] Treatment with IGF-1 was shown to protect cochlear hair cells from apoptosis and induces proliferation of supporting cells in a cochlear explant culture model of aminoglycoside-induced

ototoxicity.[3] Intratympanic IGF-1 delivery had prophylactic and therapeutic effects on noise-induced hearing loss as well as ischemic cochlear damage in animal studies.[3] In one study, rats treated with a hydrogel impregnated with recombinant human IGF-1 that was placed on the round window membrane were protected from noise trauma.[19] The loss of OHCs was significantly lower than in control rats.[19] This treatment approach was subsequently used in a randomized trial that compared single middle ear applications of recombinant human IGF-1 hydrogels placed in the round window niche after tympanostomy (n=62) with 4 intratympanic dexamethasone injections (n=58) in patients with sudden deafness refractory to systemic corticosteroids.[20] After 8 weeks, more patients in the IGF-1 treatment group had improved hearing than those in the dexamethasone group (66.7% vs 53.6%; *P*=.109). Changes in pure-tone average hearing thresholds were superior in the IGF-1 group (*P*=.003), and tympanic membrane perforation did not persist in the IGF-1 group compared with 15.5% of patients in the dexamethasone group (*P*=.001).[20]

Hearing Assessment

Standard otolaryngological examination includes the medical history and clinical and laboratory assessments that supplement audiometric findings.[12] Hearing is commonly assessed using a combination of methods, including audiometry, otoacoustic emission measurement, and auditory brainstem response.[12]

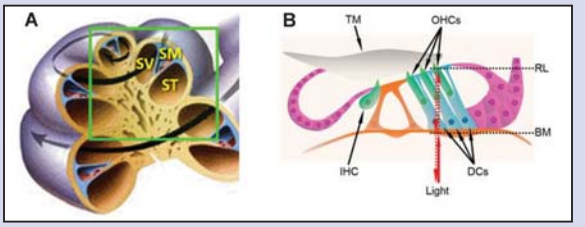
Audiometry

Pure-tone threshold audiometry measures hearing sensitivity separately in each ear, with single-frequency tones generated electronically and transduced through an earphone or bone conduction vibrator.[12] Pure-tone thresholds are assessed in air conduction and bone conduction modes, with air conduction reflecting the sensitivity of the entire auditory system and bone conduction reflecting inner ear function.[12] Speech recognition testing or word recognition is an important part of standard audiometry.

Otoacoustic Emissions

Assessing otoacoustic emissions are an OHC-dependent, objective measurement—that is, results are not based on a person's response.[12] In contrast to IHCs, which release neurotransmitters to initiate activity in the primary auditory nerve, OHCs amplify vibrations in specific regions of the cochlea by expanding and contracting in response to sound.[12] The OHCs are generally more vulnerable to disease and damage than the IHCs.[12] Therefore, if otoacoustic emissions are functioning normally, the OHCs are assumed to be functioning normally, and in most cases the IHCs will also be functional.

Figure. Mammalian Inner Ear



(**A**) Cochlea. (**B**) Organ of Corti. BM = basilar membrane; DCs = Deiters' cells; IHC = inner hair cell; OHCs = outer hair cells; RL = reticular lamina; SM = scala media; ST = scala tympani; SV = scala vestibule; TM = tectorial membrane.

Source: Lee HY, et al.[5] Open Access; Ren T, et al.[6] Open Access.

Devices that measure these emissions can be used in infants, children, and adults.

Auditory Brainstem Response

Neural activity evoked by sound can be recorded as auditory-evoked potentials collected from ⩾3 surface electrodes placed on the scalp and near the ear.[12] Computer-generated sounds presented to the person through earphones trigger synchronized neural activity recordings.[12] The auditory brainstem response reflects the earliest activity after each stimulation, which is generated in the auditory nerve and brainstem auditory pathway.[12] Electrode-recorded activity is averaged after presentation of hundreds of stimuli, allowing nanovolt-level changes in electrical potentials in the brainstem that respond to sound to be distinguished from other electrical activity in the brain and muscles of the head and neck.[12] The person being tested must recline and remain nearly motionless in a darkened, sound-proofed room during the test, which may take from 15 minutes to 2 hours.[12]

Summary

Insulin-like growth factor-1 has many essential roles in several body systems, including healthy hearing. Understanding the anatomy and physiology of the processes involved and potential pathogenicity associated with disruption of the IGF-1 pathway can be beneficial in the setting of intradisciplinary patient care.

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Auditory Symptoms and Patulous Eustachian Tube

Elias Michaelides, MD

Documenting auditory symptoms is an essential part of an otolaryngological examination.[1] Hearing loss may not be the primary symptom. Other symptoms, such as tinnitus, vertigo, otalgia, or otorrhea, may have prompted the visit. Several symptoms that are noted in all forms of eustachian tube dysfunction are nonspecific and common to several middle and inner ear pathologies,[2] such as ear fullness, popping, and pain.

Functions of the Eustachian Tube

The eustachian tube is a functional organ that connects the middle ear to the nasopharynx, supporting ventilation and the overall health of the middle ear (Figure).[2,3] Its primary function is to optimize sound transfer through the middle ear to the inner ear by facilitating gas transfer and pressure equalization between the middle ear and the nasopharynx.[2,3] The ciliated pseudostratified columnar epithelium of the eustachian tube clears secretions from the middle ear and prevents the passage of sound, pathogens, and reflux into the middle ear from the nasopharynx.[2,3] The oval-shaped lumen of the eustachian tube is collapsed at rest, and opens during swallowing, which equalizes changes in middle ear pressure.[2,3] With an estimated prevalence of 1% in adults, eustachian tube dysfunction is common in patients presenting to ear, nose, and throat clinics.[2,3]

The eustachian tube runs anteriorly, medially, and inferiorly from the middle ear to the nasopharynx.[2] The tensor veli palatini muscle, arising from the skull base and inserting in the soft palate, is the most important muscle in eustachian tube opening.[2] The levator veli palatini muscle is attached to the floor of the eustachian tube by loose connective tissue. The tube itself comprises anatomically distinct components of bone and cartilage covered by a mucous membrane.[2,4] The bony component represents the lateral one-third of the adult eustachian tube, or approximately 12 mm, and the cartilaginous portion comprises the remaining 44 mm.[2,4] The tubal isthmus is near the bone and cartilage junction.[5] A tubal valve comprises the mucosal and mobile fibrocartilaginous portion of the eustachian tube, extending approximately 5 mm proximally toward the nasopharynx.[5]

Patulous Eustachian Tube

Symptoms of patulous eustachian tube (PET), characterized by a pathologically patent pharyngeal eustachian tube orifice, include autophony (an unusual perception of one's own voice), respiratory synchronous tinnitus, and hearing physiological sounds at an increased level.[2,6,7] Nonspecific aural fullness and hearing loss are also common. Symptoms of PET may improve when the patient reclines. It is estimated to affect 0.3% to 6.6% of the population.[2,6,7]

Causes and Risk Factors

The cause of PET is unclear, although several theories have been proposed.[7] Loss of tissue in the cartilaginous eustachian tube, including that resulting from weight loss, pregnancy, use of high-dose oral contraceptives, and estrogen therapy, has been suggested.[7] Atrophy or scarring within the nasopharynx or involving the musculature associated with eustachian tube function, including adenoidectomy, radiation therapy, poliomyelitis, and other iatrogenic trauma, are also potential causes.[7]

Because the symptoms are often ameliorated by assuming a recumbent position, a magnetic resonance imaging study investigated soft tissues before and after neck compression in 5 healthy persons.[8] The volume of venous plexus between the medial pterygoid muscle and tensor veli platini muscle was increased after neck compression, and the lateral pterygoid muscle was enlarged.[8]

Ostmann's fat pad is located between the tensor veli palatini and the inferolateral border of the cartilaginous portion of the eustachian tube and may have a role in tube closure.[2,9] It is unclear whether loss of the fat pad contributes to the PET that develops after weight loss, because it naturally shrinks with aging without effect.[9]

Diagnosis and Management

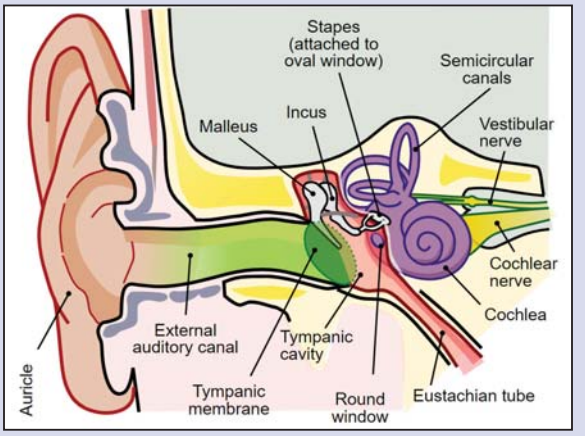
A recent systematic review summarized diagnostic (n=10) and management (n=49) practices for 59 qualifying PET studies.[10] Diagnostic options included 678-Hz acoustic intermittence testing, patient-reported outcome measures, sonotubometry acoustic click stimulus, nasal-noise–masking audiometry, sonotubometry, and computed tomography with the patient in a seated position.[10] Some methods, such as patient-reported outcome measures, were accurate only when healthy controls were used for comparison and had poor specificity when other otological disorders were included.[10]

Conservative treatment, including self-instillation of physiological saline, irrigation, use of mucus-thickening agents, and topical irritants, have been reported to provide some symptom relief.[10,11] Ten studies that performed tympanic membrane mass loading (using a clay-like, nontoxic substance) resolved symptoms in 29% to 79% of patients.[10,11] Several studies investigated eustachian tube occlusion with plugging, cautery, or injections, reporting complete resolution in 13% to 100% of cases across all approaches.[10,11] Submucosal graft implantation for augmentation or reconstruction has also been reported to restore normal convexity and provide lasting symptom relief.[12,13]

PET in Thyroid Eye Disease

Patulous eustachian tube related to treatment with teprotumumab has been reported.[14] The theory suggests an association between the reduced orbital fat and atrophy of Ostmann's fat pad in patients receiving this drug.[14] Cases of PET and autophony were observed in teprotumumab clinical trials, with a case of autophony and mild PET resolving during follow-up in the OPTIC trial.[15] One autophony case was not resolved by the time of the last visit in the OPTIC-X open-label extension study.[16] A real-world report listed autophony as the main symptom in 17 of 26 patients treated with ≥4 teprotumumab infusions.[14] In that series, 3 patients had PET with symptoms that had improved but not resolved 3 months after cessation of therapy.[14]

Figure. Eustachian Tube Relationship to Ear Anatomy



Source: Wikipedia.[3]

SUMMARY

Patulous eustachian tube is among the auditory complications that are reportedly associated with teprotumumab treatment. Many symptoms of this disorder are nonspecific. Accurate diagnosis and proper management require the involvement of specialists. Accordingly, clinicians managing patients with thyroid eye disease should be aware of the possibility of this adverse event and refer the patient to a specialist as warranted.

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Hearing Function Changes Reported With Teprotumumab

Raymond S. Douglas, MD, PhD

Observations of changes in hearing during teprotumumab therapy began with the clinical trials,[1] and postmarketing reports have documented these events in patients receiving infusions of the drug for thyroid eye disease (TED). A closer examination of how these hearing function symptoms were assessed and characterized is warranted to inform strategies for prevention and management of hearing impairment.

In pooled data from the pivotal clinical trials, hearing impairment was reported in 10% of 84 patients treated with teprotumumab, with no hearing adverse events reported for 86 placebo group patients.[2,3] Hearing impairment was reported as deafness, eustachian tube dysfunction, hyperacusis, hypoacusis, and autophony.[2,3] All events were classified as nonserious and did not progress. No patients discontinued treatment because of hearing impairment.[2,3] One patient whose hearing adverse event continued but improved was lost to follow-up.[2,3] Another patient had a history of noise-induced tinnitus, which continued at the time of the last poststudy follow-up report.[2,3] Patients were asked whether they had noticed any changes since they had been on the medication, as opposed to any hearing-specific queries.[2,3] Since the approval of teprotumumab, several case series of teprotumumab-associated hearing loss have been published.

Case Series: Subjective and Objective Hearing Loss

Audiograms that were done before, during, and after completion of teprotumumab treatment for 2 patients whose hearing symptoms developed during therapy supported the general observation that subjective hearing changes do not correlate with actual hearing loss in more than one-fourth of cases and exemplified the need for objective hearing tests in patients receiving teprotumumab therapy.[4]

Patient 1

A 74-year-old woman had a history of bilateral tinnitus and noted improvement after the second teprotumumab infusion. She also had mild-to-moderate sensorineural hearing loss before starting teprotumumab that progressed rapidly according to audiograms obtained during and after treatment. Her case suggests that teprotumumab may play a role in potentiating sensorineural hearing loss.

Patient 2

A 42-year-old man reported worsening intermittent tinnitus and low-pitched hearing loss after the third infusion at week 6.[4] However, an audiogram done at week 7 and on the day of therapy completion revealed no changes in hearing, average functional hearing thresholds, or word recognition.

Case Series: 22 Patients With New Subjective Otologic Symptoms

Data from a prospective study that included 27 patients at an average age of 56.3 years who received at least 4 teprotumumab infusions were presented at the October 2021 American Thyroid Association meeting.[5] These patients received an eye examination and assessment of adverse events, including otologic symptoms, at 0, 6, 12, and 24 weeks.[5] Potential risk factors for hearing loss were documented. Audiometry and patulous eustachian tube testing were done at baseline, during therapy, and if patients reported new hearing dysfunction.[5] Otolaryngologic evaluation was performed for objective changes.[5]

Twenty-two patients (81.5%) reported new-onset subjective otologic symptoms after starting teprotumumab treatment after a mean of 3.8 ± 1.8 infusions.[5] Clinical and demographic characteristics were similar in patients with and without otologic symptoms.[5] After an average follow-up of 8.3 months since the first infusion, 45% of patients had complete resolution, whereas symptoms persisted in 55% of patients.[5] Among 12 ears that had audiometry testing before and after treatment, 7 (58.3%) patients had sensorineural loss that met ototoxicity criteria. However, overall audiometric changes were modest.[5] One of 10 patients with pre- and posttreatment patulous eustachian tube testing developed abnormal results.[5]

The authors noted that the mechanism and reversibility of hearing loss during teprotumumab treatment should be studied further and that screening, monitoring, and prevention guidelines are needed.[5] They recommended baseline pure-tone and speech audiometry with patulous eustachian tube testing and repeated testing if new otologic symptoms develop.[5]

Case Series: 4 Cases of Significant Hearing Loss

A multi-institutional focus group in the United States reviewed 4 cases of significant hearing loss documented by formal audiologic testing by 3 clinicians who had treated

28 patients with teprotumumab.[6] The group endorsed prospective investigations of hearing loss in the setting of teprotumumab treatment. Until relevant research is done and data are available, the authors proposed adoption of a surveillance protocol that includes an audiogram and tympanometry before, during, and after the infusion course and if new symptoms of hearing dysfunction arise.

Summary

Continuing reports of auditory symptoms in patients being treated with teprotumumab support that this adverse event requires further study and monitoring.

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DISCUSSION

Auditory Testing, Monitoring, and Management for Teprotumumab

Kimberly Cockerham, MD, FACS; Raymond S. Douglas, MD, PhD; Marlan R. Hansen, MD, FACS; Andrea Lora Kossler, MD, FACS; Elias Michaelides, MD; Erin M. Shriver, MD, FACS

Developing a Consensus

The following is a summary of the Expert Consensus that was recorded on October 23, 2021. The recommendations are based on expert opinion and current published literature.

Dr. Michaelides: As an introduction, evidence has been presented that correlates hearing problems with teprotumumab therapy. Background information on the theoretical physiological effect on the ear has also been presented. With the potential risk for hearing loss, some form of auditory monitoring is warranted for these patients. Expert opinions will be considered as part of developing consensus recommendations for audiology testing in patients receiving teprotumumab therapy for thyroid eye disease (TED).

Dr. Shriver: Thank you for reviewing our 2 case reports, which we believe make 2 important points: (1) how hearing is perceived by the patient may be very different from the objective audiogram findings, and (2) baseline auditory testing is important for these patients.

Our first patient, the 74-year-old woman who experienced sensorineural hearing loss on treatment that was beyond her baseline level, did not report any hearing problems. Instead, she was pleased with her reduction in tinnitus as well as the improvement in her TED symptoms. Six-month data that became available after her case was published revealed that her hearing loss has remained stable.

Our second patient, the 42-year-old man who reported a decline in his hearing after starting teprotumumab infusions, had auditory testing during and at the end of teprotumumab treatment that showed no difference from baseline.

Of note, I have a close working relationship with the university's audiometry team. They are also conveniently located for easy patient referral. My patients get an audiogram at baseline and at the end of treatment, with mid-treatment testing decisions made on a case-by-case basis, depending on the patient's symptoms.

More data are necessary. We need further details about these cases and increased efforts to determine an accurate incidence of objective hearing impairment.

Dr. Kossler: We just submitted a manuscript with expanded information on the 22 of the 27 patients who noted otologic symptoms after teprotumumab therapy that we reported at the American

Thyroid Association meeting. I agree that patients should have their hearing monitored. They should also be questioned proactively about their hearing before starting therapy, be offered a baseline hearing test, and have their hearing monitored during treatment. Our study was not able to identify risk factors for hearing loss in the symptomatic versus nonsymptomatic group, probably because of the low number of patients studied. However, all patients who developed objective hearing loss on audiograms had a baseline history of hearing loss. We need studies to determine the incidence, severity, significance, and reversibility of hearing impairment in patients receiving teprotumumab.

Dr. Hansen: As a neurotologist, I agree that symptoms are not always valid indicators of actual physiological function. This speaks to the importance of baseline testing, to distinguish cases like the patient who did not report hearing loss when significant loss has occurred with the patients who report new-onset hearing loss when objective testing shows no difference from baseline. Hearing loss is underdocumented in the general population and is disregarded by most people. Asking patients about their hearing status *before* treatment is an important complement to objective baseline testing.

Dr. Cockerham: My understanding of the risks and their management has evolved over time. I now plan to ask patients about hearing symptoms before starting therapy and offer audiometry. Symptoms reported after starting treatment are difficult to interpret without a baseline comparison. Adequate follow-up, testing, and documentation are necessary. Most of the middle ear symptoms and tinnitus resolved during 1-year of follow-up. However, only half of hearing symptoms resolved.

Dr. Michaelides: We all agree that, at a minimum, patients starting teprotumumab therapy should be offered and strongly encouraged to have a baseline hearing test. *The next question is, should patients with a baseline audiogram be tested regularly during treatment or only if symptoms develop?*

Dr. Hansen: The evidence on sensorineural hearing loss support making assessments during treatment. Patients with baseline hearing problems may be more vulnerable to exacerbation of these problems during treatment and may progress to a point where rehabilitation will be difficult. However, we do not yet have evidence proving or disproving this theory, which supports the importance of closely monitoring these patients.

By having baseline hearing assessments, patients will be alerted to recognize hearing impairment that may develop during therapy. Although I believe it would be useful to perform routine in-therapy testing for these patients, it may not be necessary and could be impractical in some settings.

It is important to have a solid relationship with audiologists. Hearing assessment is simple, and audiologists are familiar with drug-toxicity hearing-assessment protocols that could easily be duplicated in this setting.

Dr. Kossler: At our institution, 1 of 5 patients with worsening sensorineural hearing loss during treatment was asymptomatic, which prompted our neurotologist to recommend also testing asymptomatic patients. However, testing these patients during treatment may not be feasible. In addition, patients may resist testing if they believe that hearing loss could result in treatment discontinuation.

Dr. Michaelides: We also must consider what the response should be if hearing loss is detected during treatment. Balancing risk versus benefit should include input from the patients, letting them decide whether they want to continue therapy with the knowledge that there could be further hearing changes.

Dr. Douglas: This is a difficult conversation to have until we know the risks for long-term hearing loss. We need more data on reversibility and its timeframe. This can also be related to the specific event the patient experiences; for example, was it a true audiogram change or does the patient have a patulous eustachian tube (PET)?

Discussing risk versus benefit with patients in the current setting without adequate data can be perplexing. How do you explain why we are monitoring? How do you define the risk patients are facing? What is the long-term risk? If a patient has a decline in audiometry results during treatment yet remains asymptomatic, should treatment be discontinued?

Dr. Hansen: Because we don't have answers to these questions, I believe that at this stage these patients need to be monitored. Hearing loss is not given much attention until it becomes critical. At that point, it limits social functioning and employability. It is also the number one modifiable risk factor for cognitive decline. Patients may not need to stop therapy if the treatment's benefits outweigh its risks. However, patients should be made aware of what is happening to their hearing.

Dr. Cockerham: As a neuro-ophthalmologist, I can monitor the status of visual fields and color vision using a mobile app. *Is anything similar available for testing hearing?*

Dr. Hansen: Tests are available and under development. However, I'm not sure how reliable they are for longitudinal assessment of this population.

Dr. Douglas: *Are any reliable tests available that could be done in the ophthalmologist's office?* Some patients will not agree to go to another specialist but will allow in-office testing.

Dr. Michaelides: Some apps have been validated for detecting and monitoring hearing loss. They require calibrated

headphones and a quiet location. However, for ototoxicity, we often see early changes at the highest frequencies. These are best tested in a sound booth, instead of an open room with headphones. Some audiometers monitor higher frequencies, which may detect the earliest changes, before a standard audiogram is done.

Dr. Kossler: High-frequency testing has been used for chemotherapy patients as an early indicator of hearing loss. We are starting a teprotumumab study with our neurotology colleagues, where we check the high-frequency audiogram and test for PET at baseline, 12 weeks, and 24 weeks. A comparison group will include patients with Graves' disease, because these patients in general have risk factors for hearing loss, such as age, history of thyroid dysfunction, and use of antithyroid drugs.

Dr. Michaelides: *What percentage of patients with thyroid imbalances have hearing changes? Are they permanent?*

Dr. Hansen: Severe thyroid disease is a recognized cause of hearing loss. However, there are many contributing confounding factors that preclude defining a precise risk. In most cases, hearing loss is irreversible. However, this may be related to underlying risk factors.

Dr. Michaelides: This reinforces the concept that these patients need baseline hearing testing.

Dr. Hansen: Research, such as the study Dr Kossler is doing, is essential to understand hearing loss in these patients. However, what is currently practical in the real world also needs to be determined. On-site testing instead of audiology referral has limitations; however, it is preferable to doing nothing.

Dr. Douglas: In my office, patients reporting hearing adverse events usually report short-term symptoms, perhaps lasting only a minute or two. *I am not convinced that a treatment decision should be based on an intermittent finding that is without severe manifestations. Therefore, what should be done practically for PET testing?*

Dr. Michaelides: Patulous eustachian tube is a mechanical issue that can be very bothersome to some patients. Even if symptoms are intermittent, they may be amenable to very simple medical therapy, such as topical drops. Therefore, I believe that if patients develop PET symptoms, it is worth documenting and offering conservative treatments, which do not require testing.

Dr. Douglas: Patients who start on teprotumumab usually notice PET symptoms after the third dose, and they are usually new symptoms.

Dr. Hansen: When we treat PET, we are treating the symptoms. We do not treat it because it has long-term consequences on the physiological function of the ear. Testing symptomatic patients can be helpful for a diagnosis. Patients with high-frequency hearing loss will most likely not have autophony, but they will have a sense of ear fullness or pressure. Patients with autophony or respiratory-driven symptoms are more likely to have PET.

Dr. Michaelides: I agree that there is no need to do pretreatment baseline testing for PET, except as part of a research protocol to see if it develops. If the patient develops symptoms, testing is reasonable.

Dr. Kossler: I also agree. Symptoms of autophony and middle ear symptoms were prevalent in my patients. However, most cases resolved after extended follow-up. From endoscopy studies at baseline and during treatment, we postulated that PET following teprotumumab treatment was due to a reduction in the fat pad around the eustachian tube.

I mention that PET is a possible side effect during the discussion of other possible adverse events. I am confident telling them that these symptoms resolve in most patients. We work with our ear, nose, and throat colleagues to provide patients with symptomatic relief with sprays and drops.

Dr. Cockerham: *What is the frequency of hearing loss persisting beyond 6 months?*

Dr. Douglas: Nine months elapsed before subjective symptoms resolved for 2 of my patients. Although there was no objective testing, both patients were musicians. Subjective hearing symptoms could have a major impact on their work performance, so hearing impairment opinions were sufficient for these cases.

Dr. Kossler: About 50% of our patients with teprotumumab-related hearing loss continued to have subjective symptoms 6 months after the end of treatment. Follow-up audiograms also showed that some patients had persistent worsening of their hearing. For some patients, pure-tone audiometry did not change considerably, but word recognition scores decreased by almost half, and some patients needed to start wearing hearing aids. Longer follow-up is warranted, considering the 20-day half-life of teprotumumab.

Dr. Hansen: Speech discrimination requires good neural innervation, while simply detecting a sound does not require as much nerve involvement. A considerable component of IGF-1 activity in the ear is related to innervation. Maintaining pure-tone thresholds but losing discrimination scores is recognized in audiology as representing a neural phenotype, with lost innervation to the hair cells. Word recognition can be especially compromised for these patients in situations with considerable background noise.

Dr. Cockerham: *Is there a role for prophylactic IGF-1 ear drops for these patients?*

Dr. Hansen: Drops would not reach the inner ear without a tube. The only way the inner ear can be reached by a topically

DISCUSSION

Figure. Teprotumumab Infusion Protocol: Recommended Audiology Testing Schedule[a]

	Baseline[b]	Midpoint after 4 infusions (at 12 weeks)	After completion (at 24 weeks)	6 months after treatment
Audiology Testing	☑	✓ If abnormal, repeat	✓ If abnormal, repeat; *consider* audiogram, even if asymptomatic	✓ If abnormal, *consider* repeat audiogram

[a]If a patient develops symptoms of autophony or other patulous eustachian tube symptoms, *consider* patulous eustachian tube testing. [b]Baseline audiology is *recommended* or *strongly recommended* based on baseline hearing symptoms, history of abnormal audiogram, or wearing hearing aids.

applied drop without an ear tube is through systemic absorption and delivery in the bloodstream. A study of IGF-1 gel delivered on the round window membrane reported positive outcomes for idiopathic sudden sensorineural hearing loss. However, additional research is necessary. In addition, if the drug is blocking IGF-1 at the receptor level, whether exogenous IGF-1 could overcome that inhibition is unknown.

Dr. Michaelides: *What is the best approach for counseling and monitoring patients?*

Dr. Shriver: I often give my patients teprotumumab publications, including those that mention hearing loss with teprotumumab, and we have an informed discussion about it. Also, all my patients have a baseline audiogram. I've learned that I can't always predict who will be sensitive to hearing loss problems. Several patients with baseline hearing loss believed that it was impacting their lives more than TED, and they chose not to proceed with the therapy. Others who had mild hearing loss at baseline believed that TED was affecting them more than hearing loss, and they chose to proceed with treatment. It is an individual decision.

With regard to monitoring during treatment, standardized protocols are needed to determine how closely these patients should be monitored. Our department is currently following a protocol that includes baseline testing and repeated hearing assessment at the end of treatment, with interim testing in response to symptom development. I usually tell patients we will check their hearing again between the second and third dose, or at the onset of symptoms, whichever is sooner. Having an audiologist on the team is important for testing and interpretation as well as for the valuable advice the specialists can provide.

I would like to take this opportunity to stress the importance of partnering with an audiologist. Reading and interpreting audiograms can be challenging. It is important to have a go-to person who can be asked about the meaning of the results. For example, is a 10-Hz hearing loss at baseline meaningful? Proper interpretation of hearing assessment results can be especially important when there is a change in the audiogram, because a nonspecialist may have difficulty determining the significance of the change. Having an audiologist as a regular part of the team is needed throughout patient selection, treatment, and monitoring.

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1. Teprotumumab. Package insert. Horizon Therapeutics USA, Inc; 2021.

Consensus Recommendations on Audiology Testing for Teprotumumab-Prescribing Physicians

Teprotumumab is an insulin-like growth factor-1–receptor inhibitor indicated for thyroid eye disease.[1] It is infused intra-venously starting with 10 mg/kg, followed by 20 mg/kg every 3 weeks for 7 additional infusions (8 total infusions), with the last infusion 21 weeks from baseline.[1] The following recommendations were developed by the expert panel members in response to the hearing impairment that was observed in teprotumumab clinical trials and described in postmarketing reports.

1. Discuss with the patient the risks and benefits of teprotumumab, including the potential risk for hearing adverse events.
2. Document pretreatment symptoms and consider audiology testing.
   a. Patients with hearing symptoms at baseline or with a history of abnormal audiogram or wearing hearing aids.
      ✓ Pretreatment audiology testing *strongly recommended*
   b. Patients with no baseline hearing symptoms.
      ✓ Pretreatment audiology testing *recommended*
   c. If abnormal or symptoms develop, repeat audiogram at 12 and 24 weeks.
   d. Consider audiogram at week 24, even if asymptomatic.
3. Acquire informed consent regarding possible side effects. Consider written and signed consent document.
4. Identify which provider involved in patient care will monitor for side effects, including hearing.

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CME Posttest

1. After receiving conventional therapies for TED, ___% of patients believed that their appearance had not returned to baseline.

A. 41
B. 51
C. 61
D. 71

2. Which statement regarding the use of steroids in patients with TED is *false*?

A. The efficacy of glucocorticoids in TED ranges between 50% and 88%.
B. Intravenous administration is more effective than oral dosing for moderate-to-severe disease.
C. Intravenous glucocorticoids are approximately 70% to 80% effective in reducing inflammatory signs in TED, compared with an approximate 60% short-term benefit with oral prednisone.
D. Steroids are extremely effective for treating patients with strabismus and eyelid retraction.

3. In a phase 2 clinical trial, significant differences in response between the teprotumumab and placebo groups were observed, with ____% of patients responding to teprotumumab compared with 20% responding to placebo at week 24.

A. 79
B. 69
C. 59
D. 49

4. The primary outcome in the OPTIC trial was met, with ___% of teprotumumab and 10% of placebo group achieving a proptosis response at week 24.

A. 83
B. 73
C. 63
D. 53

5. Which statement regarding the OPTIC trials is *false*?

A. The overall response of placebo group patients who switched to teprotumumab during OPTIC-X closely paralleled the 24-week responses of teprotumumab group patients in the core OPTIC study.
B. At 24 weeks, 60.9% of OPTIC-X crossover patients with diplopia at baseline responded compared with 67.9% in the OPTIC trial teprotumumab group.
C. The overall response rates in the 2 trials were similar.
D. Patients receiving placebo who switched to teprotumumab after 6 additional months of active TED did not respond as well as those treated earlier in the active phase.

6. Which statement regarding the side effects of teprotumumab based on pooled data from clinical trials is *false*?

A. A minimal increase in muscle spasms, hyperglycemia, dysgeusia, dry skin, and hearing impairment was observed.
B. Patients with inflammatory bowel disease should be monitored for flares.
C. Glucose levels should be checked, and treatment provided as warranted.
D. Women of childbearing potential should use effective contraception before and during treatment and for 6 months after the last teprotumumab dose.

7. Which statement regarding physiological functions of the ear that are regulated by IGF-1 is *false*?

A. Critical process modulation by IGF-1 includes gene expression in chondrocytes, protein synthesis in osteoblasts, cell cycle in enterocytes, and metabolism in adipocytes.
B. Mutations in IGF-1 and IGF-1R are not associated with hearing loss.
C. A deficiency in IGF-1 is associated with severe cochlear defects and sensorineural deafness.
D. IGF-1 promotes proliferation and survival of otic progenitor cells and supports neurogenesis, facilitating late differentiation and maturation of innervation patterns.

8. Which statement regarding auditory brainstem responses is *true*?

A. They reflect the earliest activity after each stimulation, which is generated in the auditory nerve and brainstem auditory pathway.
B. The person being tested can be sitting or standing.
C. The test must be performed in a well-lit, sound-proofed room.
D. The test takes less than 10 minutes to perform.

9. Which statement regarding PET is *true*?

A. It is related to treatment with teprotumumab.
B. Autophony and mild PET did not resolve during follow-up in the OPTIC trial.
C. A real-world report listed autophony as the main symptom in 24 of 26 patients treated with $\geqslant$2 teprotumumab infusions.
D. Several studies investigated eustachian tube occlusion with plugging, cautery, or injections, reporting complete resolution in $<$10% of cases across all approaches.

10. Which statement regarding hearing impairment related to teprotumumab is *false*?

A. In pooled data from pivotal clinical trials, hearing impairment was reported in 10% of 84 patients treated with teprotumumab, with no hearing adverse events reported for 86 placebo group patients.
B. Some patients discontinued treatment because of hearing impairment.
C. Hearing impairment was reported as deafness, eustachian tube dysfunction, hyperacusis, hypoacusis, and autophony.
D. All events were classified as nonserious and did not progress.

Insulin-like Growth Factor-1–Receptor Inhibitors in Thyroid Eye Disease:

Developing a Consensus to Address and Manage Hearing-related Impairment

CME Registration Form

Answer Sheet

1	2	3	4	5	6	7	8	9	10

***Time spent on this activity: Hours ☐ Minutes ☐**
(Includes reading articles and completing the learning assessment and evaluation.)
This information MUST be completed for the quiz to be scored.

THE MONOGRAPH AND TEST EXPIRE JANUARY 1, 2023

PRINT OR TYPE

Last Name First Name Degree

Mailing Address

City State Zip Code

Date of Birth (used for tracking and reporting credits ONLY)

Phone Number FAX Number

*Email Address

Activity Evaluation

Your evaluation of this activity is extremely important, as it allows us to plan for future educational programs. Please take a moment to answer the following questions:

1. **How many years have you been treating patients with thyroid eye disease?**
   ❑ 1 to 9 ❑ 10 to 20 ❑ 21 to 30 ❑ More than 30 ❑ N/A
2. **Approximately how many patients with thyroid eye disease do you see per month?**
   ❑ 1 to 9 ❑ 10 to 30 ❑ 31 to 50 ❑ More than 50 ❑ N/A
3. **How likely are you to recommend this activity to a colleague (1 = Not at all likely; 10 = Extremely likely).**
   ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10
4. **Do you believe this program:**

	Y=Yes	N=No	4=N/A
Achieved its identified educational goals and learning objectives?	Y	N	4
Covered content that is relevant and will be useful to your practice?	Y	N	4
Will increase your competence in managing these patients?	Y	N	4
Used teaching methods and educational formats that were effective for learning?	Y	N	4
Provided you with resources to use in your practice and/or with your patients?	Y	N	4
Addressed and provided strategies for overcoming barriers to optimal patient care?	Y	N	4
*Was presented objectively and was free of commercial bias?	Y	N	4

***If you indicated that the activity <u>was not</u> free of commercial bias, please provide additional comments here:**

	Y=Yes	N=No
5. **Future activities concerning this subject matter are necessary.**	Y	N

6. **Approximately what percentage of the activity's content was NEW to you?**
   ❑ 0% ❑ 25% ❑ 50% ❑ 75% ❑ 100%
7. **How often do you plan to incorporate best practices that can improve the testing and monitoring of patients prescribed insulin-like growth factor 1 receptor (IGF-1R) inhibitor therapy, to proactively address potential safety issues?**
   ❑ Always ❑ Frequently ❑ Sometimes ❑ Rarely ❑ Never ❑ N/A
8. **How often do you plan to offer auditory testing at baseline with teprotumumab?**
   ❑ Always ❑ Frequently ❑ Sometimes ❑ Rarely ❑ Never ❑ N/A
9. **How often do you currently use multidisciplinary management (audiologist and/or otolaryngologist) to obtain a baseline hearing assessment when you prescribe teprotumumab?**
   ❑ Always ❑ Frequently ❑ Sometimes ❑ Rarely ❑ Never ❑ N/A
10. **I plan to make the following changes to my practice:**

	Y=Yes	N=No	3=Already Do	4=N/A
Apply the efficacy and safety of conventional and new therapies for TED when selecting treatment.	Y	N	3	4
Recognize physiological mechanisms that may lend to adverse events in patients receiving IGF-1R inhibitor therapy for the treatment of TED.	Y	N	3	4
Incorporate practices and procedures that can improve the multidisciplinary management of hearing-related adverse effects relating to IGF-1R inhibitor therapy for TED.	Y	N	3	4
Other (please provide below):	Y	N	3	4

If you do not intend to make changes to your practice, please indicate why:

11. **The following are barriers I face most often in my current practice that impact my ability to provide optimal care:**

	Y=Yes	N=No	4=N/A
Lack of time to stay up-to-date on the latest evidence-based care		Y N	4
Implementing value-based metrics/quality measures		Y N	4
Insurance/financial restrictions		Y N	4
Lack of patient adherence/compliance to therapy		Y N	4

12. **How confident are you in your ability to incorporate best practices that can improve the testing and monitoring of patients prescribed IGF-1R inhibitor therapy, to proactively address potential safety issues?**
    ❑ Extremely Confident
    ❑ Very Confident
    ❑ Somewhat Confident
    ❑ Not at All Confident
    ❑ Does Not Apply
13. **What educational topics would be of value to you for future CME activities? Please be specific.**
14. **Please indicate your degree:**
    ❑ MD/DO ❑ RN/BSN/MSN ❑ Industry
    ❑ PharmD/RPh ❑ PhD ❑ Other:_____
    ❑ NP ❑ OD
    ❑ PA ❑ Other Health Care
15. **Please indicate your primary specialty:**
    ❑ Ophthalmology ❑ Neurotology
    ❑ Endocrinology: Thyroid ❑ Oculoplastic surgeon
    ❑ General Endocrinology ❑ Pharmacy
    ❑ Internal Medicine ❑ Nursing
    ❑ Family Medicine ❑ Industry
    ❑ Otolaryngology ❑ Other:_____
16. **Please indicate your primary professional/practice setting:**
    ❑ Office/Private Practice ❑ Hospital
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    ❑ Administration ❑ Other:_____

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