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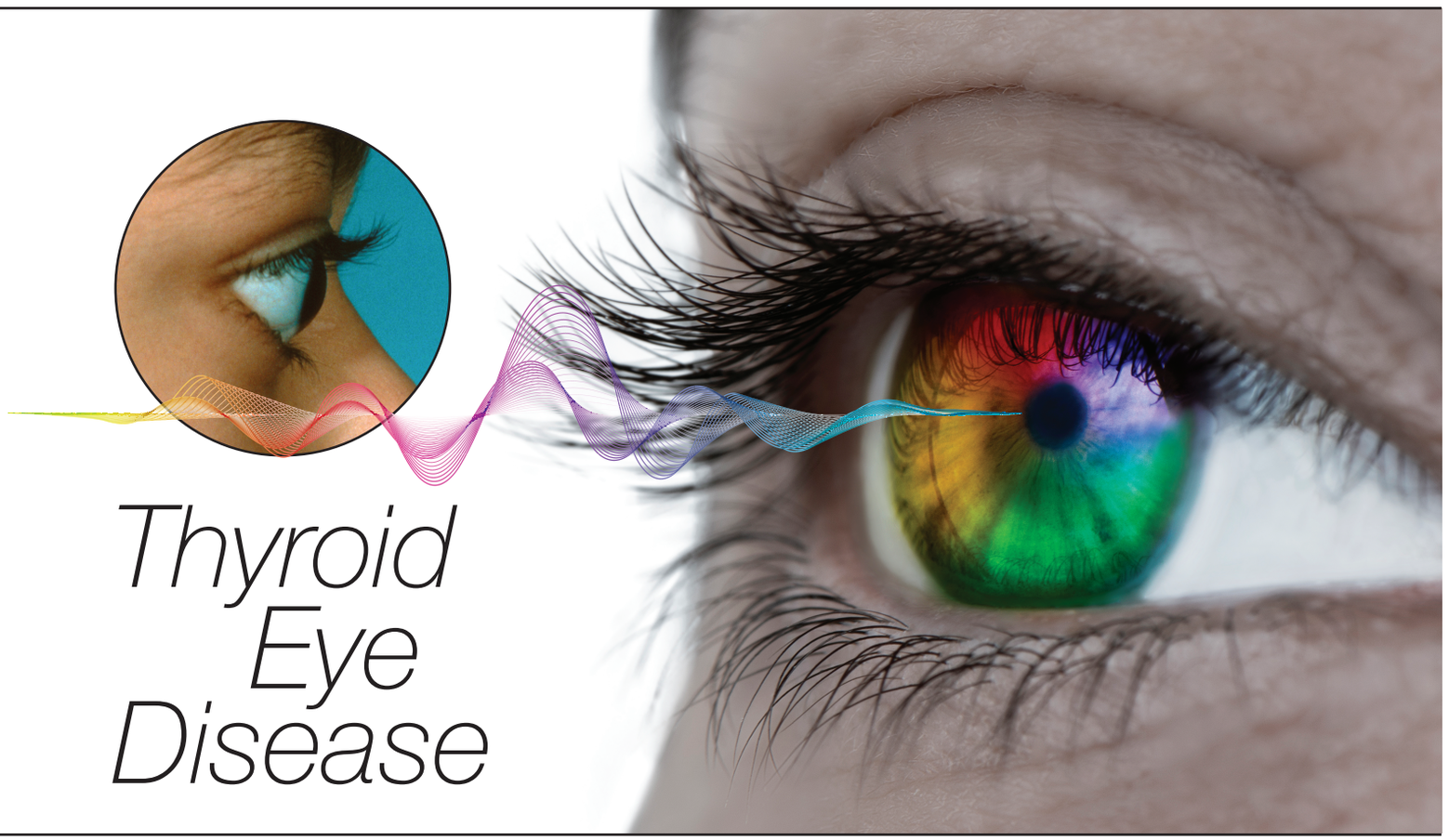

Thyroid Eye Disease

Management Across the Spectrum of Severity and Chronicity

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Faculty

Wendy W. Lee, MD, MS (Chair)
Roger A. Dailey, MD, FACS
Andrew R. Harrison, MD
Sonalika Khachikian, MD

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Activity Description and Purpose

This educational activity provides clinicians who currently treat patients with thyroid eye disease (TED) or have an interest in managing patients with TED with expert advice on diagnosis, current treatment approaches, and comanagement across the multidisciplinary team. A focused discussion on comanagement among eye care professionals and an endocrinologist provides the learner with practical strategies to optimize patient care. The desired results of this activity are to increase appropriate treatment of chronic TED in practice and to foster competent interdisciplinary collaboration to ensure the best possible outcomes for patients with chronic TED.

Target Audience

This educational activity is intended for ophthalmologists.

Learning Objectives

After completing this activity, participants will be better able to:

- Identify patients with thyroid eye disease who would be optimal candidates for treatment with biologic therapies
- Apply evidence to manage thyroid eye disease in patients with chronic disease

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Faculty

Roger A. Dailey, MD, is a consultant for Horizon Therapeutics plc and Viridian Therapeutics, Inc.

Andrew R. Harrison, MD, is a consultant for Horizon Therapeutics plc and RVL Pharmaceuticals, Inc; and is on the speakers bureau for Horizon Therapeutics plc and RVL Pharmaceuticals, Inc.

Sonalika Khachikian, MD, is a consultant for Horizon Therapeutics plc; and is on the advisory board of Novo Nordisk A/S*.

Wendy W. Lee, MD, MS, is a consultant for Allergan, Horizon Therapeutics plc, Novabay Pharmaceuticals, Inc, Revance Therapeutics, Inc, RVL Pharmaceuticals, Inc, and Tarsus Pharmaceuticals, Inc; and is a contracted researcher for Viridian Therapeutics, Inc.

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Faculty

Wendy W. Lee, MD, MS (Chair)
Professor of Clinical Ophthalmology and Dermatology
Oculofacial Plastic & Reconstructive Surgery, Orbit, and Oncology
Bascom Palmer Eye Institute
University of Miami Miller School of Medicine
Miami, Florida

Roger A. Dailey, MD, FACS
Professor of Ophthalmology
Lester T. Jones Chair of Oculoplastic Surgery
Casey Eye Institute
Oregon Health & Science University
Portland, Oregon

Andrew R. Harrison, MD
Professor
Department of Ophthalmology and Visual Neurosciences
Professor
Department of Otolaryngology, Head and Neck Surgery
Director, Ophthalmic Plastic and Reconstructive Surgery Service
Co-Director, Center for Thyroid Eye Disease
University of Minnesota
Minneapolis, Minnesota

Sonalika Khachikian, MD
Endocrinologist
Monument Health Rapid City Clinic
Rapid City, South Dakota

Introduction

Thyroid eye disease (TED) is the most common extrathyroid complication in the approximately 4 million Americans with systemic hyperthyroidism.[1] Manifestations of TED can range from the cosmetic—ocular injection, proptosis, and strabismus—to sight-threatening issues, such as compressive optic neuropathy. Historically, the management of TED has been primarily directed at controlling the underlying systemic hyperthyroidism, with TED-specific treatments being largely supportive. In 2020, the US Food and Drug Administration approved teprotumumab, which is currently the only agent approved to treat TED.[2] Teprotumumab is a monoclonal antibody and is considered to be disease modifying. This educational activity will review the pathophysiology and clinical management of TED.

Best Practices for Identifying Candidates for Treatment of Chronic Thyroid Eye Disease

Wendy W. Lee, MD, MS

TED, also called Graves orbitopathy, is the most common extrathyroid manifestation of hyperthyroidism.[3] Although some patients who develop TED are euthyroid, most patients who develop TED have preexisting thyroid disease. In other cases, inflammation of the orbit and associated symptoms may occur before hyperthyroidism. Regardless of the order in which TED or hyperthyroidism appears, 80% of patients will develop 1 condition within 18 months of the other; some cases of TED and hyperthyroidism will not co-occur until years or decades later.[3]

The pathophysiology of TED is driven by autoantibody activation of IGF-1 receptor (IGF-1R) and thyroid-stimulating hormone (TSH) receptor (TSHR). When activated, IGF-1R and TSHR stimulate the release of inflammatory cytokines and the production of hyaluronan and other glycosaminoglycans, which combine with collagen fibrils to form a matrix that jointly expands orbital tissues, including both fat and muscle cells **(Figure 1)**,[3,4] resulting in an overcrowded orbit with proptosis, apical crowding, and optic nerve damage.[4] These changes represent the first stage of TED, characterized by acute

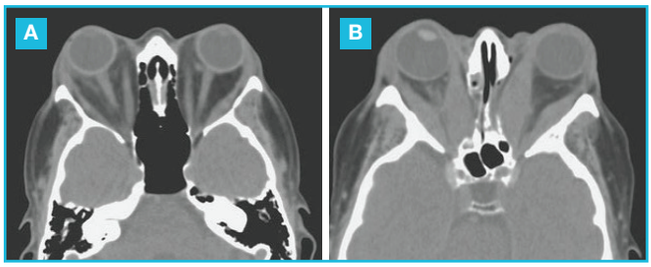

Figure 1. Enlargement of fat (A) and muscle (B) in thyroid eye disease[4]

From *The New England Journal of Medicine*, Bahn RS, Graves' ophthalmopathy, 362, 726-738. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

inflammation, deposition of the ground substance matrix, and remodeling of orbital tissues that typically occur within the first 1 to 3 years of the disease.[5] Over time, fibrosis of myofibroblasts leads to irreversible scarring and restrictive myopathy in the chronic fibrotic second stage of the disease.[4,5]

Risk factors for the development of TED include a positive family history of thyroid disease, smoking, life stressors, and poorly controlled hypothyroidism after radioactive iodine therapy.[6] Factors that are predictive of more severe disease include male sex, increasing age, smoking, and the rapid onset of orbitopathy.[7]

The clinical presentation of TED is characterized by a typical wide-eyed stare associated with eyelid retraction **(Figure 2)**. Retraction of both upper and lower lids results in scleral show both superiorly and inferiorly. Eyelid retraction is the most sensitive of the clinical signs of TED and is present in more than 90% of cases.[8] Additionally, proptosis is present in 60% of patients, extraocular muscle restriction in 40%, pain in 30%, superior limbic keratoconjunctivitis in less than 4%, tearing and photophobia in 15% to 20%, blurred vision in 7.5%, and optic nerve dysfunction in 5%.

The diagnosis of TED is straightforward when classic clinical signs are present in a patient with hyperthyroidism. The diagnosis can be more challenging if the ocular features are mild or inconclusive and/or if the patient has no objective laboratory evidence of thyroid dysfunction.[6]

The clinical findings associated with TED can be seen in patients with other ocular conditions. Although TED is the most common cause of both bilateral and unilateral proptosis, the differential diagnosis of proptosis includes tumors and carotid-cavernous fistulae, which will often be accompanied by signs of inflammation, such as scleral injection, tearing, and discomfort. Eyelid retraction can be a compensatory mechanism in the setting of lid ptosis. Extraocular muscle impairment with diplopia may arise owing to a cranial nerve palsy. Ocular surface disease with blurred vision, surface staining, tearing, and photophobia can also mimic some aspects of TED.

Patients presenting with suspected TED who do not have established hyperthyroidism should be assessed. Laboratory testing should include TSH, free thyroid hormones 3 and 4 (T3 and T4), and the autoantibodies thyroid-simulating immunoglobulin (TSI) and thyroid-binding inhibitory immunoglobulin, the latter 2 of which correlate with TED disease activity.[9,10] TSI exhibits significant association with the clinical features of TED and serves as a functional biomarker for TED, correlating with clinical disease severity and potentially identifying patients with recent-onset compressive optic neuropathy.[10] Antithyroid peroxidase and antithyroglobulin antibodies can also be assayed.

Imaging can further clarify the diagnosis of TED.[11] Computed tomography (CT) scanning can reveal enlargement of the extraocular muscles with typical sparing of the muscle tendons. Magnetic resonance imaging (MRI) outperforms CT scanning in the assessment of disease activity and is better able to estimate the water content of the extraocular muscles.

The management of TED often requires a multidisciplinary team approach. On the basis of the nature and severity of findings, patients with TED may benefit from consultation and comanagement with specialists in oculoplastics, neuro-ophthalmology, and endocrinology.

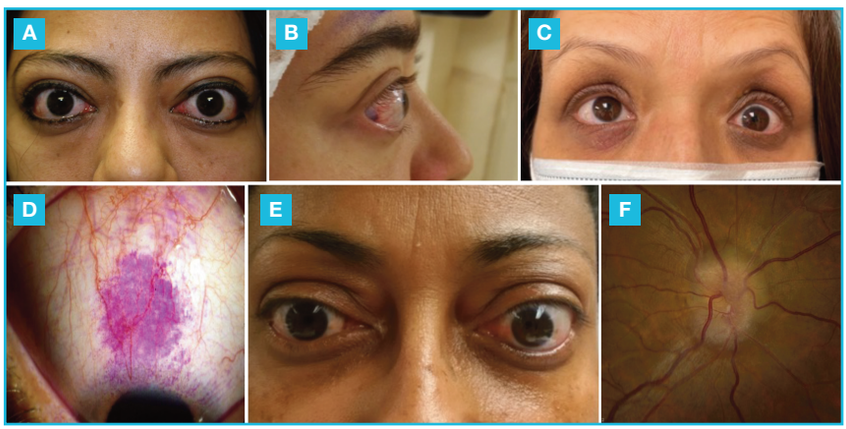

Figure 2. Clinical manifestations of thyroid eye disease: (A) wide-eyed stare due to eyelid retraction and proptosis; (B) proptosis; (C) extraocular muscle restriction; (D) optic nerve dysfunction; (E) tearing and photophobia; and (F) superior limbic keratoconjunctivitis

Images courtesy of Wendy W. Lee, MD, MS

Comprehensive Approach to the Treatment of Thyroid Eye Disease

Andrew R. Harrison, MD

The successful management of patients with TED requires an individualized approach that considers each patient's findings, the impact of these findings on health and health-related quality of life (QOL), and specific therapeutic goals tailored to the specific nature of each patient's disease status. The management of active progressive TED may include a combination of supportive management, medical therapies, and both on-label and off-label biologic therapies, whereas the management of inactive fibrotic TED typically includes surgery and/or biologics.

Supportive management takes many forms. Among these, education and psychologic care are critically important because patients with TED are often emotionally distressed about changes in their appearance and the potential threat to their visual function.[12] QOL is diminished in patients with TED because of various aspects of the disease, including TED activity and ocular pain, proptosis and asymmetry of proptosis (≥ 3-mm difference between eyes), diplopia, and blurred vision.[13-21] Therapy should be aimed at least in part at maintaining or improving QOL.[22] This may start with assuring the patient that a comprehensive plan will be developed to address the physical and psychological manifestations of the disease.

Achievement of euthyroid control is an essential first step in the supportive management of TED and is typically achieved in collaboration with a primary care provider and/or an endocrinology specialist. Smoking cessation should be encouraged. A 6-month course of the antioxidant selenium (100 µg twice daily) has been shown in a double-masked randomized trial to decrease ocular findings, reduce the rate of progression of TED, and improve QOL in patients with mild TED by theoretically decreasing the generation of oxygen free radicals involved in the disease's pathophysiology.[23] A caveat of this trial is that it was conducted in a geographic region with low soil concentrations of selenium. Other supportive measures include ocular surface treatments for those with dry eye disease, prisms incorporated into spectacles to address diplopia, and the use of neurotoxins to lessen the extent of lid retraction.

For patients with more clinically significant findings, systemic steroids can improve symptoms but are rarely effective in halting disease progression.[24] Steroids can be administered either orally or intravenously. Oral steroids are approximately 50% effective at preventing worsening of the disease.[25] Intravenous methylprednisolone is 80% effective at arresting disease progression, but is associated with a significant treatment burden—500 mg weekly for 6 weeks, followed by 250 mg weekly for an additional 6 weeks.[25-27] This approach also has a high relapse rate—40% to 50%—upon completion of therapy.[18,26] In addition, high-dose steroids (6-8 g of methylprednisolone over a 12-week course of therapy) have an unfavorable safety profile that includes catastrophic outcomes, such as liver failure and death, and less catastrophic but still severe outcomes, such as Cushing syndrome, weight gain, diabetes, hypertension, osteoporosis, and infections.[18,27-29] These adverse effects are less common with oral administration than with intravenous administration.[27]

Orbital radiotherapy (ORT) is an alternative or adjunct to systemic steroid therapy to slow the progression of disease in patients who have moderate to severe TED or when rapid progression is occurring, including in patients with significant motility deficits and compressive optic neuropathy.[30] A regimen of 20 Gy per orbit delivered over 10 days is 60% effective in patients with early active progressive moderate to severe TED, so patient selection for this therapy is essential to success.[25,31] ORT induces terminal differentiation of progenitor fibroblasts and halts the inflammatory response,[32] which in turn can improve ocular mobility but has variable to no effect on proptosis.[30] Contraindications of ORT include younger age (aged < 35 years) given the risk of carcinogenesis and retinopathy associated with hypertension or diabetes because radiation can exacerbate the severity of retinopathy.[25]

For patients who do not respond to steroid and/or orbital radiation therapy, several biologic therapies are available. These include 1 drug that is indicated specifically for TED (teprotumumab) and several others that can be used off-label for TED (eg, rituximab and tocilizumab). Teprotumumab is discussed in more detail in the next section. Rituximab is a monoclonal antibody that targets CD20, leading to the depletion of peripheral B cells but not mature plasma cells, and has demonstrated mixed results in studies of TED.[33,34] Tocilizumab is a monoclonal antibody that targets interleukin-6. Interleukin-6 increases expression of TSHR and stimulates B cells to produce TSI, so blocking this action decreases TSHR expression and reduces TSI production.[35] In a randomized clinical trial, patients with TED receiving intravenous tocilizumab 8 mg/kg monthly for 3 months were more likely to achieve a ≥ 2-point improvement in clinical activity score than those treated with placebo (87% vs 35%, respectively; $P = .005$).[35] Common adverse events associated with tocilizumab included infections and neutropenia. These regressed with the discontinuation of therapy.

Once TED has reached the inactive fibrotic stage, treatment is aimed at cosmetic outcomes and is largely surgical in nature. The traditional approach consists of orbital decompression to address proptosis, strabismus repair, eyelid retraction repair, and blepharoplasty as needed to fine-tune reapproximation of the lids. The overarching goal of this "aesthetic-functional" reconstruction approach is to regain the pre-TED

appearance and function of the eye and orbit as much as possible. A customized orbital decompression technique with targeted bone removal (specifically the zygomatic basin) can achieve a decrease in proptosis while also enhancing final globe and lid position, without the need for additional surgeries such as lower eyelid retraction repair.[36] The removal of fat from the superonasal and inferotemporal quadrants can reduce diplopia when performed as an adjunctive procedure through blepharoplasty incisions.

Compressive optic neuropathy represents one of the most important sight-threatening complications of TED and requires prompt and aggressive therapy to prevent permanent loss of visual function. Both steroids and orbital radiation can be used. The acute steroid protocol for compressive optic neuropathy consists of intravenous methylprednisolone 0.5 to 1 g for 3 days and repeated 1 to 2 weeks later, which has led to visual recovery in 43% of patients.[37-39] Orbital radiation can be applied alone or in combination with steroids. The combination of orbital radiation and oral steroid therapy was 94% effective in avoiding the need for orbital decompression surgery in the active phase of TED in 1 study.[40] For severe or recalcitrant cases, surgical decompression of the orbit can be undertaken. Typically, the medial wall of the orbit, with or without the orbital floor, is sufficient to relieve optic nerve compression. Three-wall decompression that includes the lateral wall of the orbit can be undertaken, but may increase the risk of complications such as new-onset diplopia.[41]

Current and Emerging Treatments for Thyroid Eye Disease

Roger A. Dailey, MD, FACS

The clinical course of TED includes an initial active phase that lasts for 1 to 2 years on average, followed by a protracted inactive fibrotic phase. Traditional therapies, such as steroids and orbital radiation, can effectively prevent disease progression but generally do little to reverse the cosmetic and functional adverse effects of TED. An ideal therapy would be applied during the active stage of TED to halt progression and restore and maintain form and function into the inactive phase of the disease.

Modern biologic therapies offer the potential to accomplish this goal. Biologics include a diverse group of medications, including vaccines, growth factors, immune modulators, and monoclonal antibodies. Collectively, these therapies modulate normal and abnormal biologic processes via therapeutic targeting of specific aspects of the varied pathophysiologies of human disease.

Teprotumumab is a biologic approved by the US Food and Drug Administration specifically for the treatment of TED.[42] It is a monoclonal antibody inhibitor of IGF-1R, with targeted binding to the IGF-1R/TSHR signaling

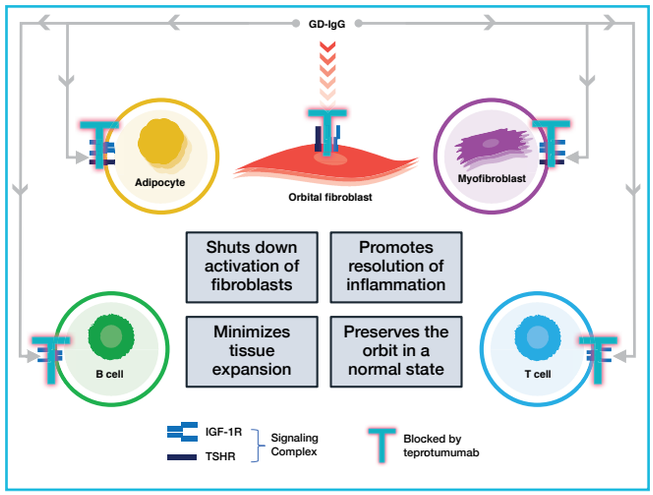

Figure 3. Mechanism of action of teprotumumab for the treatment of thyroid eye disease[6,43]

Abbreviations: GD, Graves disease; IGF-1R, insulin-like growth factor 1 receptor; IgG, immunoglobulin G; TSHR, thyroid-stimulating hormone receptor.

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complex. When bound to this complex, teprotumumab is disease modifying, blocking autoantibodies from attacking orbital cells and turning off the IGF-1R/TSHR signaling that leads to TED, reducing inflammation, preventing excessive cell growth, and decreasing hyaluronan accumulation, thus preserving the orbit in a normal state **(Figure 3)**.[6,43] A series of clinical trials showed teprotumumab effectively reduced proptosis, diplopia, compressive optic neuropathy, and chronic TED—and improved QOL.

In the phase 3 OPTIC trial conducted in patients with new-onset (< 9 months) TED and clinical activity score > 4, mean reduction in proptosis was -3.32 mm in 41 patients receiving teprotumumab and -0.53 mm in 42 patients receiving placebo ($P < .001$).[44] A ≥ 2-mm reduction in proptosis occurred more frequently in patients receiving teprotumumab than in those receiving placebo (83% vs 9.5%, respectively; $P < .001$) **(Figure 4)**.[44] Among patients in the OPTIC trial with diplopia at baseline (n = 28 in each group), response rate (those with a ≥ 1-grade improvement in diplopia on a 0-3 scale, ranging from no diplopia [0] to constant diplopia [3]) at week 24 was 68% with teprotumumab vs 29% with placebo ($P = .001$). QOL was measured using the Graves orbitopathy–QOL 16-item survey, which includes 8 questions each on patients' perceptions of their visual function and their appearance, scaled to a final score of 0 (worst possible QOL) to 100 (best possible QOL). Mean improvement in QOL scores was 17.28 points with teprotumumab and 2.00 points with placebo ($P < .001$).

The most common adverse events observed in clinical trials in 84 patients receiving teprotumumab vs 86 patients receiving placebo were muscle spasms (25% vs 7%, respectively), nausea (17% vs 9%, respectively), alopecia

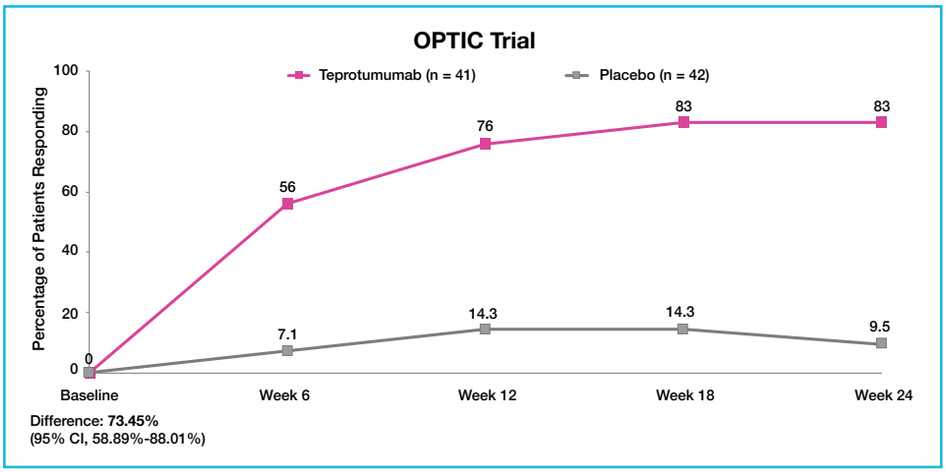

Figure 4. Proptosis changes in the OPTIC trial: teprotumumab vs placebo for thyroid eye disease[44]

Abbreviation: CI, confidence interval.

From *The New England Journal of Medicine*, Douglas RS, Kahaly GJ, Patel A, et al, Teprotumumab for the treatment of active thyroid eye disease, 382, 341-352. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

(13% vs 8%, respectively), diarrhea (12% vs 8%, respectively), and fatigue (12% vs 7%, respectively).[45] Two additional adverse events of note were hyperglycemia and hearing impairment, which will be discussed subsequently. The package insert of teprotumumab has several precautions of importance, including embryo-fetal toxicity (contraception is recommended during and for 6 months after treatment), infusion-related reactions, exacerbation of preexisting inflammatory bowel disease, hyperglycemia, and hearing impairment and hearing loss.[45]

Hearing impairment was noted in 5 patients in the phase 3 OPTIC trial.[44] The nature of the impairment was variable among patients, affecting some unilaterally and others bilaterally, occurring at different times in the course of treatment, and variably described as decreased hearing, tinnitus, and autophony (echoing of one's voice). In addition, recovery was complete in some ears and incomplete in others. In a case series of 44 ears of 22 patients with hearing dysfunction while receiving teprotumumab, 50% of patients met the audiology criteria for ototoxicity in 1 or both ears, and 39% of ears were affected, with older age being a risk factor for hearing loss.[46] In a prospective case series, subjective otologic symptoms were reported in 22 of 27 patients (81.5%) after a mean of approximately 4 infusions; symptoms included tinnitus, ear plugging/fullness, and autophony (each had > 80% resolution rates) as well as sensorineural hearing loss/decreased word comprehension that was less likely to resolve (46% resolution rate).[47] Prior hearing loss was identified as a risk factor for further hearing loss during therapy. A case report of a woman with hearing loss during therapy who subsequently required a second course of therapy demonstrated that halving the dose of teprotumumab can deliver compatible efficacy without recurrent hearing loss.[48] The implementation of routine audiologic monitoring has been proposed before, during, and after teprotumumab therapy, although the nature of such monitoring has not been optimally clarified.[47,49] The prescribing information of teprotrumumab states, "Assess patients' hearing before, during, and after treatment...and consider the benefit-risk of treatment with patients."[45]

Discussion on Hearing Loss

Dr Harrison: What is the proposed mechanism for hearing loss?

Dr Dailey: There are IGF receptors in the ear that are theoretically blocked, resulting in sensorineural loss. Many patients who develop sensorineural loss had congenital or acquired hearing issues to begin with. As for autophony, this is a common symptom of a patulous Eustachian tube. The Eustachian tube is typically closed at rest to protect the middle ear from secretions of the nasopharynx. In some people, and perhaps as a result of teprotumumab therapy, this protective closure of the tube is deficient, perhaps related to loss of a fat pad at its opening, leading to autophony.[50]

Dr Lee: I have not observed an 80% incidence of hearing issues in my patients on teprotumumab.

Dr Harrison: Nor have I. I inform my patients of the risk of both sensorineural hearing loss and other hearing symptoms, such as autophony. The latter is likely to resolve over time, whereas the former may not.

Dr Dailey: Our role in the evaluation and monitoring of auditory function remains unclear. Perhaps we should obtain baseline audiograms to identify preexisting sensorineural hearing loss so we can counsel patients with a high risk of further impairment. There is also the question of what to do with new-onset hearing loss during treatment. Should we stop treatment? This will be a decision we make one-on-one with patients according to their responses to therapy, magnitude of hearing loss, and overall risk-benefit ratio.

Dr Harrison: Our protocol at the University of Minnesota is to obtain audiograms midtreatment—between the third and fourth infusions—and again at the end of treatment.

Endocrinologic Perspectives on Managing TED

Sonalika Khachikian, MD

TED represents the ocular manifestation of systemic hyperthyroidism and cannot be managed in a vacuum. Instead, management necessitates collaboration with the medical team, which can include the primary care physician or endocrinologist overseeing the systemic management of the disease. It is therefore of value to consider the endocrinologist's perspective when managing TED.

Hyperthyroidism is caused by increased thyroid hormone T3 and T4 circulating in the bloodstream that causes the TSH to be suppressed.[51] It can be due to increased production by the gland or due to destruction of thyroid tissue releasing stored thyroid hormone into the bloodstream **(Figure 5)**. An abundance of thyroid hormone is characterized by a number of systemic findings that include weight loss or gain, tachycardia/palpitations, irritability, difficulty sleeping, nervousness/tremor, menstrual irregularities, impaired fertility and increased rate of miscarriage, and sudden paralysis, among others. The most common cause of hyperthyroidism is autoimmune (Graves disease); other causes include toxic nodular goiter and thyroiditis.[51,52]

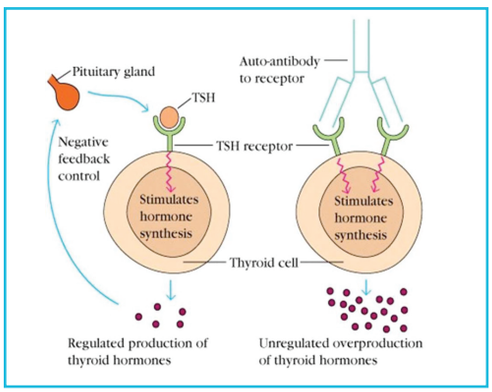

Figure 5. Schematic of the difference between normal thyroid hormone production in response to thyroid-stimulating hormone and excessive production in response to thyroid-stimulating hormone receptor autoantibodies[51]

Abbreviation: TSH, thyroid-stimulating hormone.

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The diagnosis of hyperthyroidism is based on laboratory testing that should include TSH, free T3 and free T4, TSI, TRAb (TSHR-binding antibody), and a comprehensive metabolic panel.[52] Once diagnosed, treatments available for hyperthyroidism include radioactive iodine therapy, antithyroid medications (methimazole and propylthiouracil), beta blockers, and surgical thyroidectomy.[52]

TED is seen in as many as 50% of patients with Graves disease, but it is considered a separate disease.[3]
The risk of progression of TED appears to be similar when treated with antithyroid drugs vs surgical thyroidectomy, but seems to be significantly higher (close to 30%) with radioactive iodine therapy.[52] In an interventional case series, 73% of patients with TED had regression of proptosis (by an average of approximately 2 mm) following total thyroidectomy; the remaining patients stayed stable, with no eyes worsening postoperatively.[53] A retrospective comparison of radioactive iodine therapy vs total thyroidectomy in patients with TED refractory to antithyroid drugs demonstrated that radioactive iodine therapy was associated with a more rapid resolution of hyperthyroidism, although its widespread application is limited by cost and invasiveness.[54] There is also evidence that persistent untreated hypothyroidism following therapy for hyperthyroidism is a risk factor for TED progression.[52,55]

A 5-step approach to reducing morbidity and improving QOL in patients with TED has been proposed by the American and European Thyroid Associations[56]:

1. Accurately diagnose Graves disease by measuring TSH receptor antibodies, including both inhibitory and stimulating antibodies.
2. Screen all patients with Graves disease for TED using specific tools to detect the signs and symptoms of TED.
3. Educate all patients with Graves disease about TED so they can monitor themselves for characteristic changes.
4. Prevent TED development or progression by facilitating smoking cessation, achieving and maintaining euthyroidism, avoiding radioactive iodine therapy in patients with active TED and using steroid prophylaxis following radioactive iodine therapy when essential, avoiding hypothyroidism after hyperthyroidism therapy, and considering selenium as indicated for mild TED.
5. Prompt referral to the appropriate specialist for management of moderate to severe and/or sight-threatening TED.

As mentioned previously, 1 observed complication of teprotumumab is hyperglycemia, which was seen in 10% of patients in clinical trials.[45] Hyperglycemia and diabetes are common, and are more common in overweight or obese adults, particularly those with a family history of diabetes or who are African American, Latino, Native American, Asian American, or Pacific Islander.[57] By current standards, a fasting glucose > 100 mg/dL represents impaired fasting glucose and a fasting glucose > 126 mg/dL represents diabetes. HbA_{1c} levels specify the presence of diabetes as follows: < 5.7% signifies no diabetes, > 5.7% to < 6.5% signifies prediabetes, and > 6.5% signifies diabetes.[57]

Hyperglycemia in patients with TED receiving teprotumumab was studied over 48 weeks in patients without diabetes, prediabetes, and diabetes.[58] The change in HbA_{1c} after starting teprotumumab depended on baseline HbA_{1c}, meaning that patients with underlying diabetes were more likely to see large rises in HbA_{1c} than those without diabetes.[59] Among patients with prediabetes and diabetes, HbA_{1c} elevations were most significant 3 months after starting therapy and tended to decrease at 6 and 9 months after starting therapy. The overall mean rise in HbA_{1c} was 0.5%. Significant risk factors for HbA_{1c} increase were age, preexisting diabetes, and Hispanic or Asian ethnicity, and, notably, only 36% of patients with posttreatment hyperglycemia returned to baseline. Furthermore, a post hoc analysis of the 8 participants in the phase 2 and 3 trials who developed hyperglycemia revealed a mean change in HbA_{1c} of 0.2%, and most returned to baseline following therapy; none discontinued study therapy because of changes in blood glucose during the trials.[58]

There are no consensus guidelines to-date on the best way to monitor patients for complications related to hyperglycemia. In the meantime, it is reasonable to obtain both blood glucose and HbA_{1c} at baseline. If the HbA_{1c} is high (> 8%), consider optimizing systemic glucose control before starting teprotumumab. Monitor patients with elevated glucose or HbA_{1c} periodically during treatment and again 12 months after the completion of therapy. Collaboration with the primary care or endocrine specialist is helpful in this setting. Consider notifying the primary care provider and endocrine specialist of the specific plan to treat with teprotumumab and its effect on blood glucose in order to aid in patient management should these clinicians not be aware of this correlation.

Discussion on Hyperglycemia and Hyperthyroidism Management

Dr Lee: Given the impact of teprotumumab on blood glucose, how should we approach patients with so-called brittle diabetes?

Dr Khachikian: The issue comes down to severity and QOL. If TED is severe enough to meaningfully affect their QOL, then the risk is worth the benefit. We engage these patients, let them know the risk, and work with them and their diabetes care provider to control their diabetes as robustly as possible during therapy to comanage their multiple health conditions. The pattern of hyperglycemia is interesting. I have noticed that blood glucose level rises and stays elevated for approximately 10 days—just shy of 2 weeks—after each infusion before it returns to the pretreatment baseline level. This happens after every infusion, so we can plan for the times when we need to be more vigilant. To summarize, patients with uncontrolled diabetes and TED may benefit the most from comanagement with their diabetes care provider.

Dr Dailey: Dr Khachikian, you presented data that total thyroidectomy is ultimately the best treatment for hyperthyroidism in terms of both systemic euthyroidism and avoidance of TED. Given this, why is total thyroidectomy not the standard of care for the management of hyperthyroidism?

Dr Khachikian: It comes down to cost and complications. The prevalence of hyperthyroidism in the United States is approximately 1.2%.[1] That is just shy of 4 million patients with hyperthyroidism in the United States alone. The cost of surgery for that many people would be astronomical compared with the cost of alternative therapies, even with a low complication rate. Also, some of these patients will end up hypothyroid, which, as we discussed, is an exacerbating factor for progression of TED.[52]

Furthermore, in 1 trial, there was a faster onset of immunologic remission in patients receiving antithyroid medication (6 months) vs surgery (1 year).[54] Thus, antithyroid drugs are often preferred over surgery in most cases. Surgery does have a role in some cases of severe hyperthyroidism complicated with severe TED that may compromise vision.[53]

Case Presentation and Discussion

From the Files of Andrew R. Harrison, MD

A 49-year-old woman presented to an outside facility with left-sided proptosis, blurred vision, ocular dryness, and a pressure sensation behind the left eye. She had no significant past medical or ocular history. On examination, her visual acuity was 20/15 OD and 20/20 OS. Intraocular pressure was 25 mm Hg OD and 28 mm Hg OS. Her pupil examination, color vision, and visual fields were intact. Extraocular motility was intact OD and trace upgaze restriction OS. Hertel measurements were 20 mm OD and 22 mm OS at a base of 93 mm. The left pupillary fissure was 2 mm larger than the right, as was the marginal reflex distance 1.

Dr Lee: Did the patient undergo imaging? The proptosis is unilateral or at least significantly asymmetric. TED is the most common cause of unilateral and bilateral proptosis, but when I see unilateral disease, I always consider the differential diagnosis.

Dr Harrison: I always use the VEIN mnemonic—Vascular, Endocrine, Infection/Inflammation, and Neoplasms—for the differential diagnosis. Her orbits were scanned with both CT and MRI **(Figure 6)**. Computed tomography is great for seeing muscle, bone, and tumors, but MRI is better for visualizing apical masses.

Dr Dailey: Computed tomography has the advantage of showing us the bones we may ultimately remove if we progress to decompression surgery.

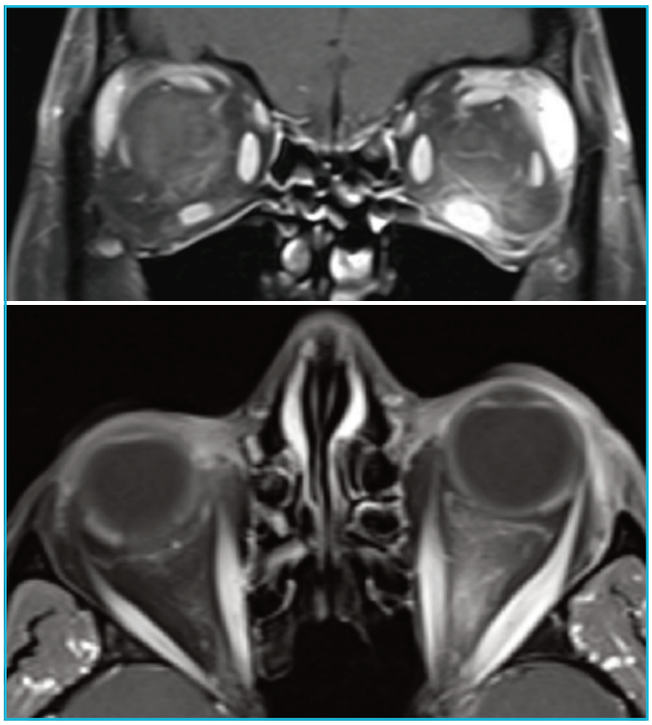

Figure 6. Magnetic resonance images showing left-sided proptosis of the patient presented in the Case

Dr Harrison: The patient also had thyroid function tests performed. TSH level was low (< 0.01), whereas free T3 (126) and T4 (1.77) levels were normal.

Dr Khachikian: She appears to be hyperthyroid. The only caveat is whether she is on treatment because her free T3 and T4 levels are normal. Therefore, she is either hyperthyroid if she is untreated or she is on the way to becoming euthyroid if she has recently begun treatment.

Dr Harrison: She was untreated at this point. What if her TSH level had been normal?

Dr Khachikian: Then, either she is therapeutically euthyroid or she is one of the approximately 5% of patients who develop TED while being systemically euthyroid.[60]

Dr Harrison: This patient was diagnosed at an outside facility with hyperthyroidism and TED. She received a steroid taper and started selenium. After 2 months, her left proptosis had worsened. At this point, on the basis of the lack of therapeutic response as well as a few atypical aspects of the presentation—her being euthyroid, the preferential involvement of the lateral rectus muscle, and the involvement of the left lacrimal gland on neuroimaging—the diagnosis was reconsidered and an orbitotomy with lacrimal and muscle biopsy was undertaken that revealed chronic inflammation. The diagnosis of orbital pseudotumor was considered, and

Figure 7. Ocular appearance of the patient presented in the Case before (A) and after (B) a series of 8 teprotumumab infusions 3 weeks apart

additional steroid therapy was administered. When significant improvement was not evident, she was referred to our thyroid eye clinic for further evaluation. Her vision remained 20/20 OU with no pupillary defect, intraocular pressure was still slightly elevated, Hertel measurements were 23 mm OD and 26 mm OS, esotropia was present, lids were edematous, and the sclera was injected. What would you do next?

Dr Lee: Teprotumumab.

Dr Dailey: I agree.

Dr Khachikian: I agree as well.

Dr Harrison: She received a series of 8 teprotumumab infusions 3 weeks apart. **Figure 7** shows her appearance before and after therapy.

Closing Remark

Dr Lee: I think the most important take-home message from this discussion is that we have to think in terms of a collaborative approach to managing patients with TED. It really is not the eye care provider's job to assess and monitor thyroid status, hearing, or blood glucose. We need help with these aspects of patient care. What has become abundantly clear to me in the setting of TED and teprotumumab is that we need to set up a collaborative network at the outset of therapy. We need to make sure someone is monitoring and optimizing thyroid status and blood glucose. We also need a referral path for our patients who report hearing loss either before or during therapy. This is definitely a team approach. Because we are prescribing the medication, we must be the team leaders.

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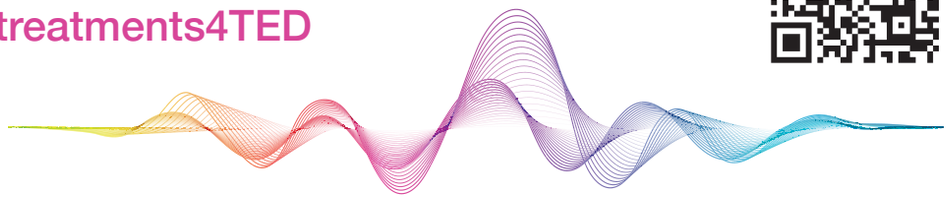

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1. A 42-year-old woman presents with bilateral lid retraction and proptosis. She does not have a history of hyperthyroidism. Which laboratory test should be performed?
    a. Free T3, TSI, and fasting blood glucose
    b. Free T3 and T4 and TSH
    c. Free T3 and T4 and white blood count
    d. Autoantibodies TSI and thyroid-binding inhibitory immunoglobulin and fasting blood glucose

2. A 45-year-old woman presents with a 3-month history of progressive bilateral proptosis and scleral injection. Thyroid function testing reveals systemic hyperthyroidism. Which treatment for hyperthyroidism should be avoided because it could worsen her TED?
    a. Total thyroidectomy
    b. Radioactive iodine
    c. Antithyroid drug
    d. Teprotumumab

3. Which is NOT a contraindication to orbital radiation for TED?
    a. Aged < 35 years
    b. Cataracts
    c. Diabetic retinopathy
    d. Hypertensive retinopathy

4. A 41-year-old man with a 5-year history of TED returns to your office with stable proptosis and restrictive strabismus. Which of the following is the most appropriate treatment approach?
    a. Radiotherapy
    b. Rehabilitative surgery
    c. Intravenous glucocorticoids
    d. Tocilizumab

5. A 39-year-old woman with TED presents with a 6-month history of severe bilateral exophthalmos, diplopia, and intraorbital fat proliferation. She has hyperthyroidism, type 2 diabetes, and hyperlipidemia. Which is the most appropriate treatment approach?
    a. Intravenous glucocorticoids
    b. Teprotumumab
    c. Rituximab
    d. Orbital radiation

6. Which of the following was NOT a finding of the phase 3 OPTIC trial of teprotumumab for TED?
    a. 68% of treated patients exhibited a ≥ 1-grade improvement in diplopia
    b. 83% of treated patients exhibited a ≥ 2-mm reduction in proptosis
    c. QOL improved significantly with treatment
    d. The most common adverse effect was fatigue