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Clinician Update

Thyroid Eye Disease

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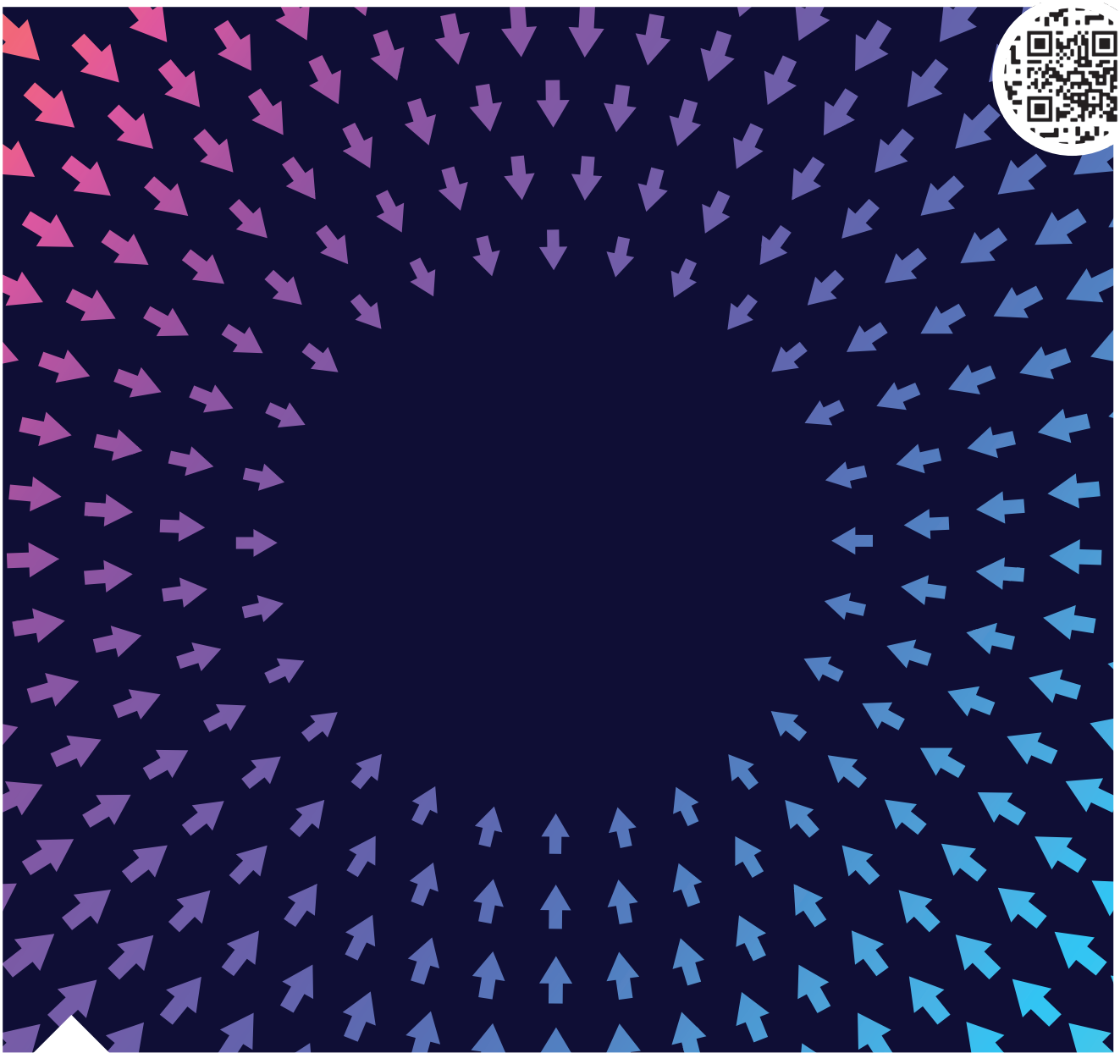

THYROID EYE DISEASE (TED):

WHY EARLY DIAGNOSIS AND TREATMENT ARE CRUCIAL

These strategies for detecting signs of TED will facilitate treatment to help modify the disease course and improve quality of life.

Thyroid eye disease (TED) is a chronic autoimmune condition that not only has bothersome physical symptoms but also can produce cosmetic changes that leave some patients in a state of profound psychological distress. Moreover, severe cases that are not aggressively and adequately treated increase the risk for permanent vision loss. "Thyroid eye disease can have a great impact on quality of life," says Ana Carolina Victoria, MD, FACS, an oculofacial plastic surgeon at the Center for Excellence in Eye Care in Miami. "You don't want the patient to suffer unnecessarily, so the earlier you intervene, the better."

Recognizing the symptoms

TED is a rare condition that occurs in some patients with autoimmune-related hyperthyroidism.[1] Between 25% and 50% of patients with Graves' disease develop TED, which is characterized by inflammation of the orbit, or eye socket. Orbital adipose and muscle tissues become enlarged, which contributes to some of the hallmark symptoms of TED (also known as Graves' ophthalmopathy or Graves' orbitopathy) including proptosis and dry eye.[2]

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Presentation of TED is highly variable, from mild to severe, says Dr. Victoria, and transitions from an active phase with high levels of inflammation and tissue changes that may last several months or years to an inactive phase, when disease progression slows, but many of its most challenging symptoms remain. Some common patient complaints are nonspecific, such as:

- Dry, "gritty" eyes
- Swelling and redness around the eyes and eyelids
- Watery eyes
- Pain/pressure behind the eye
- Photosensitivity

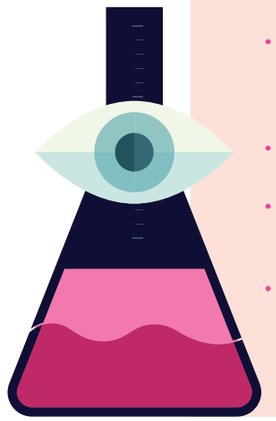
In about one-fifth of cases, eye symptoms precede a diagnosis of Graves' disease, so nonspecific symptoms should be considered carefully, especially if they occur in the context of other non-eye symptoms, such as palpitations and weight gain, that could be indicative of hyperthyroidism, says Dr. Victoria.[2] Some of the more distinctive signs and symptoms of TED include the following:

- Eyelid retraction. "The muscle that opens the eyelid is working harder than it should—it's almost becoming fibrotic—which makes the eyes wide open," says Dr. Victoria. More than 90% of TED patients develop upper eyelid retraction.[3]
- Proptosis (bulging eyes). Enlargement of orbital fatty tissue and musculature push the eyeball forward.
- Diplopia (double vision) and strabismus (misaligned eyes), which are also caused by inflammation of fatty tissue and muscle.

LIFESTYLE STRATEGIES TO HELP MANAGE TED

Patients with thyroid eye disease (TED) can use various self-care strategies to relieve or mitigate certain symptoms, such as dryness, pain and the functional/visual effects, says Kimberly Cockerham, MD, an oculoplastic surgeon, orbital expert and surgical neuro-ophthalmologist in San Diego. Indeed, joint guidelines from the American Thyroid Association and the European Thyroid Association cite several nondrug interventions, including the following:[3]

- Smoking cessation and avoiding second-hand smoke to avoid worsening of inflammation and help maintain eye health.
- Lubricating eye drops, gels and ointments. People with TED aren't able to blink properly, which can lead to dry, irritated eyes. "Lubricating drops are a great self-treatment for dry eyes," says Dr. Cockerham. She recommends using them 4 to 6 times per day and choosing preservative-free formulations to reduce the risk of irritation.
- Selenium (100 mcg twice daily), which may improve symptoms and slow disease progression in mild TED.[5]
- Eyeglasses fitted with prisms to relieve diplopia.
- Sunglasses (preferably wraparound style) to protect eyes from the sun and wind.
- Cool compresses to combat swelling and warm compresses to help with dry eye symptoms.
- A sleep mask or taping the eyelids shut when sleeping. (These and other eye comfort products can be found at *eyeeco.com*.) Being unable to close the eyes can lead to dryness and a corneal ulcer, which can cause scars on the eyes and loss of vision.
- Using a clip or patch over one eye to reduce double vision.
- Avoiding salty foods and monosodium glutamate, as these can cause fluid retention that worsens eyelid puffiness, double vision and even the amount of proptosis.
- Staying hydrated. "Advise patients to drink at least eight cups of water throughout the day to avoid dehydration, which can also help with brain fog due to thyroid disease," Dr. Cockerham says. "And try to avoid caffeine if hyperthyroid, as this can worsen anxiety and mood swings."



> **"We used to just 'watch and wait'...now, the thinking is that if you intervene early with medications, we can prevent these patients from having the disabling and disfiguring effects from TED."**
>
> *—Ana Carolina Victoria, MD, FACS*

Confirming suspicion of TED

If TED is suspected, clinical tests that can support the diagnosis include:

- Exophthalmometry to measure proptosis. Baseline measurement and follow-up evaluations can be used to track progression of TED and response to therapy.
- Orbital magnetic resonance imaging (MRI) or computed tomography (CT), which can identify orbital tissue enlargement, including extraocular muscles, orbital fat and lacrimal glands.[3]
- Lab work, which can detect antibodies specific to or correlated with TED, thyroid-stimulating immunoglobulin (TSI) or thyrotropin receptor antibody (TRAb). "It's pretty much a slam-dunk diagnosis if they have those biomarkers," says Dr. Victoria.

Why it's important to intervene early

Dr. Victoria says early treatment is designed to achieve these two overarching goals:

1. MODIFYING THE COURSE OF THE DISEASE.

The availability of medications that target the root causes of TED has led to a change in the approach to treating this challenging condition, says Dr. Victoria. "We used to just 'watch and wait' until the disease burned out, then intervene with surgical procedures to restore anatomy to as close as possible to what it was," she observes. "Now, the thinking is that if you intervene early with medications that are specific for TED, we can prevent these patients from having the disabling and disfiguring effects from TED."

And while TED is often mild, severe cases can cause blindness, underscoring the importance of prompt treatment, says Dr. Victoria. Vision loss may occur for several reasons, including:

- Anatomical changes in the orbit that can increase pressure on the optic nerve, resulting in compressive optic neuropathy, which can block visual signals to the brain.
- A forward-bulging eyeball and eyelids that can't close leave the cornea vulnerable to ulceration that can cause sight-robbing scarring of tissue.

Note: The concurrent management of Graves' is essential, as uncontrolled thyroid disease can worsen TED. However, controlling TED requires a separate treatment plan.

2. RESTORING QUALITY OF LIFE.

The effect of TED on a patient's appearance can have a major impact on quality of life, says Dr. Victoria. "It can be extremely distressful. I have had patients who quit their jobs because they were so upset about their appearance. Many became socially isolated because they didn't want to be asked about their TED."

A 2023 study in *Frontiers in Endocrinology* quantifies many of Dr. Victoria's clinical observations.[4] A team of healthcare

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professionals (including ophthalmologists, psychiatrists and endocrinologists) created a 62-question survey to gauge the physical and emotional impact of TED, which was administered to 443 patients, some of whom had lived with the disease for up to a decade. The survey revealed significant psychological difficulties related to TED:

- 49% of patients felt less confident and a decline in general well-being.
- 45% reported feeling depressed and/or anxious.
- 44% were concerned about their appearance.
- 20% felt unable to achieve their goals.
- 19% avoided going out in public.

Multidisciplinary treatment is key

Care of TED often requires a coordinated effort by a multidisciplinary team of clinicians that includes an endocrinologist and an ophthalmologist with expertise in the management of the disease, as well as a psychotherapist or other specialist, depending on the treatment plan.

The 2022 consensus statement by the American Thyroid Association and the European Thyroid Association (ATA/ETA) on the management of TED offers a treatment decision aid based on disease activity level, duration and severity of disease and other factors.[3] Common TED treatments include:

MEDICAL THERAPY

The monoclonal antibody teprotumumab is the first targeted treatment for TED approved by the FDA and has been shown in clinical trials to reduce proptosis, improve diplopia and reduce overall disease activity scores (for more information, see story, *opposite*). Intravenous glucocorticoid (IVGC) therapy is a preferred treatment for the active (inflammatory) phase of moderate-to-severe TED inflammation of the eyelids and ocular surface areas, the prominent features in the absence of either significant proptosis or diplopia, per the ATA/ETA guidelines.[3]

SURGERY

Rehabilitative surgical procedures are typically recommended for cases of moderate-to-severe TED that have inadequate response to medical therapy and are usually performed when the disease is in the inactive phase. Orbital decompression, which involves removal of bone and sometimes fatty tissue from the orbit, is the most common surgical option for correction of proptosis. Eyelid retraction usually requires recession of muscles responsible for opening the eyelids, which include the Mülleres and levator muscle, says Dr. Victoria.

RADIATION

The ATA/ETA guidelines deem orbital radiotherapy, one of the oldest treatments for TED, to be a preferred treatment for disease with the principal feature of progressive diplopia and an acceptable therapy for moderate-to-severe or sight-threatening disease.[3] "I don't use radiotherapy very frequently, but I have used it," says Dr. Victoria. "It's another tool in the toolbelt." ●

—by Tim Gower

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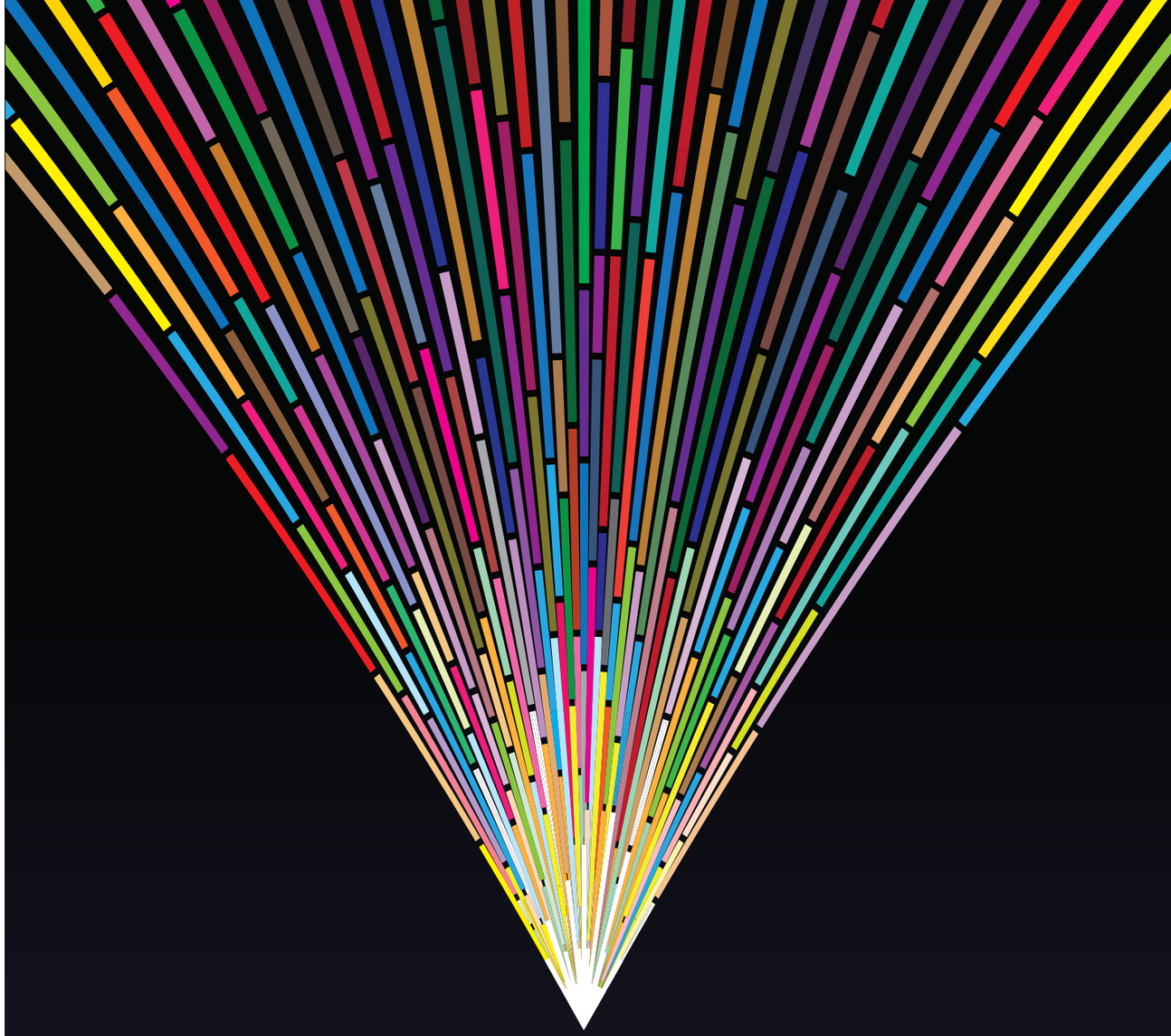

PRACTICE PEARLS

Insight on using **teprotumumab** for TED

Illustration by Daniel Hertzberg

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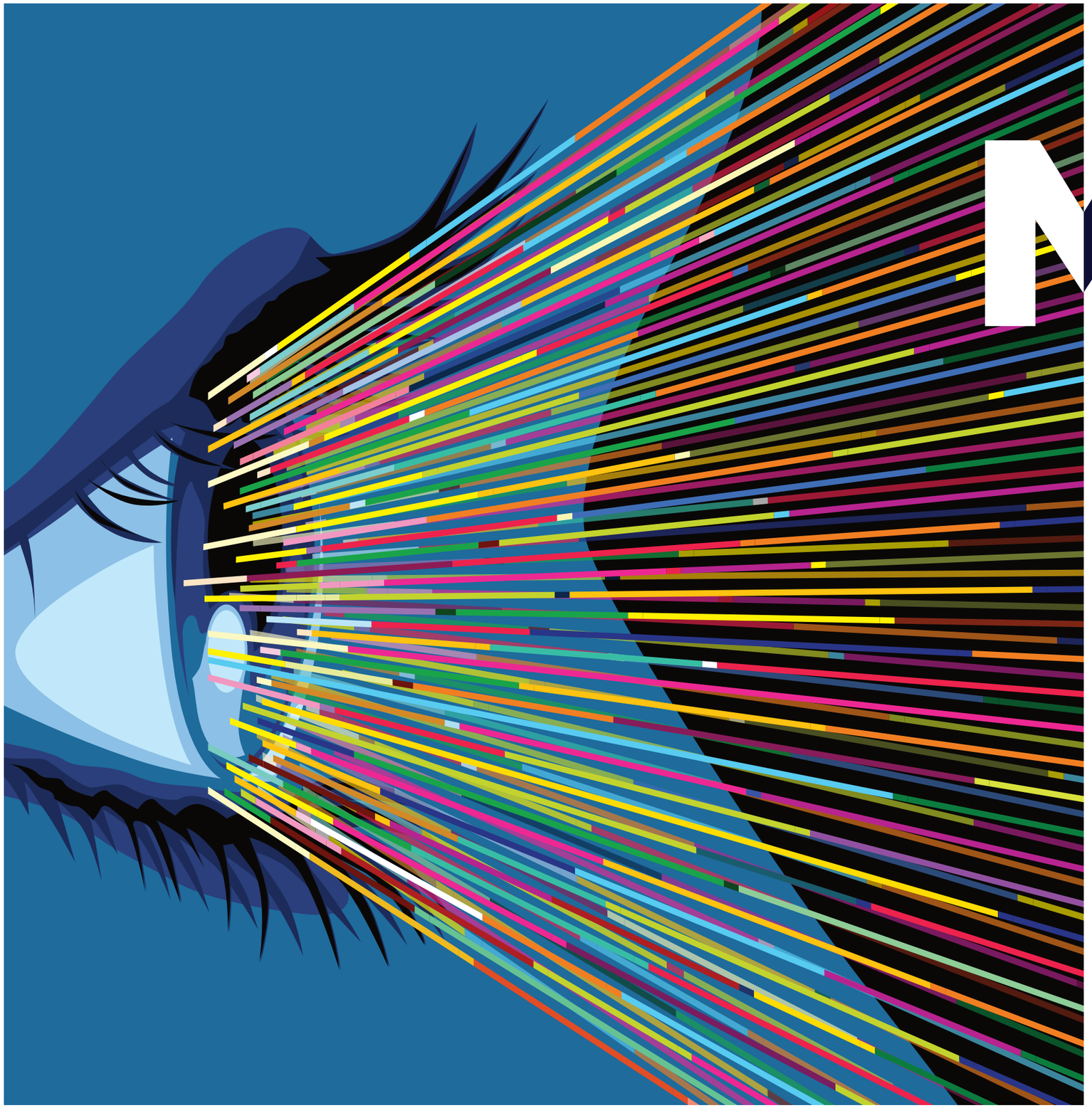

Illustration by Daniel Hertzberg

Managing thyroid eye disease (TED) has long posed a clinical challenge—in fact, the first description of a case of ophthalmopathy linked to goiter was documented by a Persian physician around 1,000 AD.[1] Until recently, medical therapy options for this complex condition were limited, but in 2020, the Food and Drug Administration (FDA) approved teprotumumab, the first medication developed specifically for the treatment of TED.[2]

"Teprotumumab is a breakthrough," says Ana Carolina Victoria, MD, FACS, an oculofacial plastic surgeon at the Center for Excellence in Eye Care in Miami. "It's very targeted therapy, so you are specifically treating what's causing the thyroid eye disease and all of its manifestations." Not only will many patients gain significant symptom relief from teprotumumab, says Dr. Victoria, but even patients who require corrective surgery stand to benefit from treatment, which will minimize the burden of TED prior to the operation. "And with surgery," she notes, "the less urgent the need and the more controlled the environment you have, the better."

Evidence from clinical trials

The FDA approved teprotumumab on the basis of the OPTIC trial, which was conducted at 13 sites in the United States and Europe.[3] OPTIC included 83 patients who were diagnosed with Graves' disease and had active moderate-to-severe TED, meaning they met at least one of the following criteria: eyelid retraction of ≥2 mm, moderate or severe soft-tissue involvement, proptosis of ≥3 mm above the normal values for race and sex, and occasional or persistent diplopia. Patients had a Clinical Activity Score (CAS) of ≥4 and ocular symptoms that began within 9 months of baseline assessment. The primary outcome was clinically significant reduction in proptosis.

In the trial, which was published in the *New England Journal of Medicine*, patients were randomly selected 1:1 to receive eight infusions of teprotumumab, spaced 3 weeks apart, or placebo. At week 24, 83% of the patients in the teprotumumab group had a proptosis response, meaning improvement of at least 2 mm, compared with 10% in the placebo group. The mean change in proptosis in the teprotumumab group was superior to placebo, –2.82 mm versus –0.54 mm, and the authors noted that the results were comparable to the best expected outcomes from orbital decompression surgery. All other secondary outcomes favored the teprotumumab arm, including improvements in diplopia, CAS and quality of life scores.

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In OPTIC, the median duration of TED in treated patients was 6.3 months. An extension trial, OPTIC-X, found that patients with longer-duration TED (median 12.9 months) also benefited from teprotumumab therapy.[4] OPTIC-X found that 33 of 37 patients who had received placebo treatment in OPTIC responded to teprotumumab, with results similar to those in the original trial. Moreover, two out of five patients who didn't respond to teprotumumab in OPTIC had a proptosis response when re-treated in OPTIC-X, with one displaying a 1.5 mm reduction from baseline in the original study. Also, five of eight responders in OPTIC who flared following the study had significant proptosis responses when retreated in OPTIC-X.

Novel mechanism of action

The etiology of TED isn't entirely understood, but it is known that insulin-like growth factor 1 receptor (IGF-1R) is overexpressed by orbital fibroblasts in patients with active and inactive TED compared with healthy controls. IGF-1R plays a key role in TED by promoting inflammation and the expansion of muscle and fat tissue behind the eye, resulting in symptoms such as proptosis and diplopia. Teprotumumab is a fully human monoclonal antibody that binds to and degrades IGF-1R.[3,5]

Patients who could benefit

Teprotumumab is indicated for the treatment of TED regardless of disease activity level or duration, so clinical judgment plays an important role in identifying candidates for this novel therapy. The pivotal OPTIC trial included patients with a CAS of 4 or higher, "But in our clinic we have noticed that patients with lower CAS scores can benefit," says Dr. Victoria. Notably, in the OPTIC-X trial, five patients had minimal or no inflammation and had CAS scores of 0 or 1 at baseline. At week 24, four showed reductions in proptosis, with three meeting the

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Illustration by Daniel Hertzberg

MANY MANIFESTATIONS OF THYROID EYE DISEASE (TED)

ONE ROOT CAUSE[1-3]

TEPEZZA®
teprotumumab-trbw

TEPEZZA is indicated for the treatment of Thyroid Eye Disease (TED) *regardless* of disease activity or duration[4]

Designed to **target and block IGF-1R**, a key driver of TED pathophysiology

TEPEZZA has shown to:

- Decrease proptosis[4,5,7]
- Improve diplopia[4-7]
- Reduce orbital pain, redness, and swelling[5,7]
- Improve functional vision and patient appearance[5,7†]
  †Patient reported based on GO-QOL scale

...in two 24-week, randomized, double-masked, placebo controlled clinical studies of 171 patients with TED.[4]

See how TEPEZZA can help reduce the burden of TED

Teprotumumab-trbw's mechanism of action in patients with TED has not been fully characterized. Teprotumumab-trbw binds to IGF-1R and blocks its activation and signaling.[1]

IGF-1R, insulin-like growth factor-1 receptor.

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INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary. Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

Hearing Impairment Including Hearing Loss: TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, dry skin, weight decreased, nail disorders, and menstrual disorders.

Please see Full Prescribing Information or visit TEPEZZAhcp.com for more information.

criteria for proptosis response.[4]

Most likely responders are patients whose TED is characterized by more significant involvement of muscle versus fatty tissue, as evidenced by proptosis and double vision, notes Dr. Victoria. "That's when we know it works really well," she says.

Also important: Dr. Victoria says it's critical not to give up on teprotumumab if a patient doesn't respond immediately. "Some patients are late responders," she notes. "So even if they don't respond halfway through the regimen, we will go through the whole series of eight infusions, because some will have a late response." If a patient doesn't respond to teprotumumab, the severity of their TED will typically influence the choice of next steps. For example, if a patient is in danger of losing vision, then second-line medications or more aggressive measures such as surgery or radiation may be necessary.

Managing potential adverse effects

Some of the most commonly observed adverse effects associated with teprotumumab include muscle spasms, dry skin, nausea, hair loss and nail brittleness, but these problems tend to be temporary and improve over time, says Dr. Victoria. (She adds that muscle spasms may respond to magnesium supplements and electrolyte infusions.) A small number of patients experience infusion-site reactions, and those with pre-existing inflammatory bowel disease should be monitored for flares. In addition, two less common but more serious adverse effects include:

- ***Hyperglycemia:*** In clinical trials, 10% of patients receiving teprotumumab (two-thirds of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycemia.[2] However, hyperglycemia reported in trials was generally mild and did not lead to discontinuation.[6] To mitigate this effect, clinicians should assess patients' blood glucose prior to initiating therapy and check it regularly. "It's so important to monitor for high blood sugar and for an ophthalmologist to co-manage the patient with an endocrinologist if they have underlying diabetes or prediabetes," says Dr. Victoria.
- ***Hearing loss:*** In the OPTIC trial, five patients developed hearing loss of different etiologies, but all resolved.[3] However, there have been case reports of long-term and possibly irreversible hearing impairment.[6] Patients should be referred to an otolaryngologist (ENT) for a baseline hearing evaluation and be monitored regularly. In the event of severe hearing loss, discuss whether to continue therapy. "At that point, you need to have a risk-benefit conversation with the patient and the ENT," says Dr. Victoria.

–by Tim Gower

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>
> *–Ana Carolina Victoria, MD, FACS*

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PATIENT ENGAGEMENT

5 WAYS TO HELP PATIENTS BUILD RESILIENCE

Expert strategies for supporting patients with TED and improving their quality of life.

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Illustration by Michael Morgenstern

Illustration by Gary Bates / Ikon Images

Thyroid eye disease (TED) impacts a patient's ability to do just about everything, says TED specialist Kimberly Cockerham, MD. "From using a cell phone and computer to driving and interfacing with people. But the most disturbing feature is the alteration of your skin, hair, eyes and face," says Dr. Cockerham, an oculoplastic surgeon, orbital expert, and surgical neuro-ophthalmologist. "Hair loss and change in skin coloration and alterations of the facial shape are devastating," she says.

In particular, TED has a major impact on psychosocial stability and quality of life. "The eyes are the key communicator when we talk to people—we look at their eyes," says Dr. Cockerham. "If you have ever had a stye or pinkeye, you will understand the huge impact having an eye problem can have on your self-esteem and ability to communicate."

Decreased quality of life, increased anxiety and depression

TED patients who report the lowest quality of life (QOL) suffer from a range of physical and psychosocial problems, says Dr. Cockerham, lead author of a study that examined QOL issues in U.S. adults with TED. In the 2021 study, published in *Ophthalmology and Therapy*, the most common persistent symptoms in patients with chronic TED included dryness/grittiness (47%), itchy eyes (43%), headache (33%), watery eyes (32%), light sensitivity (27%), blurry vision (25%), and pain behind the eyes (25%).[1]

The psychosocial impacts of TED have also been widely reported, notes Dr. Cockerham, and her study found the same types of problems. For example, mental health issues occur both in chronic TED and active, recently diagnosed TED. Anxiety and depression are also prevalent, with anxiety even more prevalent in patients reporting the lowest QOL.[1-6]

In addition, patients with chronic TED require frequent medical care, visiting healthcare providers an average of 20 times a year or more.[1,2] However, negative interactions with healthcare providers are common and also impact patient QOL.[6,7] "Physicians tend to underestimate TED facial alterations and the quality of life impact of TED," Dr. Cockerham says. "Impaired quality of life in TED patients persists for years after the inflammatory symptoms and signs have resolved, since their appearance and visual function remain affected."

> **"Physicians tend to underestimate TED facial alterations and the quality-of-life impact of TED."**
>
> ***—Kimberly Cockerham, MD***

While the physical and psychosocial effects of TED are substantial, treatment may help. "With the FDA approval of teprotumumab, there may be an option that improves quality of life in both active and chronic TED patients," Dr. Cockerham says.

In addition, as their healthcare professional, there is much you can do to help patients build coping skills to overcome the everyday challenges of living with TED. Dr. Cockerham suggests the following:

1. Advise them to educate family, friends and coworkers.

"When diagnosed with any serious medical condition, it is best to involve your friends and family so they can understand and support you as you go on your health journey," Dr. Cockerham notes. "Thyroid imbalance can cause brain fog, anxiety and depression. I tell patients to educate everyone in their network about the huge impact TED has on their ability to be productive and perform tasks of daily living both at home and at work."

2. Discuss ways to manage stress.

Dr. Cockerham coaches her patients with this pep talk: "Focus on being your healthiest 'you.' Avoid stressful situations, get at least 8 hours of sleep, stay hydrated and try to eat healthy foods," she says. She also advises them on how not to cope: "Turning to alcohol, marijuana or other drugs can worsen your ability to function."

In addition, Dr. Cockerham suggests avoiding taking on extra tasks and reducing work hours or converting to a virtual job if possible, especially if double vision or blurred vision is making driving difficult. "I tell patients, 'Give yourself a break, and learn to say no rather than taking on additional responsibilities at home and at work,' " she says.

This self-care extends to outside the workplace, adds Dr. Cockerham. "If you have people or relatives in your life that you find difficult, try to avoid socializing with those individuals," she advises patients. "Choose activities that make you calm, such as walking your dog." She also suggests patients consider taking up meditation and using apps like Headspace (*headspace.com*). The bottom

line for patients: "Find your relaxation tool, and use it every day," Dr. Cockerham says.

3. Emphasize the importance of restorative sleep.

A minority of patients with TED are hypothyroid, which may cause them to sleep more than usual or take naps, notes Dr. Cockerham. If that happens, she tells them "to go with this change in sleep pattern." In contrast, patients who are hyperthyroid often have difficulty getting to sleep or staying asleep for a full 8 hours. To improve sleep hygiene, Dr. Cockerham offers her patients these tips:

- Avoid caffeine and salty foods, especially at night.
- Practice a calming activity prior to sleep time.
- Create a comfortable, quiet sleep environment.
- Sleep with the head of your bed elevated to lessen pressure on your eyes.
- Discuss using melatonin supplements with your primary care provider as needed.

4. Refer them to a therapist or support group.

A professional mental health counselor or therapist can help patients talk through their feelings and the challenges that living with TED poses, notes Dr. Cockerham. In addition, she advises patients to join a support group for people with TED. "The Graves' foundation is an excellent starting place for patients and their families," she says. (Visit the Graves' Disease & Thyroid Foundation at *gdatf.org*.)

5. Encourage self-acceptance.

Perhaps most important of all, Dr. Cockerham says, is to encourage patients "to accept that you have a chronic disease that will take some time and medical or surgical interventions to get you feeling back to 'you.' Be patient."

A simple yet important piece of advice she offers: "Do not take prolonged looks in the mirror, especially not a magnifying mirror, and obsess about your facial and eye changes," she says. "Do buy fun glasses that make you feel more comfortable with your eyes. Be kind to yourself, and remember you are bound to have good days and bad days." ●

—by David Levine

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"Impaired quality of life in TED patients persists for years after the inflammatory symptoms and signs have resolved, since their appearance and visual function remain affected."

—Kimberly Cockerham, MD

PATIENT: CLAIRE, 37, WAS DIAGNOSED WITH GRAVES' 4 YEARS PRIOR, FOLLOWED BY THE DIAGNOSIS OF THYROID EYE DISEASE (TED)

"Claire's eye discomfort and severe change in appearance caused her great distress."

PHYSICIAN:

Lilly H. Wagner, MD

Consultant, Ophthalmic Plastic and Reconstructive Surgery, Assistant Professor, Department of Ophthalmology, Mayo Clinic, Rochester, MN

History:
When I first saw Claire, she presented with bilateral lid retraction, lagophthalmos, proptosis, lid erythema, conjunctival injection, chemosis and pain with eye movements. She had developed heat intolerance and facial swelling 4 years prior, and lab workup led to a diagnosis of Graves' disease. She had radioactive iodine therapy for hyperthyroidism and was prescribed levothyroxine. Her symptoms stabilized for 2 years, after which she started developing eye-bulging that continued to worsen.

Claire had had one episode of double vision, which resolved after she used artificial tears. She complained of constant eye dryness and started using cyclosporine ophthalmic emulsion 2-4 times a day in both eyes. Claire's bulging eyes were so severe that her eyelids would get stuck behind the globe. She had pain with upgaze, which improved over time. In addition to dry eye discomfort, her proptosis had caused a marked change in her appearance, to the point where she no longer wanted to be included in family photos.

A CT scan showed extraocular muscle enlargement, particularly of the medial and inferior rectus muscles bilaterally, as we would expect in thyroid eye disease. Her thyroid antibodies were elevated (TRAb 35, TSI 4.5), but thyroid hormone levels were normal. Claire, who has two children, developed TED symptoms postpartum.

Initiating treatment:
Although Claire had a known history of Graves' disease, it took 2 years after onset of eye symptoms for her to see a TED specialist. She had signs and symptoms of inflammation (CAS=4) and elevated antibody levels. Due to severe proptosis (Hertel 30/29 mm), I did not feel that orbital decompression surgery alone could correct her globe position. Her eye discomfort and severe change in appearance caused her great distress. I recommended teprotumumab because of the ongoing inflammation and, since she didn't plan further pregnancies, I explained the need for reliable birth control. We also discussed the risk of hyperglycemia and hearing loss. Based on her age and not having prediabetes, as well as having a normal baseline audiogram, I felt she was relatively low risk for adverse effects, and she agreed to start therapy. Claire also had a 6-month course of selenium after initial presentation. I modified her topical dry eye treatments and recommended lubricating ointment at night and a bedroom humidifier, especially during the dry winter months. She was not a smoker and had no secondhand smoke exposure. After 2-3 infusions of monoclonal antibodies, Claire reported improvement of eye pain and bulging. When the complete course of 8 infusions was finished, her proptosis was reduced to 26/25 mm (4 mm reduction). She felt better but was not quite back to her pre-disease appearance. She did not show signs of flare-up 6 months after the final dose, and she planned to have bilateral orbital decompression for residual proptosis.

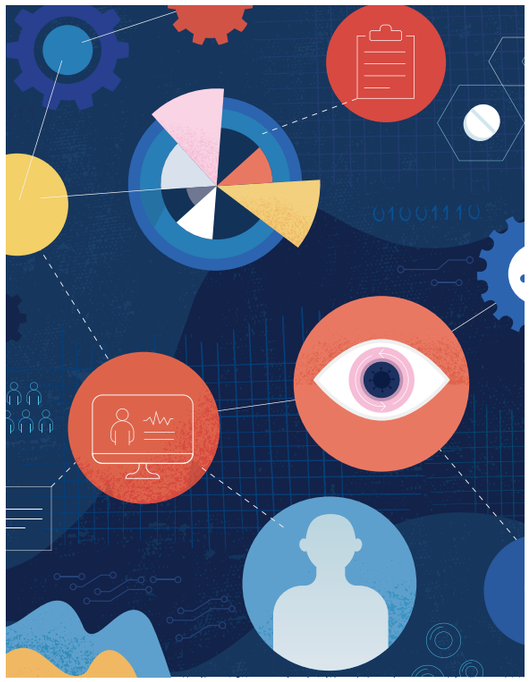
Considerations:
Claire's case demonstrates that TED treatment should be tailored to each patient. Patients with severe proptosis, and no indication for urgent orbital decompression due to dysthyroid optic neuropathy, can now start treatment of proptosis in the active phases of the disease. Later, rehabilitative surgery may achieve a more complete result in cases of severe proptosis if the patients are "pre-treated" with a disease-modifying medication. If the disease is moderate to severe, we may use monoclonal antibodies or corticosteroids. Our goal is to bring every patient back to the best possible visual function and quality of life. ●

Illustration by Juhee Kim

NEW!
KOL ON DEMAND VIDEO
Scan here for more insight on Claire's case.

Q&A

Insight on managing thyroid eye disease



Under-the-radar TED symptoms

Q: What TED symptoms are easily mistaken for other conditions? What are common red flags?

A: Thyroid eye disease (TED) can be challenging to diagnose. While objective data measures such as Hertel measurements and orbital imaging MRI or CT of the orbits provide support for the diagnosis, ultimately it is a clinical diagnosis based on clinical judgment of the provider. I find that patients who have very classic signs of TED, such as those with significant proptosis, lid retraction and signs of inflammation, are often diagnosed early. However, patients who have minimal inflammation or have an atypical presentation are often missed because they don't have the classic signs of redness and periorbital edema. And while dry eye can be one of the primary symptoms TED patients present with, it is often missed because dry eye is a common standalone condition. It is important to remember this is a heterogeneous disease with varying presentations. It is also important to uncouple a diagnosis of Graves' disease from TED. Although they are commonly found together, patients who are euthyroid or hypothyroid can also be diagnosed with TED.

Treatment factors

Q: What do you consider when treating TED?

A: Treatment is generally dictated by how the disease burden is affecting quality of life. The two key components of TED are visual impairment and cosmetic disfigurement. Coupled together, these conditions translate to a psychosocial burden and diminished quality of life. At a patient's initial visit, I introduce supportive measures such as using artificial tears for dry eye and reducing salt intake to help mitigate periorbital swelling. I also emphasize the importance of working with their endocrinologist to maintain a euthyroid state. Lastly, all patients receive smoking cessation counseling. I emphasize that treatment should be disease modifying and reverse some of the changes we see with TED. For me, the two treatment options available today are teprotumumab and surgery. I have an extensive conversation about the risks and benefits of each option and address each patient with an individualized approach. I tell patients these are all the tools we have in our tool kit to provide supportive measures and also modify the disease. The ability to offer teprotumumab in the early disease state has really created a paradigm shift in the management of TED.

Illustration by DrAfter123 / Getty Images

Illustration by Juhee Kim

Easing TED anxiety

Q: When patients are first diagnosed, what are their concerns and how do you allay their fears?

A: Autoimmune conditions can be quite scary and anxiety inducing for patients and there are two questions that often come up: 1. Why did I get this disease? 2. How do I know how bad it is going to get? There is a feeling of a loss of control which can understandably create a lot of fear and anxiety. I allow my patients to have the opportunity to share their fears about the diagnosis, and then we come up with a plan that can help mitigate some of their fears. I let them know that, yes, there is nothing they necessarily did to cause the disease, but there are things we can do to help decrease symptoms. I emphasize there are treatments that can help and go over their options. In addition, I always have a conversation about smoking cessation and lifestyle measures such as dietary modifications that can help patients with their symptoms. Gluten-free, dairy-free, and whole-food, plant-based diets are the types of diets I recommend. I always let the patient know these lifestyle modifications are not necessarily curative but can help them feel better. I also stress the 80/20 rule and that what works for one person may not work for another. A patient may come back to me and say they tolerated gluten okay but they noticed a significant improvement with eliminating dairy. It is about balance.

Understanding the cosmetic burden

Q: Are there any aspects of living with TED that may be underappreciated by HCPs?

A: I think understanding that each patient's TED journey is unique is important to understand. For one patient, their dry eye symptoms may be reducing their quality of life significantly. Another patient may be more affected by orbital pain. I also think HCPs should discuss cosmetic disfigurement and ask patients if they are bothered by their change in appearance. Patients are often fearful of bringing this up during a medical appointment, so if a provider initiates, it may make the patient feel more comfortable to open up about the psychosocial burden of looking in the mirror and not recognizing themselves. When a patient opens up about their facial disfigurement and vulnerabilities, I always validate how they feel. It's important to recognize the impact of what they are going through. It is important to recognize for both male and female patients that a change in appearance due to thyroid eye disease is not a trivial issue. I also stress that undergoing cosmetic procedures to reverse what this disease has done is not something to be embarrassed about. We then discuss what treatment options are available. Small interventions such as sleeping with an extra pillow or using a nice eye cream may help mitigate eyelid swelling. I also bring up the conversation of the types of surgery that are available to help address these symptoms. We discuss surgical options including orbital decompression and upper and lower lid blepharoplasty. All patients who undergo surgery have a customized approach tailored to their concerns and their clinical exam. Often, surgery is a blend of functional and cosmetic procedures to help meet the patient's goal.

OUR EXPERT

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Clinician Update

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EXAM TOOL

THYROID EYE DISEASE (TED) ASSESSMENT

The effects of TED not only cause debilitating eye symptoms such as pain, proptosis and chronic dryness, they also impact every area of a patient's life, from their ability to work to their confidence when socializing. While TED is closely linked to Graves' disease, they are distinct diseases that require co-management by a TED eye specialist and an endocrinologist. To ensure timely diagnosis and treatment, guidelines from the American Thyroid Association and European Thyroid Association recommend evaluating patients with Graves' for signs of TED at each eye exam, based on the criteria below.

ASSESS DISEASE ACTIVITY

Does the patient have any of the following signs of TED?

- ☐ Spontaneous retrobulbar pain
- ☐ Pain on attempted up or lateral gaze
- ☐ Redness of the eyelids
- ☐ Redness of the conjunctiva
- ☐ Swelling of the eyelids
- ☐ Inflammation of the caruncle and/or plica
- ☐ Conjunctival edema, also known as chemosis

ASK PATIENTS ABOUT THEIR QUALITY OF LIFE

Do your eye symptoms interfere with any of the following?

☐ Driving ☐ Computer work ☐ Reading ☐ Watching television

Do your eye symptoms affect your ability to work or socialize?

☐ Yes ☐ No ☐ Sometimes

Are you bothered by changes in your appearance because of your eye symptoms?

☐ Yes ☐ No ☐ Sometimes

Have you felt depressed or anxious because of your eye symptoms?

☐ Yes ☐ No ☐ Sometimes

Source: Burch HB, et al. *Eur Thyroid J.* 2022;11(6):e220189. Note: Not complete. For full guidelines, visit *thyroid.org*.