A NEW FRONTIER IN THE CO-MANAGEMENT OF THYROID EYE DISEASE

Overview

Thyroid eye disease (TED), also known as Graves' orbitopathy, is a potentially serious, progressive autoimmune disease that most often occurs in people with hyperthyroidism, ie Graves' disease. Kimberly Cockerham, MD, moderates this series of 6, paired conversations between endocrinologist Terry J. Smith, MD, and eye specialists Wendy W. Lee, MD, and Raymond Douglas, MD, PhD, to explore current and emerging treatment options for thyroid eye disease. In these conversations, faculty review the current understanding of the burden and pathophysiology of thyroid eye disease—including treatment targets—and describe the key features of thyroid eye disease and how they are different from other diseases of the eye. Faculty explore the role of nonpharmacologic, pharmacologic and surgical options for thyroid eye disease and discuss how to implement strategies that help patients with thyroid eye disease improve their quality of life.

Content Areas

- Burden of Disease
- Pathophysiology
- Patient Evaluation
- Nonpharmacologic Treatment
- Pharmacologic Treatment
- Clinical Trial Experience
- Surgical and Radiation Treatment

Faculty

Moderator

Kimberly Cockerham, MD
Adjunct Clinical Associate Professor
Stanford University School of Medicine
Central Valley Eye Medical Group
Stockton, California

Endocrinologist

Terry J. Smith, MD
Frederick G.L. Huetwell Professor
Ophthalmology and Visual Sciences
Professor, Department of Internal Medicine
Kellogg Eye Center
Ann Arbor, Michigan

Eye Specialists

Raymond Douglas, MD, PhD
Professor of Surgery
Division of Ophthalmology
Director, Orbital and Thyroid Eye Disease Program
Cedars-Sinai Medical Center
Los Angeles, California

Wendy W. Lee, MD
Professor of Clinical Ophthalmology and Dermatology
Director of the Bascom Palmer Aesthetics Center, Palmer Eye Institute
University of Miami Miller School of Medicine
Miami, Florida

Target Audience

This activity is intended for a national audience of endocrinologists, ophthalmologists and other clinicians who diagnose and treat patients with thyroid eye disease.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Describe the current understanding of the pathophysiology of TED, including targets for treatment
- Describe key features of TED and how they are different from other diseases involving the eye
- Describe the role of nonpharmacologic, pharmacologic, and surgical options for TED
- Implement strategies to help patients with TED improve their quality of life

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Kimberly Cockerham, MD
Consultant: 3T Ophthalmics, Horizon Therapeutics, Viridian
Research support: Horizon Therapeutics

Raymond Douglas, MD, PhD
Consultant: Immunovant, Horizon Therapeutics, Valencia bio, Viridian
Employee: Osmotica
Research support: Horizon Therapeutics
Speakers bureau: Horizon Therapeutics

Wendy W. Lee, MD
Consultant: Allergan, Bausch Health, Galderma, Horizon Therapeutics, Mallinckrodt, Osmotica, Revance

Terry J. Smith, MD
Consultant: Horizon Therapeutics
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The estimated time to complete the activity is 1.25 hours.

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CONTACT INFORMATION
For help or questions about this activity please contact Continuing Education:
ce@annenberg.net

Abbreviations

CAS = clinical activity score
EUGOGO = European Group on Graves' Orbitopathy
FT4 = free thyroxine
GO-QOL = Graves' Orbitopathy Quality of Life
IGF-1 = insulin-like growth factor
MMF = mycophenolate mofetil
PTU = propylthiouracil
T3 = thyroid hormone
TED = thyroid eye disease
TRAB = thyrotropin receptor antibody
TSH = thyroid stimulating hormone
TSHR = thyroid stimulating hormone receptor
TSI = thyroid-stimulating immunoglobulins

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Introduction

Kimberly Cockerham, MD: Welcome to *A New Frontier in the Comanagement of Thyroid Eye Disease*. This CME activity is certified to provide continuing medical education for endocrinologists, ophthalmologists and other clinicians with an interest in thyroid eye disease.

As you know, thyroid eye disease is often associated with Grave's ophthalmopathy. It's a potentially serious and progressive autoimmune disease that occurs in patients living with hypothyroidism, euthyroidism and hyperthyroidism. In these 6 short modules, we'll be presenting some information through a casual conversation with our faculty.

We'll first describe the current understanding of the pathophysiology of thyroid eye disease, including the targets for the treatment. Second, we'll describe the key features of thyroid eye disease and how it is different from other diseases of the eye. Third, we'll describe the role of nonpharmacologic, pharmacologic and surgical options for thyroid eye disease. And fourth, we'll implement strategies to help patients with thyroid eye disease improve their quality of life.

As moderator, I'll go ahead and introduce each module, ask the initial question, let our panelists battle it out, chat about it and the faculty will share their expertise and their perspectives on the burden and pathophysiology of thyroid eye disease, screening and diagnosis of thyroid patients, and finally the medical and surgical treatment options.

Module 1 – Burden of Disease

How rare is thyroid eye disease and what is it?

Terry J. Smith, MD: The frequency and prevalence data for TED are not particularly revealing or accurate, given the fact that of course it's not a reportable condition. You know, it's known by several different names which, in and of itself, can cause confusion, even among those of us who routinely take care of these patients. Thyroid eye disease, thyroid-associated ophthalmopathy, Graves' orbitopathy are all pretty much equivalent terminologies indicating the same clinical entity.

Autoimmune eye disease or TED is just that. It's an example of how the immune system misidentifies self as foreign. It's a progressive disease that begins with an active phase and then lingers for anywhere from 12 to 36 months, progressing, and then becomes what we commonly refer to as the stable or nonprogressive phase of the disease. The active phase, of course, is highlighted by inflammation and tissue remodeling and, most importantly, change from one day to the next.

The incidence of Graves' eye disease or TED is said to be around 16 per 100,000 females with an incidence in males of about one-fifth that number.

What are the clinical implications of TED for patients?

Wendy W. Lee, MD: I'll start with the fact that thyroid disease and thyroid eye disease has a huge psychosocial impact on patients' lives, even for those who are undergoing variations in their thyroid levels. They can undergo distress, anxiety. They can be really on edge and then, you know, when you have a change in your appearance from these manifestations of thyroid eye disease, you can have anger and lack of self-confidence. And I think that our own moderator, Dr. Cockerham, was the lead investigator on a study that actually looked at quality of life and found that up to 50% of

patients with thyroid eye disease actually suffer from depression and other mental illness. It's a real thing and it's a big thing to pay attention to.

How it affects the eyes in general, we know—and we'll talk more about this later in the modules—that patients often come in with eyelid retraction, proptosis, ocular misalignment and so that leads to the whole change in appearance that can also lead to some of these mental illnesses or mood instability.

I find it important, as clinicians, to really identify with our patients and really let them know that this is a journey that we're going to be there with them for long term. It's not just one visit, it's not 2 visits, it's really a long-term thing and we're going to be by their side to help them through this. We're going to manage their thyroid, we're going to manage their eye disease and then, in addition, there are a lot of different support groups. I like to tell my patients there are support groups through different societies and there are also groups on Facebook and social media of patients who are suffering from the same types of issues and they're both for the patients and for family and friends who are living with patients with thyroid disease and thyroid eye disease. I think that's really important to let our patients know as well.

What is the traditional course of the disease?

Terry J. Smith, MD: The typical course of TED was immortalized to the literature by Rundle in 1945 as a crescendoing process, activity or progression which continues anywhere from a few months to 3 or 4 years and then plateaus so that things stop changing and, instead, we believe that the underpinnings of the stable or nonprogressive disease then persist, perhaps lifelong. And immunologically, there seems to be some divergence from the clinical course in that probably the immunologic events that really are proximate to the cause of the disease, such as the loss of immune tolerance both within the thymus and peripherally, occur months to years before any clinical manifestations occur.

Now, many of the audience, I think, correctly and tightly associate TED with Graves' disease of the thyroid and most of us, in this space, believe that there are important common threads to the pathogenesis of the disease. Importantly, both clinically important, TED and the hyperthyroidism which frequently accompanies the disease occur sometimes at very different times. Sometimes with decades intervening between the development of one vs the other. The important thing is that we need to consider TED apart and separate from thyroid Graves' disease with regard to the appropriate therapies and the potential impact of 1 therapy, for instance directed at controlling hyperthyroidism, with that of the course of TED.

Kimberly Cockerham, MD: Let's wrap up module 1. We were talking about the burden of disease and I think we nicely overviewed that this is a tough disease. It's affecting patients in their most productive work years, it's causing psychosocial issues, it's creating a burden that can be decades long and it has different manifestations in each patient, that each patient has a more acute phase with greater unstability, changing day to day, and then often have a chronic, inactive phase that's just as burdensome in the sense that they feel altered, they feel depressed, anxious, their eyes don't function as they should.

Module 2 - Pathophysiology

Kimberly Cockerman MD: In module 1, we talked about the burden of thyroid eye disease for patients and their families. In module 2, we're going to explore the pathophysiology and risk factors for thyroid eye disease.

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What is the cause of thyroid eye disease?

Terry J. Smith, MD: This remains a highly contested and uncertain question to answer adequately. Importantly, as I mentioned in module 1, the underpinnings of TED are thought to be the loss of immune tolerance centrally, that is within the thymus, and peripherally, to critical autoantigens. Among these are the TSH receptor and the IGF-1 receptor, but there's a lot more to TED than just the autoantibodies that circulate in patients and the levels of which appear to at least roughly parallel the activity and severity of TED.

We must also include, as suspects in the disease, activated T-cells and B-cells and their communication with antigen-presenting cells, cells like fibrocytes and monocytes and macrophage and dendritic cells.

Now, one of the current concepts has to do with the fact that maybe TED, the inflammation, the tissue remodeling and the immune responses that directly activate tissues in the orbit, are confined to that space, in those tissues, when, in fact, we're now beginning to realize that TED, in and of itself, is a systemic autoimmune process and that TED itself is merely a local manifestation of something that's occurring, essentially, throughout the entire body.

Now, central to the disease itself is the IGF-1 receptor which not only plays a role as a coreceptor with the TSH receptor, but also there is cross talk between the 2 receptor proteins, and the IGF-1 receptor probably has direct actions that are independent of the TSH receptor in activating downstream cell-signaling cascades and the upregulation of responsive genes which encode, then, the proteins that are involved in the actual manifestations of the disease within the orbit.

Mast cells and helper T-cells also play important roles with regard to their cross talk, activation and promotion of tissue remodeling. The TSH receptor and the IGF-1 receptor are over-expressed, not only within the orbit, also by circulating lymphocytes. And thus we should think of the IGF-1 receptor and the TSH receptor as commingling important molecular information, sharing that information, if you will. And we need to begin to think of the pathogenesis of TED very much like we think of the disease that occurs within the thyroid gland itself. And because of all of this, one of the first issues to be confronted by the clinician is the timely reregulation to normal thyroid function because we know that excursions above and beyond the normal range of thyroid hormones and TSH have a deleterious impact on the course of TED.

What are the known risk factors in thyroid eye disease?

Raymond Douglas, MD, PhD: First, we can start with at least talking about genetics. Now, there is no single genetic test or over-expression mutation that is associated with the development of thyroid eye disease; however we do know from family studies and concordant studies, even in identical twins, that there is a genetic association of this disease, often as much as 30%. Clinically, that means that this runs in families, so to speak, and there is an increased predisposition. Also, likely with a genetic basis, but, you know, hypothesizing. There's also usually an increase of other autoimmune diseases associated with thyroid eye disease and Graves' disease and so it's important to at least consider other autoimmune processes as patients present.

Now, who gets thyroid eye disease? You know, diving into the risk factors more, as Dr. Smith mentioned a little bit earlier, women get this disease more than men and the rate has been

anywhere from 3- to about 7-fold and about 5-fold more frequent for women than men is pretty common. Now, men, when they do get this disease, tend to get a much more severe version of the disease. It can actually be a bit more difficult to control as far as medical and even surgical treatment because the disease can be more severe.

We know that all forms of smoking and tobacco increase the risk of developing the disease, but also make the disease much more recalcitrant to treat. One of the first factors that we can use to intervene, that I've mentioned thus far, is to absolutely encourage patients to stop smoking and to stop using alcohol. I think it's very important to make that recommendation for patients.

Radioiodine therapy has been controversial in the past and has been associated with an increased risk of thyroid eye disease for these patients. Typically this risk is offset with the use of concomitant steroids with radioactive iodine, but it really has to be discussed in detail on a patient-by-patient basis that this risk can be increased anywhere from about 10%–15% as far as the likelihood of worsening eye disease. And certainly, if someone has moderate-to-severe eye disease, the use of radioactive, radioiodine therapy should really be considered very carefully amongst the options for thyroid management.

Other associated risk factors include advancing age. This is not something people outgrow and advancing age can be a little tricky as far as a treatment standpoint in that you want to use less and less aggressive treatments as these patients get older. Also, many patients have reported stress, family events, etc, that they will attribute to the onset, and there is a high correlation, though this has been difficult to prove in studies. Finally, poorly controlled thyroid function is definitely associated with worsening eye disease, especially in some studies that have gender, demonstrated that increased TSH levels or hypothyroidism has been associated with worsening eye disease. Control and proper control of thyroid function is very important, whether that be medical or surgical.

Kimberly Cockerham, MD: Let's wrap up module 2. The first part was a little dense. It's hard if you're not an immunologist. There's coacting, colocated IGF-1 and TSH receptors that are the bad guys. B-cells, T-cells, lymphocytes, mast cells, are all involved. The bottom line is there's definitely risk factors, so this is a local manifestation of a systemic autoimmune disease that's definitely worse in women. We don't want our patients smoking or even chewing tobacco. We want to try to avoid things like stress. Sometimes patients need to change their job to actually get over this. We want to have our endocrinologists try to control their thyroid function. At the end of the day, this is a disease with significant burden and very complex pathophysiology that creates a disease that can be very difficult to manage.

Module 3 – Patient Evaluation

Kimberly Cockerham, MD: In module 2, we reviewed the pathophysiology of thyroid eye disease and also the risk factors that make it worse. In this module, we're going to explore how patients present with thyroid eye disease and the best practices for your patient evaluation and your therapeutic interventions.

How do patients present with thyroid eye disease?

Wendy W. Lee, MD: Thyroid eye disease patients present with a gamut of findings, from dry eyes all the way to compressive optic neuropathy. Talking about the dry eye aspect, a lot of my patients will come in with photophobia and tearing and foreign body sensation that

indicate that their eyes are dry. Sometimes, they come in with periorbital inflammation. They may come in seeking a blepharoplasty and you look and they've got soft tissue swelling around their eyes and fat prolapse. I think that's important to look at as well as eyelid retraction, which is very, very common, as we know, in thyroid eye disease. They may have proptosis. They may have diplopia, so you may find that you're examining them and their eyes don't move as well, they may complain of diplopia and then they may just complain of colors not seeming as bright because they have color desaturation. They may have vision loss as well.

What is the differential diagnosis for thyroid eye disease?

Terry J. Smith, MD: Identifying TED can be challenging, especially in the patient without a diagnosis already being made from, for instance, their clinical hyperthyroidism or the enlargement of their thyroid glands which certainly then increase the suspicion that one is dealing with TED. Other processes that certainly have substantial clinical presentation overlap, depending upon the specific symptomatology and signs that Dr. Lee has just referred to in the presentation, would include things like orbital cellulitis, IgG-4 disease if, in fact, it exists as a discrete entity, idiopathic inflammation, rarely Cushing's disease, myositis, myasthenia gravis especially in patients with problems with motility or eyelid movements, orbital tumors, especially in those TED patients who have unilateral disease or highly-asymmetrical disease. All of these, I think, come into play in one's consideration that we're dealing with TED.

Now, in terms of how one goes about getting through all of these possibilities. Certainly, there's nothing more important than a thorough eye examination, looking for proptosis, examining tear film and adequacy, looking for periorbital edema. Certainly, imaging of the orbits is critically important, in many cases defining the tissue compartments that are involved, the EOMs vs the connective adipose tissue compartment.

Laboratory examination should include a second-generation serum TSH, FT4 and T3 and, certainly at initial evaluation, determining whether detectable anti-TSH receptor antibodies, TSIs, TRABs, are present. These will all certainly make a diagnosis of TED more likely. And, in terms of disease severity, looking at the extent of proptosis, if it's present, looking at motility of the globes, diplopia, all of these things are particularly important.

How do endocrinologists and ophthalmologists differ in their approach to patient evaluation?

Wendy W. Lee, MD: I do think there's a lot of overlap between endocrinologists and ophthalmologists with how we evaluate thyroid patients. For instance, like the things you just mentioned, evaluations of the eyes and some of the labs and some of the imaging studies. I do strongly feel that the endocrinologist is key to the initial diagnosis and management of patients because endocrinologists are seeing dysthyroid patients frequently. You're the ones who are diagnosing it and counseling patients on smoking cessation, maybe using radioactive iodine, possibly even looking at surgical options and I think that it's also, you know, that many endocrinologists are very good at looking for early signs of thyroid eye disease. It's very easy to look and see if a patient has proptosis, looking for corneal exposure just by looking at lagophthalmos, can the patient close their eyes or not. I think that you can evaluate actually with color plates, you can use Ishihara plates, check an APD to see if maybe the optic nerve is affected and then, if there are signs of thyroid eye disease, then I would recommend a full ophthalmic evaluation where we would come in and do visual field testing and maybe get more

specific, you know, do an indirect ophthalmic exam, get some measurements.

If someone's, let's say, a general ophthalmologist or non-oculoplastic, non-endocrinologist, when do you refer out? Well, I think that if you're managing patients with thyroid disease, then if you see patients with thyroid eye disease and it starts to tip over into maybe the sight-threatening signs, feel free. You know, we're always happy to see patients and evaluate whether they need intervention. I think that the endocrinologist is a key player in helping manage a euthyroid state and honestly, for me, comanagement is the best. I like to work with the endocrinologists in the management of my thyroid patients, whether they're stable or whether they have sight-threatening disease. I think it's really important to have a team of players in the management of these patients.

Terry J. Smith, MD: Dr. Lee, I suspect that you and I, by virtue of the fact that we both practice in academic medical centers and therefore work cheek to jowl with multiple specialties, probably our referral patterns are handled with greater facility than those of our colleagues in the community, but I certainly agree with you that the comanagement pattern of practice seems to optimize the patient experience.

Wendy W. Lee, MD: I agree with you, because I think that, in an academic center, it's easier because we have all the teams there assembled in the same academic institution, but I have definitely made connections with private practice endocrinologists, those who specialize in thyroid disease, and so it's been nice for my patients to just connect and I think it helps to make those connections, as well, outside and inside the university.

Kimberly Cockerham, MD: Let's wrap up module 3. I think what we've heard is that ideally this is going to be a comanagement situation, but I think from the standpoint of ophthalmologists and other specialists, it's just listening to the patient. A lot of times, patients, by the time they come to see one of us, they've seen 5, 6, 7 different care providers who've actually missed the diagnosis. I think getting a sense of that look, the look of thyroid eye disease which has proptosis, lid retraction, that gives that kind of stare combined with the conjunctival injection and chemosis, sometimes dysmotility that's worse in the morning, that that look is something that the earlier you recognize it, the earlier the patient's referred for the appropriate support and intervention, the better the patient's going to do from a psychosocial standpoint. Certainly, community physicians can pair with academic physicians, and definitely getting the whole patient treated is super-important and, as you've heard, the workup is definitely going to include some laboratory evaluation and a CT scan of the orbits. If you're an endocrinologist and you are seeing a patient who has symptoms of any kind, burning, tearing, irritation, double vision, it's really important to get an ophthalmologist involved who can do the complete exam and make sure the patient doesn't have, for instance, an occult optic neuropathy, as was described by both Dr. Lee and Dr. Smith. Super-important, the more we can work together, the better for the patient.

Module 4 – Treatment

Kimberly Cockerham, MD: In module 3, we reviewed the patient evaluation and differential diagnosis of thyroid eye disease. We talked about the importance of comanagement. In module 4, we're going to move on to explore the treatment options. The clinical course of thyroid eye disease can be highly variable.

When do you recommend intervention in the treatment plan for patients with thyroid eye disease?

Raymond Douglas MD, PhD: Not only is the course of this disease highly variable from patient to patient, but the impact of that variability, and what symptoms each has, impacts their life quite differently. For example, if someone is largely retired and not driving or something, the impact of double vision will be much, much less than if someone is actively driving, in their 30s and doing other aspects at work, including computer use.

The first thing that I think of when establishing a goal for therapy is thinking about what is the risk vs benefit and what do I really want to achieve. If we're just going to achieve symptomatic relief, that could be very important for someone who has just chronic swelling and chronic discomfort, etc, and that could be a very realistic goal for short-term symptom relief in an active stage vs someone else. The first thing is let's look at the risk and benefit for these patients and thinking also about their concomitant other diseases which include diabetes, etc, and really establish and speak to the patient as far as what part of this disease is inhibiting their life the most. I think that really helps to define goals for therapy as we move forward.

Then, as we think about the disease itself, we can break that down into the early stages or active and progressive disease vs how severe this disease is. When we think about early and progressive disease, we often think about medical therapies. We often think about comanagement, especially working with my endocrine colleagues. And I know Dr. Smith will talk more about this. We want to make sure that each of the medical aspects in their lives that are part of the Graves' disease and are separate from Graves' disease are being addressed properly for their medical condition. Then to think about if we're going to use medical therapy early in the disease, what is our goal? Is our goal to improve symptoms? Is our goal to improve the underlying biologic process that has occurred, the proptosis, double vision, etc? Then, looking at severity. If it is mild—which often doesn't require these types of intervention, you know, especially in the active phase—we can often use supportive therapy, artificial tears, etc, especially once we know the dry eye may be a very important component interfering in their lives. In moderate, and much more severe diseases, we want to start to think about processes that have a higher potential for both achieving a reduction in severity but may also have a higher potential for adverse events, such as biologic treatment, medical treatments that can help to reverse this disease.

For me, it's taking into account the entire medical management. Then also thinking about the disease activity, whether we can use medical therapies or whether—also thinking about the severity of disease, mild vs more moderate and severe, and then even in, in rarer cases, vision-threatening disease—how we can partition those treatments to make sense, you know, in a reasonable risk and benefit manner.

How do you approach therapy selection for patients with thyroid eye disease?

Terry J. Smith, MD: I thoroughly endorse the notion that patients need to be provided personalized considerations and none of the decisions that we make in this disease is more important than what therapies should be applied. Certainly, those individuals with what we term mild disease deserve every consideration for ameliorating the symptoms that they may be experiencing, but also they should be carefully followed at regular intervals to make certain that the disease severity isn't on the upswing because, as was mentioned earlier, the sooner we recognize more severe disease, I think the greater impact we have on the management of our patients.

Now, for me, as an endocrinologist, one of my first tasks is to control any excursions of thyroid functions, either those that have to do with hyperthyroidism or hypothyroidism. As mentioned earlier, it seems as if elevations in serum TSH, which are characteristic of primary hypothyroidism, seem to have a particularly negative impact on both the activity and the severity of the disease. I'm going to institute medical therapy most likely early on in the recognition of either hypo- or hyperthyroidism and, for me, the first thing that I reach for in my hyperthyroid patients, which account for approximately 85% or 90% of those with newly developed Graves' disease, antithyroid medications. Most frequently that's going to be methimazole given the comparative adverse effects of that compared to PTU. I'm going to strive to get the patients back to normal or euthyroid function and then, from there, I have the panoply of currently available medications for mild disease.

It's my clinical style to not use glucocorticosteroids particularly frequently unless I'm dealing with a highly symptomatic patient with mild disease. There are those, especially in Europe, but the practice has now spread across the Atlantic, for empirically starting patients on over-the-counter dosages of selenium. This is really most impactful in those individuals who live in a geographically low selenium soil content. But certainly, at these dosages that we're talking about, one is not going to do any harm, and it may have salutary effects.

The hyperthyroidism should really be governed not only by getting the serum thyroxine and triiodothyronine levels into the normal range, but also to normalize, as quickly as possible, serum TSH, which of course can lag relative to normalization of the thyroid hormone levels. Then, I don't think that we can overlook the potential benefit of local measures. For instance, I certainly admonish my patients to avoid desiccating conditions, such as wind and high, dry temperatures, especially in the summertime. I suggest that they wear wrap-around sunglasses. I spend a good part of the clinical session, especially with newly presenting patients who smoke, with the great importance of curtailing their tobacco use. I can think of no more important correctable factor in our tool kit than having our patients quit smoking and doing so as quickly as possible.

How do you evaluate treatment responses?

Raymond Douglas, MD, PhD: I won't discuss individual treatments, but rather I'll try to focus upon the evaluation. I break it down in thinking about the symptoms vs measurable endpoints. And symptoms primarily wrap around the swelling, inflammatory symptoms that patients feel and see in the mirror. These are primarily encompassed with dry eye symptomology. Certainly, encouraging those topical treatments, having a discussion about tearing and dryness, can really dramatically improve their outcome and those are mostly assessed for me in a discussion as far as their history and how they've been doing since the treatment has been instituted.

Proptosis reduction is largely evaluated by Hertel exophthalmometry. It's relatively easy to learn, if there are those have not tried it, and it's a good way of really determining progression and disease from time point to time point. This can be really helpful as far as thinking of surgical interventions, but also giving advice to the patient. In a very similar manner, is the extraocular movements. It's a little more difficult to measure strabismus if you're not accustomed to it, but certainly always evaluating extraocular movements, evaluation double vision in various gazes, even qualitatively, I think is something to do over time.

Finally, looking at how this disease is progressing, whether that's an activity of swelling, etc, and the patient is often very insightful as far as knowing whether the swelling and the disease activity has reached a point of stability and that agrees with your exam or whether it hasn't. Certainly taking into consideration their feedback and what they think as far as how this treatment has been effective or is impacting the disease is in large measure something that I utilize in helping to guide us forward. Finally, in evaluating any treatment, we always have to think of risk and benefit. And the risk is primarily around toxicity, adverse events, a little bit of a large topic to dive into, but always has to be a consideration for these patients because sometimes we're using systemic measures that have systemic effects and we certainly want to make sure that we're not inducing anything untoward for these patients.

Kimberly Cockerham, MD: Let's wrap up module 4. I think it comes down to that you have to tailor the treatment to the patient. I've literally had patients tell me who have pretty massive proptosis, "Mom looked like this. I'm good." You really don't want to push people towards things that are not important to them. As far as the mitigating things, we talked about the super important, they need to stop smoking, they need to try to avoid stress, they need to avoid environmental issues like wind, sun, that sort of thing, but one thing we didn't talk about was sleep. A lot of times these patients, their eyes open up while they're sleeping and it basically exacerbates the morning-time dry eye symptomatology. Just a simple sleep mask can be super-helpful for these patients. Again, just the bottom line, look for thyroid eye disease, ask about thyroid eye disease, think about thyroid eye disease. In not every patient who has dry eye symptoms is it just dry eye.

Module 5 – Clinical Trials Experience

Kimberly Cockerham, MD: In module 4, we began to explore the treatment options. In module 5, we'll dig a little bit deeper into the recent clinical data around teprotumumab. Teprotumumab was approved as Tepezza in January of 2020. Dr. Lee, what were the characteristics of patients in the key trials? What was the approval based on? What kind of concrete information can you provide to our audience about the clinical trials and where you are now with Tepezza?

What clinical data support the approval of teprotumumab?

Wendy W. Lee, MD: The approval was based on 2 key trials and I'll just describe the patient characteristics from those trials. The patients were from age 18 to 75 in the first trial, 18 to 80 in the second trial. The patients in both trials had to have a CAS of equal to or greater than 4, so active, so moderate-to-severe disease, active thyroid eye disease. These patients usually presented with eyelid retraction, soft tissue swelling, proptosis, things we see a lot. Sometimes diplopia. These patients basically had to have an onset of symptoms that was within 9 months from baseline. They had to be euthyroid. There were specific criteria and had to be within 50% above or below normal range. These patients could not have had any surgery related to the thyroid or radiotherapy, and then they could have had steroids, but it had to be less than a gram.

How does that compare to the patients that we normally see present to our clinics? I'll say that from my experiences and those of my colleagues, I think that encompasses a lot of our patients, but we also see patients who fall out of that range because we see a lot of chronic patients. Our patients who may have had thyroid disease for much longer than 9 months.

Our patients who have had many of the same symptoms, such as eyelid retraction, diplopia, proptosis, they come in and they're stable and they've had that and they don't have active disease. They don't have CAS of 4 or higher. I often see CAS of 0 to 3, but they have proptosis and they might have diplopia, but it just hasn't changed. I think that's the difference in our daily practices and the patients we see. Some are overlapping, but I think we really need to focus on and also address the patients who don't fall within that range of what the clinical trials included and be able to offer them something as well.

How was efficacy assessed in the teprotumumab trials?

Terry J. Smith, MD: The trial design was a placebo-controlled, double-masked trial, 2 treatment arms. Half of the patients received placebo, half received teprotumumab. The primary and secondary responses were adjudicated at week 24, following 8 infusions, given at 3 weekly intervals. The primary response in the initial phase 2 trial was the aggregate of the following: a reduction of 2 or more points on a 7-point CAS scale and a 2 or greater mm reduction in the study eye without similar worsening in the fellow eye. The phase 3 or the second trial, the primary response was simplified to improvement from baseline of 2 or more mm of proptosis in the more severely affected eye.

Now, the effects of therapy were rapid and substantial so that within 6 weeks—that is within the initial 6 weeks where patients received a half test dose initially and then at 3 weeks the first full dose of the teprotumumab—already, at 6 weeks, 56% of patients receiving active drug had achieved the primary response compared with 7% of those receiving placebo. The divergence between the response curves continued to grow so that at week 24, when the primary and secondary responses were judged, 83% of patients had achieved the primary response of those receiving teprotumumab vs 10% of those in the placebo group. The secondary responses included improvement in proptosis, that is reduction of 2 or more mm from baseline; the improvement or reduction in CAS of at least 2 points from baseline, both measured as independent variables; improvement of at least 1 Gorman point in the diplopia scale and improvement in quality of life as assessed by a fully vetted instrument called GO-QOL.

Now, importantly, at week 24 in the group receiving teprotumumab or Tepezza, the proptosis reduction averaged 3.32 mm in the study eye compared with 0.53 mm in the patients receiving placebo.

The main safety signals from both trials included most commonly muscle spasms frequently involving the lower extremity, nausea, alopecia, mild diarrhea, fatigue which was generalized, hyperglycemia especially in those individuals who had baseline carbohydrate intolerance or diabetes mellitus, and hearing abnormalities which included tinnitus or reduction in auditory volume and some, but not all of these abnormalities, had self-corrected and disappeared within weeks of the final dose of teprotumumab.

What other therapies are emerging with clinical benefit for patients with thyroid eye disease?

Wendy W. Lee, MD: I think that there have been so many different drugs, I feel like, that have been studied and are still being studied for this difficult-to-treat disease. I'll go over a few of them. There are many. Rituximab is an anti-CD20 monoclonal antibody that targets and decreases B-cells. Rituximab has been used in different disease processes. As far as thyroid eye disease goes, there were 2 main conflicting trials that had different results. So that the bottom

line is there's no clear evidence that rituximab will improve the course of thyroid eye disease.

Next there's tocilizumab. Tocilizumab is an anti-IL-6 monoclonal antibody and IL-6, as we know, is a potent proinflammatory cytokine. There was a small study out of Spain that showed that tocilizumab actually reduced some of the soft tissue findings, so some of those CAS scores. There was very little improvement in proptosis, only about 1.5 mm. There was actually no change in diplopia or quality of life, so there was also no long-term benefits of tocilizumab.

Next there's mycophenolate which a lot of people talk about. Mycophenolate is an immune modulator that inhibits B- and T-cell proliferation and it might have some antifibrotic capabilities as well. There were a couple of studies on mycophenolate, one was early on in the early 2000s, a study out of China that looked at MMF vs glucocorticoids and they found that mycophenolate actually did improve the inflammatory signs out to 24 weeks. Then, EUGOGO, the European group, did another study which compared glucocorticoids vs glucocorticoids plus MMF. What they found was that there was a superior response out to 36 weeks in the combined group. Of note is that neither of these groups had an improvement in proptosis and both were equal in quality of life and diplopia.

There are a couple of new ones I'll mention. Belimumab is an anti-B-cell activating factor monoclonal antibody and B-cell activating factor is responsible for promoting B-cell survival and maturation. That's a brand-new drug that's undergoing ongoing trials right now. Fingolimod is an immune modulator that targets sphingosine 1-phosphate. Sphingosine 1-phosphate is thought to be a key player in the pathogenesis of orbitopathy. There have been studies in mice which show that these animals were actually protected against development of hyper thyroid and orbitopathy, so that's something to watch out for.

The next one is iscalimab which is an anti-CD-40 monoclonal antibody. CD-40 combines with CD-154 into a costimulator which activates B-cells, it stimulates the proliferation of thyroid tissues, it actually promotes thyroid hormone synthesis and thyroglobulin secretion. So, there was a study in 15 humans with Graves' disease and what they found was about 47% achieved a euthyroid state, so that's something to look out for too because this can have implications in thyroid eye disease.

There's thyrotropin receptor antagonists, so these are small molecules that block the stimulation of TSH-R by TSI and potentially decrease orbital fibroblast activation by TSI. That's another thing to look at. Those are currently being studied in animal models. Then another anti-IGF-1R molecule is being studied currently and they're looking at the affinity for the receptor vs teprotumumab. Also studying an increased half-life product that may be able to be injected subcutaneously by patients at home with fewer dosing.

Those are a few of the pipeline drugs and drugs that have been looked at and studied with variable results.

Kimberly Cockerham, MD: Let's wrap up module 5. That was a tough section, a lot of information. Thank you so much, Dr. Lee and Dr. Smith. The information on the teprotumumab, just to summarize, this is a chemical decompression that results in the diminished size of the muscle and the intraconal fat. The clinical trials demonstrated a proptosis reduction very similar to a 1 wall decompression. Most patients saw a change by week 6, so after 2 doses, and there was improvement not only in the double vision, proptosis, but also the clinical activity score. For general ophthalmologists and

endocrinologists out there, that just means the red and puffy stuff. So, chemosis, eyelid edema, erythema, that sort of thing. Also, there was an improvement in quality of life which was not enough to measure in the clinical trials, the proptosis was the FDA-identified outcome measure.

Dr. Lee provided a lot of information. I think teprotumumab being the first FDA-approved drug for thyroid eye disease has prompted a number of other companies to have interest, which is super-exciting because the orbital sector has not had a lot of innovation and so I think it's going to be very interesting to see what happens in the next 5–10 years.

Module 6 – Radiation, Surgery

Kimberly Cockerham, MD: In module 5, we examined the recent clinical data for teprotumumab which was approved as the first FDA-approved medication for thyroid eye disease in 2020.

What is the current role for external beam radiation in treating patients with thyroid eye disease?

Wendy W. Lee, MD: I'll talk first about how the fact that orbital radiation is a bit controversial, and I think it has been for a while, and still remains controversial. But the rationale for its use is really 2-fold. First of all, the nonspecific anti-inflammatory effect that orbital radiation has, and then secondly, the radiosensitivity of the lymphocytes that invade into the orbit. That's really the thought process for how that works and why some providers still use it. The results of studies are a bit mixed. I think there were probably 3 main pivotal trials on orbital radiation and 1 showed no benefit and 1 showed benefit. I think that mixed result, and the lack of controlled trials, really feed into the controversy of whether we should use this.

Traditionally, and I think what people mostly do, is when they treat their patients with orbital radiation, it's a total of 20 gray and that's split in 2-week sessions. The patient gets 2 gray Monday through Friday for 2 weeks. Five days and 5 days. The benefit of that is that it treats those orbital fibroblasts but is still under the radar to minimize side effects. The side effects being cataracts, retinopathy. Retinopathy usually occurs when you get to 35 gray and above. Then optic neuropathy which can occur usually at a little bit higher doses, so something like 50 gray or above. With orbital radiation for thyroid eye disease, we're sort of flying under that side effect profile at 20 gray.

If you decide to treat your patients with orbital radiation, I think that patient selection is very important. The best responders, based on clinical trials, have tended to be those patients with early, active, progressive, moderate-to-severe disease. So the patients with active disease responded better, although the patients with longstanding disease also had some improvement. They had improvement especially in diplopia and extraocular motility.

If you treat your patients, you want to make sure that they don't have severe hypertensive or diabetic retinopathy because, of course, the risk of exacerbating that. And then the recommendation is to choose patients who are greater than 35 years old because of the risk of carcinogenesis.

What is the role of orbital decompression for treating patients with thyroid eye disease?

Raymond Douglas, MD, PhD: Orbital decompression surgery, just as a field itself, has dramatically changed over many years, especially over the last 5–10 years that we've been operating. Typically, in the past, this was a deforming surgery that left people with arguably only slightly better improvement after the

surgery than before, often with intractable double vision, torsional double vision and not a very good cosmetic outcome either. More recently though, orbital decompression techniques, especially minimally invasive surgery, have really dramatically improved the outcomes, both the reduction of adverse events which would be primarily double vision or any vision-threatening adverse events, but also improvement of the predictability of proptosis reduction, improvement in the pain and pressure that's often associated with this disease, and improvement of their aesthetic function. The patients can now resume their normal lives.

Now, the surgery is still not for everyone. There are defined risks of this surgery. Coming back to the heterogeneity of this disease and putting the risk and benefits into context for every different patient, it has to be discussed with patients what this surgery will achieve and whether they really even want to achieve a reduction in proptosis or they mind their appearance as it is. Really patient selection comes down to the first subject and that is defining our goals of therapy. What really does the patient want? That can also dramatically affect the amount of surgery that we do. The more surgery that we do in a graded fashion, the more potential there is for complications or for some untoward effect, such as double vision, which will then require another surgery. These are all very important discussion points with the patient. And I do a lot of orbital decompressions, but we never skip this discussion process of defining exactly what we want to achieve.

Orbital decompression, as far as timing, is 95% done in what we would consider the nonprogressive, stable phase of at least 3–6 months, at a minimum, where there's no change, no increase in proptosis, no change in double vision. This is because often the surgery can either promote a reactivation or if this disease continues to progress, we will have to come back and do the surgery again. That's important. In 5% of the time, it's an urgency. There may be an urgency to do this for vision-threatening disease and that's kind of a special case.

The overall efficacy and safety, as I've kind of alluded to, has dramatically improved over time. I know that's so in your hands also, Dr. Lee. And the safety now I think we can represent this to patients who have moderate-to-severe disease. Again, the patients with mild disease usually can be helped with supportive therapy and also some of the other therapies.

What other surgical options are available to treat patients with thyroid eye disease?

Wendy W. Lee, MD: With surgery for thyroid eye disease, we have a recommended staging of surgeries, so it starts with orbital surgery. Orbital decompression and then, if the patients need it, then they would go on to strabismus surgery and then lastly eyelid surgery and that's because we know orbital decompression can affect the position of the muscles and the ability for the eye to move and then you go and fix the muscles. The muscle surgery can affect the position of the eyelid, as you all know. That's our staging. The staging would be orbit, then muscles, then eyelid.

As far as strabismus surgery is concerned, I often send my patients after I've decompressed them, if they still have a little bit of diplopia, to a strabismus surgeon because they can fine-tune and adjust the muscles if need be. Sometimes, it's just a matter of nonsurgical options, like prisms. After decompression, I would send them to the strabismus surgeon. Then, as far as eyelid surgeries, I think we have different things we can do. Actually, there are so many different surgeries on the eyelid that we can do for thyroid eye patients, including, once they're stable from

the other orbital aspect, you know. Eyelid retraction is probably the most common thing, and things like blepharotomies to drop the eyelid, even raising the lower eyelid to correct lower eyelid retraction using a stent, if needed, like a hard pallet graft or an implant. I think that dramatically helps the patient's appearance and it helps the patient's protection of the eye, obviously, and helps distribute the tear film across ocular surface which is super important.

Eyelid retraction surgery, eyelid tightening, sometimes in rare cases we have to do a tarsorrhaphy just to protect that corneal surface even sometimes before the decompression or after, just until it heals and the eyelid, the eye recesses a bit to protect that corneal surface.

Then there's a blepharoplasty. For the patients who are totally stable, they're euthyroid, they're kind of out of the woods but they still have that fat prolapse and that fullness in their lids, then I would say we can move on to take some of that fat out, do a blepharoplasty. Those are all different options, surgical options for the muscles and the eyelid that can be applied toward thyroid patients.

Raymond Douglas MD, PhD: I think those are great points. We have classified these treatments into surgical and pharmacologic and even radiation, etc, but I think that the paradigm is shifting. For the first time, we have teprotumumab which is a pharmacologic agent that doesn't just improve the symptoms and signs, but actually improves the double vision and proptosis, 2 things that were completely limited to the surgery armamentarium. For the first time, we have a pharmacologic option that improves symptomatology, disease activity and potentially improves the end result, the proptosis and double vision, that we thought we could only achieve surgically.

It's interesting, orbital radiation in particular, I always think that the only reason it's existed for so long is because we didn't have anything else. I predict in the next year or 2, we hopefully won't be talking about orbital radiation because there's scant, if any, real evidence that it actually does anything. For glucocorticoids also, there's no evidence in large trials that it reduces proptosis. I do think that we now are really beginning to look at our options in this changing landscape of both pharmacologic options that overlap into our world of surgery in ophthalmology.

Wendy W. Lee, MD: Absolutely, and I think you bring up a really important point and that is that we've discussed these treatment options in modules, but I think that combination therapy, as is true for many things in medicine, is really the key. Just like combination team approaches to these patients, combination therapy, surgical and nonsurgical, really work together symbiotically and nicely.

Kimberly Cockerham, MD: That's our final module, module 6, talking about the therapeutics. I want to thank so much my colleagues, Dr. Lee, Dr. Smith, Dr. Douglas. It was a fun discussion. Just to wrap it up, what do we know? We know thyroid eye disease is a rare disease, but more common than you think. If you look for it, you'll see it. We know that thyroid eye disease has an incredible impact, a psychosocial impact, that can result in depression, anxiety, lifelong impact on employability and relationships. We know that, up until now, we really were relying on primarily surgery and corticosteroids which have a lot of side effects and that we now have something new, a new tool in the toolbox, and I completely agree it's just a tool in the toolbox. It's not going to replace the toolbox, but it's a very exciting addition. Also, with its entrée into the market, hopefully there'll be more interest in orbit and orbital disease and that many of these other

medications will be coming forward as other options to be in our toolbox.

Thyroid eye disease is complex, and I think the take-home, whether you're an endocrinologist, a general ophthalmologist, an oculoplastic surgeon, is just look, look, listen. These patients will tell you how much this impacts them. Then think about tailoring the approach to the patients' concerns and communicate. If in doubt, refer, refer to an oculoplastic surgeon if you're an endocrinologist, we refer to the endocrinologists and we all work as a team.