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Hiding in Plain Sight: A Multidisciplinary Effort to Improve Identification and Treatment of Thyroid Eye Disease

Announcer:
This activity is supported by an independent medical education grant from Horizon Therapeutics. This content was captured during a live virtual symposium. Polling took place during the symposium.

Dr. Kossler:
Welcome to this session of Hiding in Plain Sight. We are going to go ahead and get started. I just want to thank you for spending your Tuesday night with us. The title of this session is: Hiding in Plain Sight. And it's my pleasure to introduce this wonderful faculty that we have for you tonight. My name is Andrea Kossler, and I am the Director of Reconstructive Surgery at the Stanford Byers Eye Institute. And I am so excited to share the co-chair and she's also a fantastic clinician, friend, and she knows how to really shake it on the dance floor. I found out this weekend. Dr. Jennifer Murdock, she is an Oculoplastic Surgeon in private practice in Miami, Florida. And then we also have Dr. Eve Bloomgarden, who's the Director of Thyroid Care, and she's a wonderful Endocrinologist in Evanston, Illinois. And we have a lot of information for you today.

This is one of the more important slides of this talk. It's really important for everybody to know that we as faculty have disclosures, and mine include several disclosures for multiple thyroid eye disease companies, including Horizon Therapeutics, Immunovant, Genentech, Acelyrin, Argenx, Corea, and I get grant support from several of those companies. Dr. Jennifer Murdock also has financial relationships with Horizon, Alastin Galderma, and she's on the Speaker's Bureau for Horizon. And then Dr. Bloomgarden has financial relationships with Horizon Therapeutics.

We just also want you to know that the Evolve staff who are hosting this webinar do not have any financial relationships, and that this is supported by an unrestricted educational grant from Horizon Therapeutics.

The learning objectives that we have for you today are here. Most importantly, we want you all to understand how to recognize and diagnose thyroid eye disease, we want you to understand the clinical signs and symptoms, the differential diagnosis of this important disease. We want you to understand and be able to implement and select different treatment options, and really importantly, to learn how to comanage with our wonderful endocrinology and ophthalmology colleagues so that we can offer our patients the best possible treatment for this complex disease.

So, without further ado, we're going to kick it off with Dr. Eve Bloomgarden, our outstanding endocrinology colleague who's going to discuss the introduction to thyroid eye disease for us all.

Dr. Bloomgarden:
Thank you for that introduction. So, we're going to jump straight in with a poll. Okay, so what percentage of your patients are diagnosed with TED and/or may develop TED? And here is a polling question for you. Somewhere between none and greater than 41%, various options. And I think this is just a getting-to-know-you question, it's going to be different for everybody. So, it looks like everybody has a different amount of experience here, somewhere between 4% and 28%, the majority kind of hanging on the 20% or less side of things.

So, Graves' disease and thyroid eye disease are similar, but are not quite the same. Graves' disease is an autoimmune thyroid disease,

and it's the most common cause of endogenous hyperthyroidism, with an annual incidence of between 20 to 50 cases per 100,000. Graves' peaks between 30 to 50 years of age, but can affect individuals at any age, and a lifetime risk is 3% for women and about 0.5% for men.

So, thyroid eye disease is an autoimmune inflammatory disorder that is related again to and synonymous with – it's not synonymous with Graves' disease, but it is closely linked. Both of these processes are autoimmune, both involve the TSH receptor and antibodies against the TSH receptor. TED may coexist, precede, or follow the diagnosis of Graves' hyperthyroidism, and TED is not directly related to the high serum thyroid concentrations. Having said that, euthyroid patients with Graves' disease do tend to have less severe thyroid eye disease. But it is not the case that thyroid treatment leads to resolution of thyroid eye disease signs and symptoms.

So, talking about incidents and leading risk factors for TED. TED more commonly affects women with 16 out of 100,000 women and 3 out of 100,000 men for an annual incidence. The leading risk factors for development of thyroid eye disease include smoking, radioactive iodine treatment, female sex, although men have an elevated risk for a more severe TED course. So, not all patients with TED have hyperthyroidism at time of diagnosis, about 5% are euthyroid, meaning they have normal thyroid function. About 10% are hypothyroid, meaning they have underactive thyroid function, and 85% do have true hyperthyroidism. Hypo and euthyroid patients do tend to have less active disease and less severe symptoms as well as more asymmetrical disease than those with hyperthyroidism. But some of that is just due to whether or not they've been treated in the past and what their current thyroid function status is, is not – does that tell you that – it does not exclude the diagnosis of TED. So again, here we have about 40% will have hyperthyroidism and thyroid eye disease at the same time, about 20% will have the diagnosis of TED within 2 years of diagnosis of hyperthyroidism. And then they – we can see sometimes up to 20%, you'll see thyroid eye disease as the first presenting symptom.

And luckily with TED, the vast majority do not have the more severe, you know, vision-threatening TED. We have about 6% with moderate to severe TED, and only 0.3% have sight-threatening TED, which is good news.

Okay, so you can see here from this slide that TED's associated with a wide range of vision impairment. The most common things that are seen are actually dry eye disease as well as diplopia seen in 65% and 51%, respectively. But you can see other impairments, photophobia, decreased acuity, visual field defects, reduced color vision, and severe vision-threatening optic neuropathy.

Alright, so we're going to get a little bit into the weeds of pathogenesis, but I'll try to keep you guys awake. So, orbital fibroblasts and immune cell interactions are where this starts. So orbital fibroblasts, which are specialized cells responsible for tissue repair, are central to the pathophysiology, and these fibroblasts are a heterogeneous population. Pathogenic orbital fibroblasts recruit bone marrow-derived pluripotent fibrocytes and lymphocytes, otherwise known as T cells and B cells, to infiltrate the orbit. These fibrocytes differentiate into orbital fibroblasts leading to enhanced T cell proliferation and activation. And these activated T cells secrete inflammatory cytokines and induce B cells to produce autoantibodies.

So, the key to – what we think the key to all of this is that this pathophysiology is driven by activation of the insulin-like growth factor 1 receptor, or the IGF-1R. And there – it's one of the main autoantigens in TED, and the autoantibodies too, this IGF-1 receptor overexpressed – or not the autoantibody, sorry – the receptors are overexpressed on orbital fibroblasts in patients with TED. This is also thought to be a gatekeeper of orbital fibroblast activation. And immune cells mistake self-antigens against the IGF-1 receptor as well as the TSH receptor which sits and co-locates in the orbital fibroblasts with the IGF-1 receptor, and these autoantibodies against both IGF-1 and the TSH receptor activate a receptor complex, which in turn stimulates downstream signaling to activate the orbital fibroblasts.

Okay, so once you have these activated orbital fibroblasts that were at the downstream effects of the activation of the TSH receptor/IGF-1 receptor complex, you see proliferation as well as production of inflammatory cytokines and hyaluronan, which leads to orbital tissue expansion. These can also lead to differentiate – these can differentiate into adipocytes, which build that up in the orbits or into myelo – myofibroblasts, which produce fibrosis of the orbital tissue. Overall tissue expansion and remodeling in the orbit leads to the signs and symptoms of thyroid eye disease.

This is a video of manifestations of thyroid eye disease. That was kind of cool. Let's see that one more time for fun.

Okay, I'm going to pass the baton over to Dr. Murdock.

Dr. Murdock:
Thanks, Dr. Bloomgarden. After learning about all of the nitty gritty of what's happening in the cells, let's take it a little bit more clinical here. And we'll talk about diagnosing thyroid eye disease.

Now, the main thing about thyroid eye disease, again, we keep talking about that it is lifelong and it's an autoimmune condition that lasts the entire lifetime. So, we look at the inflammatory signs and symptoms, and we categorize them a little bit as severe inflammation, moderate inflammation, or mild inflammation. But, you know, it's kind of hard to say that one person has thyroid eye disease when it has

such a heterogeneous presentation.

So, some people have more of a shorter duration like the patient here, but with severe inflammation, and we consider that high disease activity, or shorter duration with little inflammation. They might just have something – what this patient has here, which is just esotropia, and she happened to have worsening esotropia in the beginning, not a whole lot of inflammatory signs. Longer duration, which we consider a chronic patient, they can also have not a whole lot of inflammation, have more quiet eyes and orbits, or they might have a lot of inflammation, as you can see in the bottom photo here, because the disease can flare throughout the life.

Alright, let's do another polling question here. Which of these tests do you currently perform or order to confirm a diagnosis of thyroid eye disease? Okay, let's see what our answers are. So, most people use the comprehensive clinical exam of the eyelids and eyes, followed by testing, and then imaging, and then about 20% of you refer. Wonderful, let's take a look at.

Now, what is involved in the diagnosis of thyroid eye disease? It is a very complicated diagnosis because it is clinical primarily. And that's what you have to understand. And because it has such a variable clinical presentation, it can make it very, very challenging. So, we're really looking at the clinical assessment of the eyes and eyelids. Okay? And then there are other systemic manifestations that can come around as well. So first, orbital involvement. Like we saw in that video, the expansion of the fat and muscles behind the eye can cause proptosis, restricted extraocular motility. And we can measure that in different ways. We can feel for retropulsion, and then there's subjective symptoms as well. We look for inflammatory activity, and we'll go a little bit more into the Clinical Activity Score with signs of redness, pain, edema, and then we look at also the severity of the disease. How much is the proptosis? How open are the eyelids and retraction that can cause exposure keratopathy, impaired ocular motility, and then end-stage severe optic neuropathy? But again, due to the wide and varied nature of thyroid eye disease, we want to make sure we're always looking at the ocular surface and always assessing for optic nerve function as well. So that can be either visual field testing, Ishihara color plates, color desaturation, and force vision, and pupils.

Now laboratory tests can be helpful to see if there are other coexisting problems like Graves' disease or any other thyroid disorders, as well as immune status when thyroid eye disease is suspected. And then there are different forms of imaging to look at the orbits a little bit more closely.

So, let's look at, you know, kind of more early thyroid eye disease. What can we think of with a patient who's having early thyroid eye disease or more of a low inflammatory thyroid eye disease? So, they might complain of something simple, like dry eyes or a foreign body sensation. Now, sometimes it could just be run-of-the-mill dry eyes, but a lot of the times in about 60 something percent of patients who have thyroid eye disease, patients have dry eyes. We want to see if there's any excessive tearing. And then especially of the conjunctiva, you might see injection and chemosis. Patients will complain of blurred vision, a lot of this has to do with dry eyes as well. And they could have also retroorbital pain or headache. Eyelid retraction is seen in 91% of patients which we'll see, and that's one of the earlier signs as well – or signs and symptoms. So, we want to look for corneal staining, inflammation of the plica, which is kind of specific for thyroid eye disease. We don't see bilateral inflammation of the plica or caruncle in many other disease processes, and definitely that retraction and other signs of inflammation.

So, 56% of newly diagnosed non-ophthalmic pa – non-exophthalmic patients with Graves' disease have some degree of ocular surface disease compared to patients without Graves' disease. Okay? So ocular surface is very important in the diagnosis here. Now, as the inflammation continues to progress to more of a moderate thyroid eye disease presentation, patients might complain more about a pressure behind the eyes or pain around the eyes. There's additional redness and edema, the eyelid retraction might get worse, and in fact, they can't close their eyes and then that also is exacerbated by the proptosis as the eye's moving forward, intermittent double vision as well, that's where it starts to interfere with their activities.

Now what we see on exam, we're going to see swelling of the extraocular muscles or restriction on our motility exams, chemosis, edema, proptosis, injection over the extraocular muscle insertions, lid lag on downgaze, which is also very specific for thyroid eye disease, and then lots of orbital fat prolapse. And in thyroid eye disease patients specifically, this orbital fat prolapse tends to be firm to palpation because it's full of inflammation and it's not you're just soft, fat prolapse that happens with age. Now, as the thyroid eye disease continues to progress, we get into advanced disease. So, we have more double vision that's starting to become more constant and it interferes a lot with their activities. So, patients can't drive, they can't work, they start having more and more issues actually functioning in their day-to-day life, the vision deteriorates, and they might have changes in visual acuity, visual fields, or color vision, worsening pain, of course, as the inflammation is continuing behind the orbits. What we will see on exam is progressive proptosis, a lot of inflammation, again, the exposure keratopathy with lagophthalmos because the patients can't close their eyes at this point. And then difficulty with extraocular muscle motility. So, they'll have a lot more restriction, intraocular pressure, and then severe end-stage will be the dysthyroid optic neuropathy.

So, like I said before, eyelid retraction is seen in 91% of patients. Sometimes it's this – noticeable, but sometimes it's just very subtle.

So, the retraction's thought mainly to be due to inflammation and overreaction of the eyelid muscles. And again, specifically in thyroid eye disease, it's retraction with temporal flair. So, the upper outer eyelid flares out more than the central eyelid. And that's pretty specific for thyroid eye disease. So, they have so many symptoms and dryness because they just can't close their eyes and they have a lot more evaporation of the tear film from the surface. So, they have a lot of pain, a lot of blurred vision. Not only that, they have some – a lot of disfigurement as well. So, the social disconnect and emotional problems that these patients face can be a big burden to bear.

Exophthalmos or proptosis is seen in 62% of patients. And again, this is due to the inflammation occurring in the orbit. And as the fat and muscle tissue expands, it ends up pushing the eye anteriorly because the tissue doesn't have anywhere to go in this limited cone of bone in the orbit. So, we get the proptosis pretty much as far as the optic nerve can stretch. This can lead to dry eye, exposure keratopathy, and of course optic nerve compression, when the eye cannot move forward anymore, and the tissues continue to compress against the optic nerve. Now, this also contributes to inability to close the eyes, along with the eyelid retraction, horrible exposure keratopathy, and dry eyes.

Double vision can be seen in about half of patients, and this is mainly due to the inflammation of the extraocular muscles. They become stiff, they become painful, they're full of inflammation, so they just don't work properly. And you can see in this bottom photo of patients of Dr. Kossler how you don't even know how he can function because his eyes cannot focus in an orthotropic position. So, it's very, very difficult. Patients get headaches, nausea, they can't do their normal daily activities, and can be very debilitating.

Now let's look at some laboratory tests. And one of the main takeaways from the education in thyroid eye disease is to understand that laboratory tests alone are not diagnostic for all patients with thyroid eye disease. You know, when they have actual thyroid disease and autoimmune problems with their thyroid, we can actually – the endocrinologists who take care of those patients can see the hormone changes on a laboratory test, which makes the thyroid eye part a little bit more challenging. Now, the test can support the clinical assessment of thyroid eye disease. So, we definitely want to screen for thyroid dysfunction because the two disease processes occur so commonly in these patients. So, it's advisable to get a TSH, a T4, and a T3. And then remember, this is an autoimmune disorder, so it's really the immune system that's acting up. So, there have been some identifiable markers that we can look at. So a TRAb, a TSI, a TBI, and a TPO are different antibodies that can be positive, but if they're negative or if they're low and they're not detectable, it still doesn't rule out thyroid eye disease, that's a much harder, harder goal to achieve.

Imaging varies among different providers based on kind of what you're looking for. But really, what you are going to see is this expansion of the orbital tissues and proptosis. So, the lacrimal gland can be big, the muscles and the fat can expand as well, and you'll see the proptosis in relation to the bone. Now ultrasound is very particular, and it takes a special ultrasound technician or provider to be able to see these structures. CT scan, a lot of us oculoplastic surgeons use because we – that helps us also with surgical planning. And we, you know, also can see the apex, and see if there's any apical crowding. And then MRI, you can see a little bit more of this soft tissue involvement and inflammation in that as well.

Now, it's always important to understand the differential diagnosis because not everything that looks like thyroid eye disease is always thyroid eye disease. So, remember some of the more dangerous diagnoses to consider in your differential, especially a carotid cavernous fistula, it also can present with proptosis, decreased motility, and more of kind of a corkscrew vessel congestion in the orbit, an ocular surface sort of presentation, definitely tumors, IgG4, and other inflammatory issues that happen in the orbit.

Alright, we will continue on with classification of thyroid eye disease. Several classification systems have been studied to grade the severity and/or the activity of thyroid eye disease. And as we continue to learn, we're still sort of evolving this classification process as well. And we still haven't decided on a global classification system for thyroid eye disease because it is so complex. Now we have the VISA, the EUGOGO, different studies that have looked at severity and inflammation of thyroid eye disease. But you know, any sort of classification can help to make an early diagnosis, recognize a patient who might have a risk for more serious complications, and help to make your appropriate management decisions.

The Clinical Activity Score. And this, just remember is always part of your normal exam. Okay? These are different signs and symptoms of inflammation that are often seen in thyroid eye disease. So, two of them are subjective, and that's pain. Some of it can be orbital pain and pressure. The other pain is more related to the muscle inflammation, so it's pain when they look in different directions. And then we look to the signs that we see on exam, and that's redness of the eyelids, injection or redness of the conjunctiva, chemosis, eyelid swelling or edema, and then inflammation of the caruncle or plica. And this continues on with follow-up exams and there's a – when there's a change in their presentation, there's additional CAS components to this score. So, increase of greater than or equal to 2 mm in proptosis, decrease in visual acuity, decrease in eye movements in any direction.

Now applying the CAS system can also be a little bit challenging because we want to look, you know, at all of these different mainly 7 components in our initial exam and be able to follow them. So, let's just look at a couple of different things with these first pictures. Here, you can see this mild inflammatory thyroid eye disease patient, not a whole lot of edema happening around the eye. She definitely has

eyelid retraction, but her eye is pretty white and quiet here. Moving on to the more moderate/severe, you can see there's a lot more swelling of the eyelids, redness, you can definitely see some injection over the muscle insertions, and possibly some inflammation of the caruncle here as well. And then, you know, pain is subjective so we're not sure. And then in severe inflammatory thyroid eye disease, you can see how significant his proptosis is from a profile view. And he also has a lot of injection, potentially chemosis, eyelid swelling, redness.

Alright, the EUGOGO Severity Scale rates every – rates severity. So, we look at mild, moderate to severe, and sight-threatening. So, mild mainly means that there's a minor impact on daily life and has to do with a combination of eyelid retraction, soft tissue involvement, proptosis, double vision, and corneal exposure. Moderate to severe, it's still not sight-threatening, but the inflammation is actually having an impact on daily life, and it justifies risks of intervention. So, basically management at that point. So that's more lid retraction, moderate to severe soft tissue involvement, significant proptosis, and then double vision that's inconstant or constant. And of course, we are most concerned about sight-threatening, that's when we want to pretty much diagnose and intervene pretty quickly. And that's when they present with dysthymic optic neuropathy and/or corneal breakdown.

So, we're going to move on to the last little bit before I pass the baton to my colleagues here, and we'll look at the impact of thyroid eye disease. Now, as we talk about the diagnosis, the pathophysiology, the signs and symptoms, what really matters is that these patients' lives have been changed very – usually in a very dramatic way. There's a lot happening with this disease process in terms of pain, strange facial appearances so they become disfigured, and it can really lead to a lot of functional problems as well when it comes to the vision and double vision. So, these patients do have a lot of depression and anxiety. Social isolation is also very common, I have so many patients who are insecure about taking pictures. They don't want to be in big situations. Or even going to the grocery store and people look at them funny because of the way that their eyes appear. Patients with thyroid eye disease have been shown to have poorer quality of life than other chronic disorders such as diabetes, emphysema, heart failure, and even Graves' disease without thyroid eye disease. And a lot of it is probably because it's on your face, which is one of the first things you look at when you look at a patient. So, when the face is looking abnormal, when the eyes are looking abnormal, society tends to pay a little bit more attention to that. And these patients feel that.

Now the emotional distress can also be – have contributing factors of maybe altered circulating thyroid hormone, neurotransmitter-related molecule levels, psychological factors, of course, we talked about the reduced social interaction really taking a mental toll, and the disfigurement from these patients. Insecurity and embarrassment with the change. And we see so many changes in these patients, and they'll come with their old photos, and say, 'Look how pretty it used to be.' And then they have all these other problems with eyelid retraction and proptosis, and they just don't look who – like their normal selves. And then of course, the loss of functionality is detrimental when they cannot read, drive, work, and it interferes with their lives and their goals.

Now looking at the quality of life. In patients with thyroid eye disease, it may be severely impacted by persistent signs and symptoms even after the inflammation has improved. So, that's so important to realize, is that some of it can be inflammatory driven, but there are a lot of changes that still happen once the inflammation goes away. So, it's just a very difficult disease to deal with. And like we keep saying, it's a lifetime disorder and it causes a lifetime of decreased quality of life in these poor patients.

Now, interestingly, this is a specific – these are specific data looking at diabetic patients with thyroid eye disease. Now, it might be a potential relationship between diabetes and thyroid eye disease, that they have a higher prevalence of double vision, strabismus, and sight-threatening changes versus those without diabetes. And this can highlight the need for early detection of thyroid eye disease in patients with comorbid diabetes. So, our diabetes patients are challenging already, just because a lot of our management options affect – can cause hyperglycemia and changes in diabetes. But it's also important to know that our diabetic patients might also be more at risk for other problems with their thyroid eye disease.

Now last, I kind of want to present to you this new model that we're considering. And it's really looking at a patient burden. So, like we said, there are many different contributing factors to thyroid eye disease that are both symptomatic to the patient and important to what we see in our clinical exam. And it's a combination of really what is causing burdens in these patients' lives. Some people might have a lot of changes that we're noticing on exams, but they're living a fine, happy life, and it doesn't bother them. And maybe that's not – those are patients we don't need to intervene further with. But then other disease might be a little bit more subtle on our clinical exam findings; however, it's really causing more of a disabling burden on the patient. And it's just provoking a conversation with your patients every time that you have thyroid eye disease, to get an understanding more of what might be subclinical, and what might be causing a burden to these patients.

Alright, I'm going to pass it over to Dr. Kossler to talk about management.

Dr. Kossler:

Wonderful. Well, Dr. Murdock and Bloomgarden did an amazing job introducing thyroid eye disease and talking about the signs and symptoms. And I'm going to just switch gears a little bit and I'm going to move into discussing the nonsurgical management of thyroid eye disease.

It's actually a really exciting time right now in thyroid eye disease, because there are new treatment options available. We have our first FDA approved treatment that's available, and many other investigational drugs that are on the horizon. So, it's really exciting time to learn about these different treatment options so that you can customize your treatment to your patient.

So, Dr. Murdock already discussed the importance of diagnosing your patient and staging your patient, whether they have active inflammatory disease or if they have nonactive noninflammatory disease. And this staging can help us to properly select treatment options for our patients. Treatment options for the active inflammatory phase of the disease include treatments like steroids or radiation. And also, there are new biologic treatments that you can use. And we'll discuss each of those in a moment.

Now, if patients have entered into a noninflammatory, or we used to call it inactive phase of the disease, then we used to only offer those patients surgery. And I have to admit, I do a ton of surgery on thyroid patients. In my hands. I think that surgery can be very customizable to our patients to help return them to their pre-disease state. But more recently, studies have demonstrated that perhaps IGF-1 inhibition should be discussed with every patient when they're in that noninflammatory state. And we'll discuss some of the data that can support that. But if patients have compressive optic neuropathy or severe exposure keratopathy or sight-threatening disease, then their treatment options follow a different path. And that's outside the scope of what we'll talk about today.

Now, every single patient that comes into your clinic is scared and they have symptoms, and they've heard about thyroid eye disease, and they're very, very, very worried about their disease, no matter how mild or how severe it is. So, every single patient should be treated with supportive management and risk factor modification. There are a variety of risk factors that Dr. Bloomgarden already mentioned that we want to talk to them about.

The most important one is tobacco smoking. We know that tobacco smoke can increase their risk of thyroid eye disease by 7 times. So, you want to talk to them about cessation. You also want to make sure that they're following closely with their endocrinologist to maintain euthyroidism. Because if their thyroid is completely uncontrolled, then it is more challenging for us to get the eye disease under control. Studies have demonstrated that selenium can help to decrease the progression of disease from mild to moderate and about 30% of patients in areas where selenium is deficient in the soil. So, that's a conversation I have with every patient as well. And I always check vitamin D on my patients to ensure that they have a normal level of vitamin D, because studies have demonstrated that vitamin D can even increase your risk of thyroid eye disease. We also want to treat all of our patients for their ocular surface. As Dr. Murdock already described about, she reported that 56%, but other evidence also suggests that even up to 65% of patients can have dry eye disease concurrent to their thyroid eye disease, and this can be very debilitating and symptomatic. So, we want to put on our ophthalmology hats and treat their ocular surface symptoms.

Now I discussed that steroids was a treatment option. And we know that steroids can work really well for any type of inflammatory disease. And we know that steroids can work quickly. For thyroid eye disease, studies have demonstrated that a very high dose of IV steroids of about 500 mg weekly for 6 weeks, and then 250 mg for another 6 weeks each week, could be effective to stop the inflammatory progression of the disease. However, studies also demonstrated that patients would have relapse or recurrence of their inflammatory disease about 50% of the time after about a year after treatment. We also know that very high-dose steroids can have a lot of side effects. But most importantly, studies never demonstrated that steroids helps to decrease proptosis, and that's one of the most important and debilitating signs of this disease. So, for multiple reasons, steroids has – is no longer the first-line treatment option in my clinic for active moderate to severe thyroid eye disease.

This is one of my patients that I treated with steroids. This patient presented to an outside doctor in 2015 with active moderate to severe thyroid eye disease. She was treated with oral and IV steroids and developed glaucoma and compressive optic neuropathy. We ended up treating her with bilateral radiation, decompression, and additional steroids because at that time, we didn't have additional treatment options. This is this patient now after about a year of multiple steroid rounds, surgery, and radiation. She then had to undergo additional strabismus surgery and upper eyelid retraction repair to look and feel like she did before the disease began. This is a 2-year time course, a very painful time for this patient, because at that time, we didn't have any targeted therapies for our patients.

I'll talk a little bit about some of the more recent targeted therapies in a moment. Now, I'll talk about radiation now because this patient was treated with radiation. And actually, the radiation protocol that we used was developed at Stanford at my institution in the 70s. And it hasn't changed since. It's thought that radiation can induce terminal differentiation of fibroblasts. What that means is, radiation can stop those fibroblasts from differentiating into fat cells or to releasing inflammatory products and starting this inflammatory cascade. However, again, studies have been mixed. Some studies have demonstrated no improvement in active inflammatory thyroid eye disease with radiation, whereas others have demonstrated an impressive improvement with this treatment. What we believe is that

radiation can help some patients with early active disease, but proper patient selection is so important. You also have to be careful who you select because you should not use it in patients that are less than 35, in patients that have severe diabetes or high blood pressure, and in patients that have retinopathy. But again, what's really important to remember is that orbital radiation has never demonstrated that it can significantly improve proptosis.

Let's talk about some of the targeted therapies that have been used for thyroid eye disease. Rituximab was initially thought to be a great treatment option for thyroid eye disease, because it's a monoclonal antibody that targets CD20. And it was thought if we could decrease peripheral B cells, that perhaps we could decrease the production of the autoantibody responsible for this disease. But again, studies have been mixed. And studies have demonstrated that some patients do not respond to rituximab, whereas other studies have demonstrated that improvement, that efficacy. But no studies have demonstrated an improvement in proptosis, double vision, or quality of life with durable response.

Another treatment option that was more recently studied was atezolizumab, a monoclonal antibody against the IL-6 receptor. In a randomized clinical trial performed in Spain, 32 patients were randomized 1:1 to drug or placebo. And actually, these patients demonstrated a significant improvement in their inflammatory signs and symptoms at week 16 and an improvement in their proptosis of 2 mm or more. But when these patients were followed to the 40-week follow-up from starting the drug, they lost their significant improvement in their inflammatory signs and symptoms and proptosis. And so, we found that this drug did not have durable efficacy in this patient population studied. I should note that the patients treated in this study were steroid resistant. It is possible that if the study was repeated in nonsteroid-resistant patient, or if patients were treated with more than only four infusions every 4 weeks, that they may have different results. But in this clinical study, there was not durable improvement in proptosis. There were also some concerning adverse events, mostly included infections, that should be considered.

Now teprotumumab is the new kid on the block. Not so new because it's been around since January of 2020. And this is the only FDA approved treatment to treat thyroid eye disease. It's a human monoclonal antibody that targets the IGF-1 receptor. As was already described so nicely by Dr. Bloomgarden, the IGF-1 receptor and the TSH receptor, they bind together and co-localize on the cell membrane of the orbital fibroblasts. And it's thought that if you could shut down one of those autoantigen receptors, you could shut down both. By shutting down the autoantigens thought to be responsible for this disease, you can shut down the downstream signaling that leads to the active inflammatory cycle, fibroblast differentiation into adipocytes, or a fibroblast differentiate into myofibroblasts. And so, we believe that teprotumumab can reduce inflammation, prevent fat hypertrophy and myofibroblast hypertrophy. This study – this drug was studied in two randomized clinical trials, where 171 patients with thyroid eye disease were randomized 1:1 to teprotumumab or placebo. These patients were treated every 3 weeks for eight infusions.

The endpoints that were evaluated were the improvement in proptosis of 2 mm or more from baseline to week 24, the improvement in their Clinical Activity Score, improvement, and their diplopia score, or improvement in their quality of life. In the phase 3 clinical study, they demonstrated that 83% of patients had a significant improvement in their proptosis of 2 mm or more, compared to about 10% in the placebo group. They also showed that about 78% of patients had an improvement in their inflammation and proptosis compared to about 7% in the placebo group. When they compared the improvement in proptosis at week 24 to baseline, they found about a 2.8-mm difference from the treatment group to the placebo group. And all of this was statistically significant.

In this study, they also looked at improvement in something called the Gorman diplopia score. What they found was that about 70% of patients had an improvement of 1 point or more on the Gorman diplopia score compared to 30% in the placebo group. And then finally, they took a look at the quality-of-life scores in their patients. They found that both the Vision Functioning Subscale, and the Appearance Subscale of the quality-of-life scores were significantly better in patients treated with teprotumumab versus the placebo.

Now, since the phase 2 and 3 clinical studies, there's been a lot of additional studies that have been done. One of them is the OPTIC-X study, which actually gives us a lot of data, and I'll just kind of go through it. So, first of all, in the OPTIC-X study, they allowed the patients from the phase 3 OPTIC study that were in the placebo group to be treated with drug. So, the average disease duration in the placebo group in the phase 3 study was 6 months. But when they were allowed to be treated with drug in the OPTIC-X study, their average disease duration was 12 months. So, this study demonstrated that disease duration does not impact response to teprotumumab. And so, it doesn't matter if they've had disease for 6 months or for 2 years, it's likely that patients can have a similar response, as long as they still have the active inflammatory disease and they have moderate to severe or worse disease.

They also took patients that did not initially respond to drug, and they treated them again. Of the five patients that did not respond the first go round, two of them responded to a second round of treatment. So, that's about 40%. You know, you can kind of decide if you think that's worth it or not. Then there were about eight patients that had a flare of disease or reactivation of their disease after going through an initial eight rounds of – eight cycles – or excuse me, eight rounds of teprotumumab treatment. And five of those eight responded to the second round of treatment. That's about 62%. So basically, if patients responded the first time, they have over a 60%

chance of responding the second time. If they didn't respond the first time, they have less than a 50% chance of responding the second time.

And then the other thing that the OPTIC-X study demonstrated was that these patients were followed for about a year after stopping treatment. And they found that over 50%, about 56% of patients maintained their improvement in proptosis when you compared week 24, which was the end of their treatment, to that follow-up period of 72 weeks from starting drug. So, over 50% of patients are going to maintain their improvement in proptosis if they are initial responder; similarly, patients that have their improvement in diplopia, a similar amount of patients are going to maintain their improvement in diplopia.

Finally, a recent phase 4 randomized clinical trial was done in patients that have long disease duration and low inflammatory thyroid eye disease. These patients that were enrolled in this study had disease duration between 2 and 10 years. The mean disease duration was 5.2 years. And they had very low inflammatory scores, they had a CAS of 1 or less, and they had to have had low CAS scores for over a year. So, these patients had, you know, that typical stable, inactive disease. What this study showed, that even if patients have had disease for years and years and years with no inflammation and stability, that they can still have improvement in their proptosis. These patients had 2.14 mm of improvement in their proptosis when comparing baseline to week 24, compared to an improvement of about 0.92 mm of proptosis in the placebo group, that's a difference of about 1.5 mm in proptosis. They found that about 62% of their patients had that 2 mm of proptosis improvement compared to 25 in the treatment arm. And both of these numbers were statistically significant.

However, when they looked at double vision, they did not find a significant improvement between the treatment and the placebo group. They also did not find a significant improvement in the Appearance quality-of-life scores. But they did find a significant improvement in the Vision Functioning quality-of-life scores. So, take-home point, it doesn't matter how long their disease has been going on, or how much inflammation they have, there still seems to be an improvement in their proptosis in the majority of patients at week 24. Now importantly, we do not have long-term data like we have in the OPTIC-X study, so we do not know the disease duration in these patients yet.

And so, I hope that I've shared with you that there are many treatment options for thyroid eye disease, and you have to really determine the severity and the activity of their disease to select the right treatment option. But there's a lot of factors that you need to also think about. If patients only have inflammatory signs and symptoms, it is reasonable to give IV steroids. Let's remember that teprotumumab is not available in other parts of the country except for Brazil and the United States. And so, in other parts of the country, they're still relying on IV steroids. And IV steroids was the first line before teprotumumab came out. So, it's so reasonable to treat them with IV steroids. However, in my practice, I'm treat with teprotumumab just because it seems to be more superior in my hands and in the clinical studies that I've read. If they have a contraindication to IV steroids, then of course, I'm going to be treating them with teprotumumab. But you could consider one of the other agents listed here. If their main manifestation is double vision or proptosis, studies time and time again have not demonstrated improvement with the other treatment options that I have mentioned. And so, I am going to teprotumumab as the first treatment option. But if there's a contraindication, or they don't have access to that treatment, then it is certainly reasonable to treat them with some of our other treatment options that we've discussed.

In the next couple minutes that I have, I want to talk a little bit about the safety of teprotumumab. I've talked a lot about the efficacy of this drug. And it's been studied very well in active moderate to severe thyroid eye disease, showing improvement in inflammation, proptosis, and even double vision. It's also been studied in patients with low inflammatory disease and has shown some improvement in proptosis. I think it is important to understand the efficacy of this drug, but what is most important to me is to properly select patients so that we can treat them safely.

In a pooled analysis done by Kahaly and colleagues, looking at the phase 2 and 3 clinical studies, they looked at the adverse events. And they found that 80% of patients treated with teprotumumab experience adverse events. And that's a very accurate number. I've studied that number time and time again. So, 80% of patients are experiencing adverse events. However, 70% of patients in the placebo group also complained of some type of adverse event. And so, it's important to kind of really parse that out and figure out which adverse events are specific to teprotumumab. Overall, in both the placebo and the treatment arm, the majority of those adverse events were considered mild to moderate and reversible upon stopping the drug.

But there are some adverse events that are unique to teprotumumab. One of them is hearing loss. I'll talk a little bit more about hearing loss in a moment, but this is something that we studied a lot here at Stanford. In the clinical studies, they reported that about 10% of patients experienced some type of hearing impairment. However, none of the patients that experienced that hearing impairment discontinued treatment. And to be honest, there's not that much information on those patients as far as follow-up.

Now, when we take a look at things like serious adverse events, about 8% of patients experienced serious adverse events, whereas 4% experienced it in the placebo arm. Those serious adverse events attributed to teprotumumab were things like encephalopathy, infusion-related reactions, or severe diarrhea, with two patients experiencing inflammatory bowel disease flares. When these patients were

followed for 72 weeks, about 40% of patients had adverse events that continued into that follow-up period.

Let's talk about hearing impairment. This has been reported online and all over the place. And so, you've probably heard about teprotumumab and hearing impairment, and I think it's really important for us to just lay out on the table so that we can understand it and treat these patients safely. We can't ignore it. Our institution, we were probably the first to present hearing impairment in our patients, I think in an abstract in ENDO 2020, I think is when we first presented this. And we then followed that up with a paper in the *American Journal of Ophthalmology* of 27 patients that we had treated consecutively with at least four doses of teprotumumab. We found that of our 27 patients, over 80% of them experienced some type of otologic symptom. We had about a 40-week follow-up after stopping treatment. These symptoms began at an average of about 3.8 infusions, and the symptoms included things like middle ear symptoms, ear plugging, autophony, ringing of their ears, or inner ear symptoms like hearing loss or decreased word recognition. We found that the majority of patients that had middle ear symptoms or ear ringing had resolution of their symptoms; 100% of the ear ringing went away and over 90% of the middle ear symptoms went away with our follow-up. However, the patients that had hearing loss, only 40 – or sorry, 45% of those patients still had symptoms in our 40-week follow-up after stopping treatment.

We then took a look at patients that had pre and post audiograms. And we found that there was a significant decrease in their audiograms and their pure-tone audiometry before and after audiograms in our six patients that had both pre and post audiograms. And importantly, we found that 4 of those 12 ears that had the audiograms done, had a significant decrease in their ability to recognize words. The study demonstrated that baseline hearing loss was a risk factor for hearing loss with teprotumumab. And that age could potentially be a risk factor as well. And this study recommended that all patients be evaluated for baseline hearing loss before teprotumumab. We want to educate our patients on this potential risk factor, check an audiogram before, during, and after treatment. And if they do develop symptoms and have significant hearing loss on audiogram, you want to consider stopping their drug and you want to comanage these patients with audiology and ENT because this can happen and we want to make sure that it does not happen.

We also took a look at teprotumumab-related hyperglycemia. And we found that about in our patients – 44 patients that were treated with teprotumumab, we found that about 50% of them experienced hyperglycemia during their treatment. In our 47-week follow-up after finishing treatment, we found that the majority of patients still had hyperglycemia after treatment. And we found that risk factors for hyperglycemia were their age, pre-existing diabetes, and their ethnicity or race. We also found that patients that had pre-diabetes had a significant risk of developing an increase in their hemoglobin A1c. And patients that had diabetes also had a significant risk of increasing their hemoglobin A1x. So, we need to educate our patients. We need to check baseline glycemic status. We need to collaborate with our endocrinologists if you're an ophthalmologist so that we can make sure our patients understand this risk, if they have diabetes or prediabetes that they're checking their own blood glucose daily, and that they're getting their blood sugars checked before each and every infusion.

In the Tepezza, or the teprotumumab FDA label, it clearly states these different important warnings, including the infusion reactions, inflammatory bowel disease, hyperglycemia, and hearing impairment. And this was just updated in July to include the hearing impairment. You also want to remember, these patients cannot get pregnant during treatment, so they have to be on two forms of contraception. And the Tepezza stays in your system as a 20-day half-life and so you want them to be on contraception for 6 months after treatment. You also do not want to use this drug in growing children because the IGF-1 inhibition affects the growth hormone cycle. Finally, the studies were done in patients aged 18 to 80. And so, you want to take caution in unstudied age groups.

When I treat a patient with teprotumumab, I want to make sure that I am educating them, screening them, and monitoring throughout treatment. If they do not agree to my follow-up schedule, I cannot treat them because I can only treat my patients safely. And so, I'm going to get a baseline pregnancy test if applicable on every patient, audiograms, and a panel of labs. I repeat the blood sugar and the pregnancy tests if applicable before every infusion. I repeat my labs and my audiogram mid treatment and after treatment.

With all of that said, I'm going to pass it on now to Dr. Bloomgarden.

Dr. Bloomgarden:
Thank you for that amazing review, both of you. This is a really great overview of, I guess, deep dive, not an overview – deep dive of thyroid eye disease and management.

I'm going to talk a little bit about comanagement strategies for patients with thyroid eye disease. Because as an endocrinologist listening to this, I think there are things that, you know, the take-home points are there's a lot about the eye that we don't know. And there's a lot about systemic hormonal things and effects of steroids that we're very comfortable with. And so, it makes sense, you know, I think thyroid eye disease is a disorder or disease that really lends itself well to comanagement.

Do your best with the poll here. This is: To what extent do you currently educate patients with thyroid eye disease? Ranging from I am comfortable talking to patients about everything to do with TED, down to, you know, I educate a little bit, but then refer, or I refer, or I

don't see anyone with TED. So, about 11% feel comfortable kind of with all of the management and with the counseling, about half educate about the disease process but then refer to a TED specialist to go over treatment options, 40% if they're suspecting TED will refer, and only one does not see patients with TED.

So, the goals of multispecialty care for thyroid eye disease are to reduce the delays in diagnosis and to expedite treatment to clearly define the role of each specialist and to minimize the burden of TED and reduced quality of life that goes along with thyroid eye disease. And TED is a team sport, exclamation point. So, you know, the key here is you want to be able to – because of the heterogeneity of the presentation and because there's so many things on the differential, especially from the ophthalmologic standpoint, you really want to develop a pathway for referrals and a medical management strategy ahead of time. The truth of the matter is, we have a much easier job in endocrinology because that's where all of the Graves' patients are. So, if we have Graves' patients with any of these symptoms, you know, it's kind of a slam-dunk diagnosis, or at least it's very – it can be very suspicious for thyroid eye disease in that captive audience. We also have the option, and we employ this option to address risk factors for progression to make treatment decisions that don't worsen the likelihood of thyroid eye disease. We can screen all of our patients when we see them and educate them about the risks of thyroid eye disease. We can frequently monitor symptoms and manage comorbidities. And other healthcare providers involved maybe the primary care doctor, allergy, nurse, ophthalmic technicians, optometrists, psychology, and ENT and OMFS.

So, actually, this year, the – we have a new kind of consensus statement put out by the American Thyroid Association and the European Thyroid Association in conjunction, and it's not a set of guidelines, but it is a consensus statement to outline and clearly define the role of each person involved in the thyroid eye disease pathway. And again, a little bit on the side here is what I just mentioned, meaning that we, the endocrinologists, manages thyroid dysfunction, makes the early diagnosis of thyroid eye disease, and initiates local and lifestyle measures. We can recognize when to refer, and of course, if there's any diagnostic uncertainty or anyone where there's moderate to severe or sight-threatening thyroid eye disease, and we contribute to TED specialty care management decisions. And here are some key points kind of echoing that, what I just reviewed here.

And another way of kind of saying some of this is just really clearly identifying the roles of each and, you know, I'll put these side by side here. So, you know, we can certainly – we're very comfortable making the diagnosis in our Graves' patients, we can establish pathways, and start and provide a lot of education, monitor the physical and psychosocial impact. It's very easy to spot these patients when they come in with their eyeglass – you know, the sunglasses on and they don't take them off. And you ask them a single question about their vision, and they start crying. I mean, it's – there – these patients are really suffering. You know, we can partner with ophthalmology or subspecialties to determine the next steps of therapy. And of course, we can control things like hyperglycemia and hyperthyroidism.

The role of the ophthalmologist is to clearly be involved at all moderate to severe and sight-threatening cases, provide the definitive diagnosis and a comprehensive ophthalmic exam, to order and interpret imaging, and then to, you know, to treat, rule out and treat ocular comorbidities. And I think that the treatment decision is definitely based on your relationship and comanagement kind of back and forth with your endos. And then to monitor for progression of the ophthalmic manifestations.

And then this is at the very end of that ETA/ATA guideline – or not guideline, consensus statement that came out earlier this year, just this 5-step approach to reduce morbidity associated with thyroid eye disease and improve quality of life. I'm not going to read through all of this, because we've already really talked about almost all of it, but just the highlighted words to diagnose, to screen, to alert, to prevent, and to refer as needed.

And with that, I'm going to turn this over to get our cases started.

Dr. Kossler:
Fantastic. So, thank you so much for that. We're going to go over a case here just to kind of bring this home to everyone and just to bring it back to our patients, which at the end of the day is why we do all of this, we want to help our patients, we want to provide the best possible care. And this is a heterogenous debilitating disease, and we want to make sure we're understanding how to properly select and treat our patients.

So, this is one of my patients. And he's been very gracious to allow me to share his story. He is 45 years old. He has thyroid eye disease, and he was treated at an outside institution for thyroid eye disease because of proptosis, double vision, pain, swelling, and loss of vision. He developed the eye symptoms in his left eye first, and you can see how severe that left eye was. He had lost the vision on that left side, his vision was about 20/100. And he was treated at that outside institution with steroids, IV steroids, but then he developed a myocardial infarction. And so, he was told he could not have any more steroids and there was nothing more that could be done.

He eventually came to see me when he developed signs and symptoms on the right eye. And the left eye had been kind of ignored for over about a year and a half. So, when he came to see me, he had 20/50 vision and the right 20/100 in the left. He had a relative afferent pupillary defect in the left eye, and he really couldn't move his eyes at all, he could not look down with his right eye, and he could not

look up with his left eye. These are what his visual fields look like, which demonstrate that he has visual field defects in the center of his gaze in both sides. And these correspond to the size of extraocular muscles here on his MRI with a humongous superior rectus muscle on the right, and a humongous inferior rectus muscle and other muscles on the left. Because of his myocardial infarction, he could not have surgery, and he could not have steroids. And he was diagnosed with compressive optic neuropathy due to his relative afferent pupillary defect, his decreased vision, and his visual fields.

Since we didn't have any other treatment options, and this was at the end of 2019, we treated him with orbital radiation. Over about a month time, he did not have any response to radiation and actually had subjective worsening. Lo and behold, January of 2020, teprotumumab was approved, and we were able to treat him with teprotumumab. He was the very first patient treated after FDA approval with teprotumumab, and my first patient. I live in Silicon Valley, so of course my patient is an engineer. And he took a picture of himself every single day, the first 2 weeks of treatment. And this is what his right eye looks like. You can see at the start of this video, his pupil is hidden under his eyelid. But over 2 weeks of treatment, you can see how the center of his pupil moves into primary gaze. This was actually life changing for this patient. I remember when he first came in, he told me that his iPhone hadn't recognized him for over a year and a half, because the iPhone couldn't get his pupils. And now his iPhone unlocks when he looks at it. I mean, that almost – that was life changing for him alone. So, you can see that before the – before and after the first dose, eye is moving into primary gaze. And then before and after the second dose, eye is now, you know, completely visible and he's now able to function. This was his visual field in MRI before teprotumumab. And then after two infusions, he has a really nice improvement in the visual field, his visual acuity, his color visions, his APD. And what you can see, which is really impressive, is that the extraocular muscle size improves significantly and they're no longer compressing his optic nerve. So, this is my patient before and after teprotumumab treatment. And in these photos you can see that his compressive optic neuropathy has resolved, his orbital inflammatory size has resolved, his proptosis has improved, and the movement of his right eye is completely improved. Now his left eye obviously still needs more work. So, we took him to surgery, we did bilateral decompressions and strabismus surgery. And this is him 1 month after his strabismus surgery. And you can see he's a completely different man.

So that's the end of my case. But I showed you a picture story before of my patient that was treated with steroids and I think that these two stories are completely different. And it really just goes to show really the vision-changing effect of treatments when you properly select your patients.

Take it away, Dr. Murdock.

Dr. Murdock:
Okay. Thanks, Dr. Kossler, that was a very great case. Alright. So, my patient first presented to the optometrist. I have a great working relationship with my local optometrists who are now learning more and more about thyroid eye disease as well and have a big role in the diagnosis. She was referred to this optometrist for Horner syndrome and ptosis. And she presented with this asymmetric proptosis and eyelid retraction. So, the optometrist was very intelligent and said, I think this is actually thyroid eye disease. Now, the patient's grandmother did have a history of Graves' disease with proptosis. But her thyroid labs were normal from the referring physician and the optometrist ordered a CT scan and thyroid antibody tests and then she was sent to me.

So here is our female patient where she presented with normal vision. As you can see, she has asymmetric disease. So, she has bilateral upper eyelid retraction with temporal flare worse on the left with some superior and inferior scleral shell. You can see she has asymmetric proptosis as well, with that left having a 3-mm difference from the right. And she does have some moderate signs and symptoms of inflammation, eyelid edema, erythema, injection, chemosis on the left side, and inflammation of that plica.

So we started with a trial of oral prednisone, given her inflammatory signs and symptoms for a couple of days. She did not last very long. She had side effects of insomnia, and increased appetite. And she did not have any improvements in her thyroid eye disease symptoms. So, we took her off the steroids and decided to monitor and see how she does after that. Now, we at the initial visit, submitted authorization for teprotumumab. But that can actually take quite a little bit of time, ranging from a couple of weeks to a couple months. So sometimes we have to keep the patient comfortable until that authorization kicks in. So her teprotumumab authorization took a good 5 months to become approved and she continued to have worsening disease. So, her proptosis was worse, 17 in the right, 19 in the left. You can see she has worsening eyelid edema as well, chemosis, and injection.

She was finally started on the teprotumumab. And as you can see with the progression of her eyes, she had resolving inflammatory signs and symptoms. Now, after the first four infusions, she started complaining about eustachian tube dysfunction and tinnitus, which as Dr. Kossler was describing previously, is more of a middle ear symptom. She had a previous history of tinnitus that was elucidated at this time before starting teprotumumab, but it started to get worse. However, her eye disease was getting better. Her inflammatory signs and symptoms were resolving. And she now just had a CAS of 2 in both eyes and much improved proptosis. We decided to continue the teprotumumab and at the end, she had resolved inflammatory signs and symptoms. She still had the hearing issues previously reported.

And she continued – she, at the end, had reduced proptosis and retraction, no pain whatsoever. And then several months after the eighth infusion, her tinnitus returned back to baseline, her eustachian tube dysfunction resolved.

Now, this is just also highlighting that there is a role still of surgery in these patients. So, even though her inflammation was much improved, her proptosis was much improved, she was left with some eyelid retraction. So, we proceeded with an eyelid retraction surgery where we did an upper eyelid levator recession to improve her exposure and her lag. So, as you can see, her eyelids came back down, she looks a lot normal, they're in a much better position. And then her eyes felt a lot better with less dryness, irritation, and again, the disfigurement, that's huge. So that also improved and she was very, very happy.

Alright, thanks. I'm going to invite all my co-presenters to unmute so we can take any questions if anyone has any questions.

Dr. Kossler:
I have a question.

Dr. Bloomgarden:
Yes, Dr. Kossler.

Dr. Kossler:
So, Eve, you know how often in your practice are you the one who's prescribing teprotumumab? Is your ophthalmologist prescribing teprotumumab? Do you have a multidisciplinary clinic? How do you guys work that out?

Dr. Bloomgarden:
Yeah, so it's a really good question. And it's a little bit of I do a couple of different things. For patients that I am already seeing for Graves' disease that have eye – that have what seems to be thyroid eye disease that would benefit from treatment, but not a question of diagnostics, you know, where I'm not concerned about some other diagnosis, I will do two things at once. So, we'll start the paperwork, we'll get that process going, I'll do the counseling. And we'll get, you know, we'll give them a 30-day window. And then I'll have them see our oculoplastics in order to have a baseline exam and to answer any additional questions and to be set up for monitoring. So, we'll do those kind of concurrently.

For somebody who has a bunch of ocular comorbidities or other diagnoses, so I have a patient with glaucoma, with – and also with uveitis who now has thyroid eye disease, I'm not going to order that. I'm going to put that – I'm going to send that to my thyroid eye disease specialist who's in oculoplastics because there's a lot of stuff happening there. And I don't know if, you know, if Tepezza is the right next step.

For somebody who has – who isn't quite there yet in terms of wanting to start treatment, but I think maybe would be convinced to start treatment, I will use my, you know, my colleagues in that way as a kind of a tag team approach. Most of my patients have a baseline ophthal exam at diagnosis for Graves' so they're already in touch with an ophthalmologist or even an optometrist. And so sometimes they'll want to ask questions and go back and forth. But I'd probably order, half the time I'm doing it on my own, you know, or at least I'm initiating the process and seeing them back in clinic, and half the time I'm doing it concurrently with while establishing care. Sometimes I'll, you know – and I'll always communicate like, I think this is the plan, this is what we need, but I need your blessing on this one. You know what I mean? And I think it just depends on what's going on with the patient. And it's easy to do, you know, in the office. I think the trickiest part at the beginning was the paperwork. And now the counseling, especially the hearing loss, everyone – and we have bought audiotoxicity/phototoxicity protocol, so everyone's getting a baseline exam. Anyone who has symptoms, gets seen again by our audiometry or audiology team with our – with an MD involved and then they get a follow-up exam as well.

Dr. Kossler:
Thank you. That's great.

Dr. Bloomgarden:
Sure.

Dr. Kossler:
So, in the last second, we have asking if we take clinical photos at each follow-up? And do you measure the strabismus at each visit? Jen, I'll let you take that.

Dr. Murdock:
I do take clinical photos at each visit. It helps me to monitor the clinical presentation, but also as an oculofacial plastic surgeon, I pretty much take clinical photos of everyone every visit because that's important for my practice. And I don't measure strabismus, but I do measure motility, so I do a motility check to measure their restriction, but I don't actually do prism measurements. Do you, Dr. Kossler?

Dr. Kossler:
No, I'm pretty similar. So I do a motility exam. And of course, I ask them about their double vision.

Dr. Murdock:
Absolutely.

Dr. Kossler:
You know, I do their Gorman diplopia score. And if I am really worried, then I will send it to our orthoptists. And they do the prism, so we – they get them done, it's just done by orthoptists and it's typically done at baseline, just so we have a sense of how much improvement they're getting from the Tepezza.

Alright. Well, thank you so much for that question. And again, reach out to us, you can find us outside of – oh, we got another one. Okay.

We'll do the last one. What benefit do you see with selenium and vitamin D? I mentioned this in my part of the talk. There have been some studies that were reported in Europe where the soil is deficient in selenium that demonstrated that if you supplement with selenium 100 mcg twice a day, that patients can have a 30% decrease in the progression from mild to moderate disease. In the United States, we do not have deficiency in selenium in the majority of the country, but in the West Coast, we do. So, I am still discussing selenium for the patients just as some type of an antioxidant that could potentially help to decrease their risk factor for progression.

As far as Vitamin D, I think that study was done by Dr. Kahana, if I'm not mistaken. And if you look at the entire pathophysiology of thyroid eye disease, actually vitamin D does play a role. And if you have low vitamin D, then it shows that there can be a higher risk of developing thyroid eye disease. And so both of those are just risk factor modification. So, it's important to check. It's good – vitamin D is important for many things, and if we can do anything to decrease their risk of developing thyroid eye disease or risk of progressing in thyroid eye disease, then, you know, we want to do it because this disease can be very challenging to treat. So, we really want to try to prevent them from developing it and preventing them from developing severe disease.

Dr. Murdock:
I agree I do similar. I recommend these two supplements based on the data. However, what do I actually see in clinical practice is questionable. It can – but you know, whatever we can do to help because a multifactorial disease requires a multifactorial management.

So, I want to thank my co-presenters, Dr. Andrea Kossler, Dr. Eve Gardenbloom and to Evolve Medical Education, for this informative and interactive thyroid eye disease symposium tonight. What a great way to spend a Tuesday night and I wish everyone a lovely evening.

Dr. Kossler:
Eve, you know, it's just late at night time, she's on the East Coast, Dr. Bloomgarden.

Dr. Bloomgarden:
I love it. Oh my God, Gardenbloom is totally fine with me. It's perfect.

Dr. Kossler:
Alright, well, Dr. Bloomgarden.

Dr. Bloomgarden:
Thanks for having me.

Dr. Kossler:
One of those names that can sound good either way.

Dr. Bloomgarden:
This is fine.

Dr. Kossler:
Oh, thank you so much. Awesome doing this. I always love talking about thyroid eye disease. So, thank you all for your attention. If you have any questions, you can always reach out to us afterwards. You can send us emails or reach out to us on social media. And thanks again.