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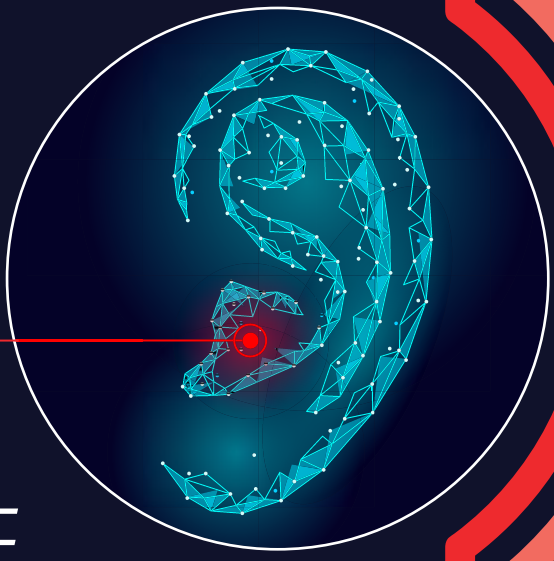

THYROID EYE DISEASE

MULTIDISCIPLINARY MANAGEMENT OF TREATMENT-ASSOCIATED HEARING LOSS

FACULTY



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ACTIVITY DESCRIPTION AND PURPOSE

This educational activity is intended to help clinicians evaluate real-world data pertaining to hearing dysfunction associated with thyroid eye disease treatment with the insulin-like growth factor 1 receptor antagonist teprotumumab. Clinicians will learn how to implement optimal strategies for monitoring and managing hearing loss in patients treated with teprotumumab. The desired results of this activity are for clinicians to use a multidisciplinary approach to increase their ability to identify and manage hearing loss in patients who require treatment of thyroid eye disease.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists, oculoplastic surgeons, and neuro-ophthalmologists.

LEARNING OBJECTIVES

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

- Evaluate key and impactful real-world data pertaining to hearing dysfunction associated with thyroid eye disease treatment
- Implement optimal strategies for monitoring and managing hearing loss in patients treated with insulin-like growth factor 1 receptor antagonists for thyroid eye disease

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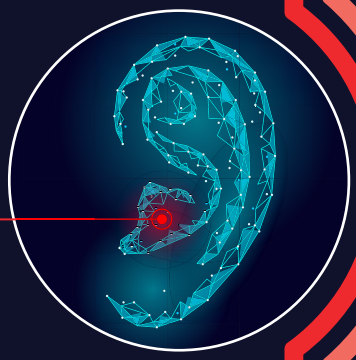
THYROID EYE DISEASE



MULTIDISCIPLINARY MANAGEMENT OF TREATMENT-ASSOCIATED HEARING LOSS

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INTRODUCTION

Thyroid eye disease (TED) is a rare, progressive, autoimmune, inflammatory disease that can cause proptosis, diplopia, extraocular muscle (EOM) restriction, photophobia, blurred vision, optic nerve dysfunction, permanent orbital/facial changes, and loss of vision.[1,2] TED can be treated with surgery or external beam radiation, but medications can also be used.[2] Medications that have been used off-label to treat TED include corticosteroids, rituximab, mycophenolate, and tocilizumab. These agents have varying degrees of effectiveness and well-established adverse event (AE) profiles.

In 2020, the US Food and Drug Administration approved teprotumumab, which is currently the only agent approved to treat TED.[2-4] Teprotumumab has been shown to improve proptosis, diplopia, and quality of life in patients with TED regardless of disease activity or duration.[3,5-8]

In the pivotal trials that led to approval, hearing impairment was found to be present in 10% of patients receiving teprotumumab compared with 0% of those receiving placebo.[3,5,6] More recent data, however, has led to a modification in the prescribing information of teprotumumab to include hearing impairment as part of the Warnings and Precautions.[3]

> *Teprotumumab may cause severe hearing impairment, including hearing loss, which in some cases may be permanent.[3] Assess patients' hearing before, during, and after treatment and consider the benefit-risk of treatment with patients.*

This has left many eye care professionals with the need to understand more about hearing impairment and screening for hearing loss, and also to learn how to incorporate ear, nose, and throat (ENT) and other hearing specialists into the multidisciplinary management of TED.

TED PATHOPHYSIOLOGY AND TEPROTUMUMAB

To understand current discussions surrounding teprotumumab-related hearing loss, the pathophysiology of TED in relation to insulin-like growth factor 1 receptor (IGF-1R) is important. In the active phase, immune cells infiltrate orbital tissues, resulting in an autoimmune response and inflammation.[1] IGF-1R is overexpressed and colocalizes with the thyrotropin receptor in orbital fibroblasts. Activation at the receptor complex leads to increased cytokines and glycosaminoglycans, including hyaluronan. Intraorbital tissue is thus expanded, and further expansion occurs with fibroblasts differentiating into additional adipocytes and myofibroblasts. The increased volume can lead to EOM restriction, proptosis, and optic nerve compression.

Teprotumumab is an inhibitor of IGF-1R.[3] The decrease in activity at this receptor reduces inflammation, decreases hyaluronan production, and prevents orbital tissue proliferation. Teprotumumab is given in a series of 8 intravenous infusions, with an initial dose of 10 mg/kg and subsequent doses of 20 mg/kg every 3 weeks.

ASK THE OTOLARYNGOLOGIST

What Should Eye Care Professionals Know About the Mechanism of Hearing Impairment With Teprotumumab?

Dr Alyono: The proposed mechanism is the alteration of the IGF-1 pathway.[9] IGF-1 and its receptor are important in inner ear development and thought to be neuroprotective, helping to protect and maintain hearing. Mice and infants born with abnormal levels of IGF-1 can have profound sensorineural hearing loss (SNHL) or they can be born with normal hearing but be more sensitive to noise-induced hearing loss.[9,10]

Two otologic issues have been observed in patients receiving teprotumumab: SNHL and patulous Eustachian tube (PET).[11] There is the potential to both have a sensorineural pure tone loss and to have the word recognition score affected disproportionately to the pure tones, thus raising the question that perhaps this medication is leading to a synaptopathy with the neural signal that comes from the cochlea to the brain.[12]

The mechanism for PET involves a pad of fat called the Ostmann fat pad, which is near the orifice of the Eustachian tube in the nasopharynx **(Figure 1)**.[13] There may be atrophy of the Ostmann fat pad with exposure to IGF-1R antagonists **(Figure 2)**.[11] PET occurs when the Eustachian tube is too open.[14] Usually, Eustachian tube dysfunction is thought of as a dilatory issue, in which the Eustachian tube is too closed. People with PET report ear fullness and characteristically complain of autophony—their breathing or voice sounds much more prominent or echoes in their own head. Often, this condition will worsen with exercise.

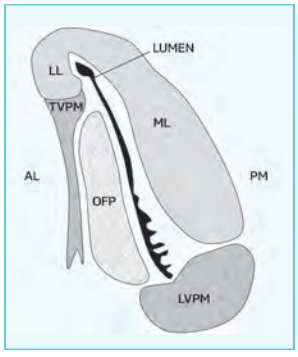

Figure 1. Schematic of a transverse section of the Eustachian tube and Ostmann fat pad with the collapsed lumen (in black)[13]

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Abbreviations: AL, anterolateral; LL, lateral lamina; LVPM, levator veli palatini muscle; ML, medial lamina of the cartilage; OFP, Ostmann fat pad; PM, posteromedial, TVPM, tensor veli palatini muscle.

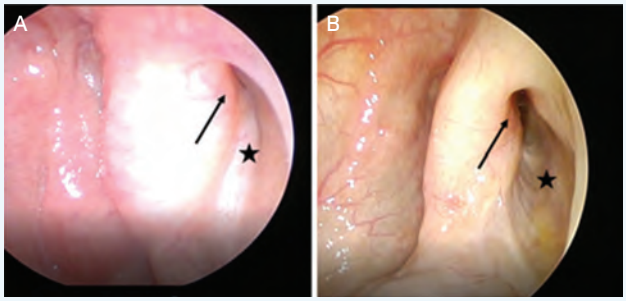

Figure 2. Normal Eustachian tube (A) compared with patulous Eustachian tube following treatment with teprotumumab (B)[11]

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ASK THE OTOLARYNGOLOGIST

What Should Eye Care Professionals Know About Hearing Loss?

Dr Alyono: We generally consider hearing loss as conductive or sensorineural. Conductive loss would be anything affecting the ossicles, eardrum, and ear canal and any mechanical issues with hearing loss. Sensorineural loss encompasses issues with the cochlea, nerve, or central processing thereof. From a clinical perspective, it is difficult to distinguish between sensory and neural loss because both of these aspects are tested together on hearing tests. Different mechanisms, such as ototoxicity, may lead to one or the other preferentially.

In a typical audiogram, a set of pure tone audiometry and speech testing will be performed. The pure tones are measured at different frequencies at increasingly loud decibels; patients report back when they can hear the sound. **Figure 3** illustrates a typical audiogram, providing a basis for understanding how hearing is measured. The audiogram is set up much like a piano keyboard: the low tones/low frequencies are on the left and the high tones/high frequencies are on the right. As you go lower on the graph, you have increasing hearing loss. The patient in **Figure 3** has a high-frequency SNHL.

Patients also receive speech testing, wherein a speech reception threshold is determined by measuring how loud the audiologist has to play a recording so that someone can detect 50% of the words. Additionally, in a word recognition score, the audiologist plays the recording louder than that speech reception threshold and records how many of the words someone gets correct. In **Figure 3**, the patient got 100% of the words correct.

Finally, there is tympanometry, an indirect measurement of the air pressure within the middle ear space. This is related to

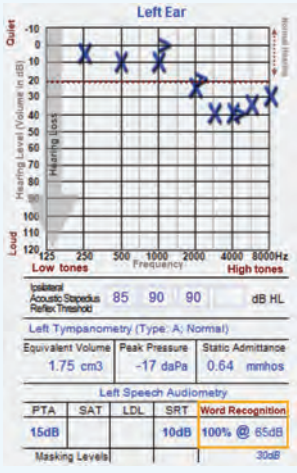

Figure 3. Baseline audiogram of a patient with high-frequency sensorineural hearing loss and normal word recognition

Image courtesy of Jennifer Alyono, MD, MS

Abbreviations: LDL, loudness discomfort level; PTA, pure-tone average; SAT, speech awareness threshold; SRT, speech reception threshold.

Symbols: X, left ear; >, left bone conduction.

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discussion of teprotumumab because tympanometry is involved when patulous testing is done. Patients can report a variety of symptoms, including ear fullness, hearing loss, tinnitus, difficulty understanding speech, or pulsatile tinnitus, and autophony.

Although some of these symptoms can be specific to hearing loss, people can often have tinnitus but no hearing loss or they can have ear fullness and no hearing loss. Alternatively, they can have ear fullness with no subjective hearing loss, but have objective hearing loss **(Table 1)**.

Many people with SNHL say their ears feel a little plugged. I think that is the most common mistake we see. People show up in an emergency room saying their ear is plugged, and they think it is wax. The ear canal is clear, and it is actually a sudden SNHL.

Table 1. Hearing-Related Symptoms to Ask Patients About

Symptoms	Examples
Ear fullness	Do your ears feel full or plugged?
Hearing loss	Do you have trouble hearing, especially in conversations?
Tinnitus	Are you hearing buzzing or ringing sounds that others do not?
Difficulty understanding speech	Are you having difficulty understanding words? When does this occur?
Autophony	Are you hearing your breathing, voice, or pulse echoing in your head?

Vague otologic symptoms may or may not relate to SNHL. They may be from PET. Patients may be asymptomatic in terms of hearing changes and yet still demonstrate changes in their sensorineural hearing that reach what is considered ototoxicity levels of change.

–Jennifer Alyono, MD, MS

Dr Briceño: Many clinicians do not have the vocabulary or the training to effectively ask questions about subjective complaints of fullness or autophony. There is heterogeneity as far as how the questions are being asked.

Dr Subramanian: It is one more thing to add to our patient selection criteria, and it is important to get comfortable with using these words and asking our patients specific hearing-related questions. I think we may not be eliciting the necessary information in the right way; we need to do it in a systematic and reasonable fashion.

Dr Briceño: I agree. We need to get used to asking questions about hearing as part of the workup and follow-up for any patient with TED whom we are treating with IGF-1R antagonists, including emerging in-class drugs.

EVIDENCE: HEARING LOSS WITH TEPROTUMUMAB

In the initial clinical trials, a reported 10% of patients given teprotumumab experienced hearing impairment, which encompassed deafness, Eustachian tube dysfunction, hyperacusis, hypoacusis, or autophony.[5,6,9] These AEs were classified as nonserious, and no patients discontinued treatment because of these events.

Real-world data sometimes provide a broader picture of AE profiles than those reported in clinical trials. In a prospective case series by Sears et al, 22 of 27 patients (81%), average age of 70.8 years, who received teprotumumab reported subjective otologic changes **(Figure 4)**,[11] covering a wide variety of symptoms, ranging from ear fullness, pressure, or plugging in 48.1% of patients to tinnitus in 37%, subjective hearing loss in 40.7%, and autophony in 25.9%. These symptoms were present after an average of 3.8 infusions.

Many otologic symptoms reported in the study were reversible. At follow-up, an average of 39 weeks after the last infusion, tinnitus had resolved in 100% of patients, ear fullness in 90.9%, and autophony in 83.3%.[11] Only 45.5% of those who experienced hearing loss had symptom resolution. For patients who exhibited symptom resolution, the average time to recovery after completing or discontinuing teprotumumab was 23 weeks for tinnitus, 22 weeks for ear fullness, 18 weeks for autophony, and 29 weeks for hearing loss.

Of the 6 patients with baseline and posttreatment audiometric testing, 5 were diagnosed with teprotumumab-related ototoxicity.[11] A history of baseline hearing loss increased the likelihood that a patient would report additional hearing loss after teprotumumab infusion.

Dr Subramanian: In this study, patients were very systematically, mindfully, and rigorously asked about their hearing and tested at set intervals and when they reported problems. There was a very strict protocol by which they were assessed that had a low threshold for recording symptoms and also for performing further testing.

Dr Alyono, was there a specific time point at which testing was repeated or were patients sent for repeat audiogram and speech testing after they reported decreased hearing?

Dr Alyono: People were recommended to get testing at baseline and repeat audiograms when they reported new

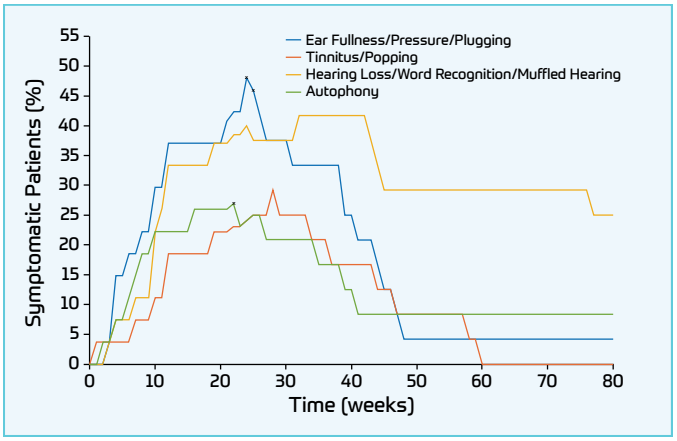

Figure 4. Subjective symptom rate and resolution of otologic symptoms in patients receiving teprotumumab[11]

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otologic symptoms. The study was conducted in early 2020 through early 2021, so baseline audiograms were not always able to be obtained owing to COVID-19 restrictions at the beginning of the study.[11] One limitation is that we had baseline audiograms on only 6 patients.

Dr Subramanian: This study generated a lot of buzz because it showed that most patients, when asked, would report subjective new otologic symptoms. **Figure 4** demonstrates that there was a wide variety of symptomatology.[11] Autophony was not as frequently reported as ear fullness, but there was a substantial reporting of tinnitus and hearing loss. It was unexpected that there would be such a high incidence of these symptoms and that they occurred over the range of treatment. Also, ear fullness, autophony, and tinnitus seemed to resolve, similar to those which occurred in the clinical trials. The hearing loss—especially word recognition—which was an unexpected finding is what worried me the most and generated much discussion among those of us who treat patients with TED.

Dr Briceño: The rigor of this study stems from the fact that there were specific questions about hearing loss rather than depending on spontaneous reports of hearing loss.[11] Before this study, this was not asked on a regular basis because we thought hearing loss was rare and reversible. This study brought the importance of asking about hearing symptoms to the forefront.

A clinical trial by Douglas et al that focused on patients who had chronic TED with low activity scores found 9 of 41 patients (22%) had hearing-related events, which was lower than that in the Sears study, and hearing impairment was reported in 2 of 20 patients (10%) in the placebo group.[7,11] Additionally, a retrospective claims analysis of hearing loss and ototoxicity codes by Smith et al found that 20% of patients with TED who were not treated with teprotumumab also had diagnoses of hearing loss, indicating there may be a substantial proportion of patients with hearing changes in the TED community before exposure to teprotumumab, highlighting the need for baseline audiometric testing.[15]

Dr Subramanian: When the Douglas study was presented, there was much discussion about the hearing loss reported in the placebo arm.[7] It was thought that there was a nocebo effect with the 2 patients who reported hearing impairment, given that this was in contrast to no patients receiving placebo reporting it in the phase 2 and 3 trials.[5,6] We were not as aware of hearing loss being a potential AE of teprotumumab at that time. Perhaps patients were more alert to hearing changes because we asked them about it or they had read about it. Consider also that this study involved chronic disease, so these patients had Graves disease for much longer and perhaps were more likely to have some preexisting hearing loss potentially related to their Graves disease.[7]

Dr Briceño: There exist data wherein the odds ratio for people with Graves disease was 14.97 vs control for having hearing loss at a frequency of 8000 Hz, specifically in patients with hyperthyroid Graves disease.[16] These data were published in 2012, long before teprotumumab was approved for TED.

RECENT STUDIES: INVESTIGATING HEARING LOSS WITH TEPROTUMUMAB

Dr Briceño: Table 2 shows the results of a study by Shah et al, on which I was a co-investigator.[17] Of 131 patients, 40 reported experiencing hearing-related AEs, but only 12 had undergone baseline audiograms. Of these, 7 had baseline hearing impairment. Nineteen patients had been exposed recently to some other potentially ototoxic medication (eg, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitor, vancomycin, and diuretics).

The Shah study is in direct contrast to another recent study done by Douglas et al, which was a prospective study examining audiometry and outcomes following teprotumumab treatment for TED.[17,18] That study showed a very different outcome, in which 1 of 32 patients with normal baseline audiograms had new-onset hearing loss after treatment with teprotumumab out to 6 months of follow-up.[18] Of the patients who had baseline hearing impairment, 20% had worsening of their hearing **(Figure 5)**.

Table 2. Hearing-Related Adverse Events Occurring in More Than 5% of Patients in a Multicenter Study Examining Teprotumumab-Related Adverse Events[17]

	Shah et al (N = 131)
Adverse event	
All ear disorders	40 (30.5%)
Hearing impairment	18 (13.7%)
Tinnitus	16 (12.2%)
Autophony	9 (6.9%)
Ear fullness	17 (13%)
Mean onset after first infusion	9.1 weeks
Mean duration of adverse events that resolved	23.5 weeks
Percentage of adverse events resolved	52.5

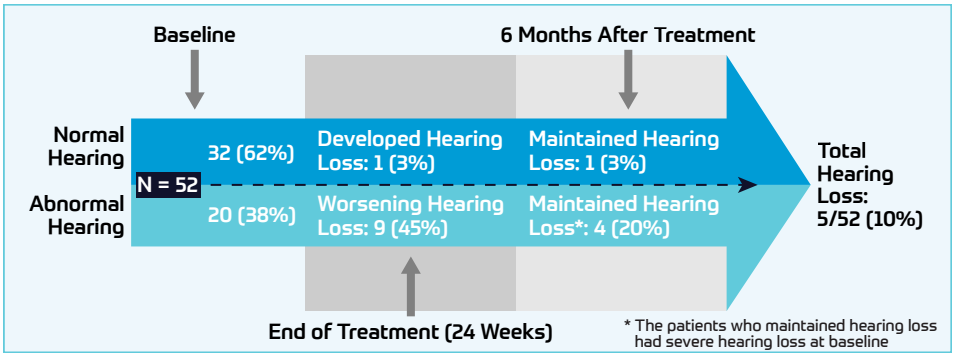


Figure 5. Hearing-related adverse events in a prospective study examining audiometry outcomes following treatment with teprotumumab[18]

This study was a more homogeneous group of patients, all of whom had baseline audiometry and none of whom were receiving other ototoxic medications.[18]

Dr Subramanian: I agree. Another study with baseline audiometry that was done by Keen et al was a retrospective review, in which they had data at baseline and up to 496 days after treatment.[19] Of the 44 ears assessed, 28 had baseline hearing loss.

Dr Alyono: The strength of both of these studies was that they performed baseline audiometry.[18,19] In the Keen study, objectively, 50% of patients met the ototoxic criteria in at least 1 of their ears after treatment. Six of the patients who met ototoxicity criteria did not report any symptoms **(Table 3)**.[19]

Table 3. Hearing Loss and Related Symptoms After Treatment With Teprotumumab[19]

	Number of Patients (%) (N = 22)	
Symptoms	Hearing Loss That Met Ototoxicity Criteria*	Hearing Loss That Did Not Meet Ototoxicity Criteria
No subjective symptoms	6 (27)	8 (36)
Subjective symptoms†‡	5 (23)	3 (14)

* Patients met the American Speech-Language-Hearing Association guidelines for hearing loss related to ototoxic exposure

† Symptoms included tinnitus, ear fullness, ear popping, hearing loss, autophony, ear pain, and vertigo

‡ All but 2 patients received all 8 infusions

MONITORING AND MANAGEMENT OF HEARING CHANGES WITH TEPROTUMUMAB

Given recent evidence, otolaryngologists recommend that those who prescribe teprotumumab work closely with audiologists and otolaryngologists.[20] Audiometric testing should occur at baseline, before teprotumumab is given.[3] Tests should be repeated if prescribers suspect that hearing changes are emerging during medication exposure and during follow-up.[11] Discontinuation should be considered if patients have ototoxicity or are concerned about hearing loss.

Hearing impairment related to teprotumumab needs further characterization. Baseline audiometry for all patients could help elucidate the true role of teprotumumab in documented hearing impairment,[21,22] with such impairment at ultrahigh frequencies being of special concern.[23] Importantly, studies have shown potential reversibility of reported hearing impairment in some patients.[7,9,11,18]

Dr Subramanian: Do you think it is useful to check hearing again 6 months following treatment to see if there has been worsening, improvement, or stability after the drug exits the system? At the end of treatment, there is still drug in the system.

Dr Alyono: I think we do not fully know the right answer. We need more data. I think patients who do have hearing loss or development of hearing loss should have a repeat hearing test at 6 months. If not, it is an open question.

CASE DISCUSSIONS

Case 1: TED With Comorbid Conditions and Hearing Loss During Teprotumumab Treatment

From the Files of Prem S. Subramanian, MD, PhD

A 67-year-old man presented in February 2020 reporting diplopia, red eyes, bilateral proptosis that was worse OD than OS, and new visual field changes.

- *Visual acuity, pupils, and motility normal*
- *Upper eyelid fullness, possible right upper lid ptosis, conjunctival injection, caruncle swollen*
- *Hertel: 25/22 base 95*
- *Thyroid-stimulating immunoglobulin and thyrotropin receptor antibody tests: Negative*
- *Thyroid function tests: WNL*
- *Clinical activity score: 4*

Other conditions of interest:

- *Strong family history of glaucoma, followed for years with borderline intraocular pressure (IOP) (maximum 21 mm Hg)*
  - *Recent concern for new visual field changes*
  - *Optical coherence tomography: Possible retinal nerve fiber layer thinning*
  - *Possible normal-tension glaucoma: Started timolol with good response*
- *Hypertension treated with 3 antihypertensive medications*
- *History of inflammatory bowel disease (IBD); off medications for more than 10 years*

Dr Subramanian: This patient was diagnosed with TED by another oculoplastic surgeon. I saw him via telemedicine consult in April 2020, just after everything shut down for the COVID-19 pandemic. He has had duration of symptoms for 6 months. His imaging demonstrated a little bit of enlargement of his EOM. This was interpreted by the radiologist as having increased T-1 signal in the inferior recti that was considered to be fatty infiltration. The STIR (short tau inversion recovery) image **(Figure 6)** was thought to be borderline hyperintensity in the EOM. He likely has moderate TED because he has proptosis. He has some diplopia, which is presumed to be from restrictive strabismus.

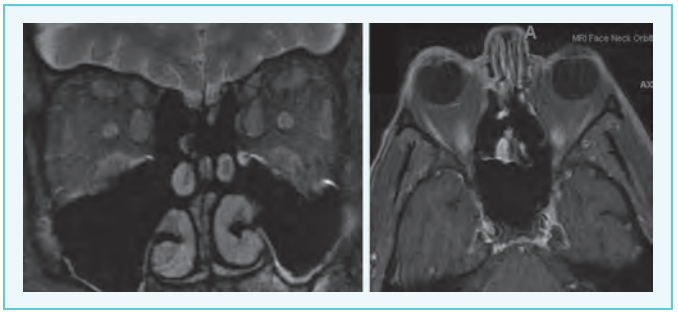


Figure 6. Short tau inversion recovery image of the patient in Case 1 showing borderline intensity in extraocular muscle

Teprotumumab had been on the market at that point for 2 months. The patient had a medical background and had heard about teprotumumab and asked if he should be treated with this agent. He takes 3 blood pressure medications and is a glaucoma suspect, so I wanted to avoid treating him with corticosteroids, if possible. The IBD is a potential contraindication, but he was willing to take that risk and wanted to be treated with teprotumumab. Dr Briceño, would you have done anything differently at this point?

Dr Briceño: No. In our center in April 2020, we were unable to do elective surgeries. The data looked promising in relation to the low percentage of patients who suffered serious AEs. So, yes, I would have felt the same way, and I would have been excited to get him on teprotumumab.

Dr Subramanian: He was excited to start treatment and came to see me just after his fourth infusion.

Follow-Up

- *After 4 infusions*
  - *Unsure of response, still having swelling in the morning*
  - *Mild flare of IBD*
  - *IOP stable*
  - *Hertel 23/22 base 95*
  - *Lateral flare OD, left upper lid retraction OS*
  - *Conjunctival injection*
- *After 5 infusions*
  - *Worsening muscle cramps, dysphagia*
  - *Notes hearing loss*
  - *Audiogram with "profound hearing loss" bilaterally*

Dr Subramanian: He was still having some swelling in the morning and was unsure if he had really had a response. He felt that possibly his IBD had actually flared a touch, but he was really not bothered by it. I was concerned that his glaucoma could be getting worse from his TED, which can happen, but his IOP was stable. His proptosis seemed to be down by 2 mm compared with what the previous oculoplastic surgeon had measured. Per my measuring, there is still relatively 1 mm as opposed to 3 mm before. As seen in the clinical trials, the more proptotic eye does seem to respond a little more than the less proptotic eye for reasons that are still unclear. He had not had a dramatic response yet, but I felt like he was improving, so we continued with therapy. At this point, he reported no hearing issue to me.

After his fifth infusion, he called in a panic, complaining of worsening muscle cramps. We know that 25% of patients in the clinical trials experienced muscle cramps; in my experience, this is up to 50%. The patient has now noticed hearing loss. An audiogram indicated that he had profound hearing loss bilaterally **(Figure 7)**. Approximately a year prior, he had been monitored for some concern for hearing loss with a baseline audiogram.

Dr Alyono, what do you think about this?

Dr Alyono: In audiometry, we classify hearing loss into different categories—mild, moderate, moderately severe, severe, and profound—according to what decibel level the pure tones reach. Frequently, we will define normal as anything 20 or 25 dB and above, mild hearing loss as up to 40 dB, moderate as 40 to 55 dB, moderately severe as 55 to 70 dB, severe as 70 to 90 dB, and profound as anything above 90 dB. So I would not have classified this patient as having profound hearing loss. I would have called his baseline level a normal down sloping to a moderately severe SNHL in his left ear. Then, 1 year later, there was progression particularly affecting the midfrequencies, which dropped from normal to mild levels, and additional progression in the higher tones. His word recognition decreased from 96% on each side to 80% in the right ear and 84% in the left ear. Is it statistically significant or not? Is that word recognition change within the test, retest variation? It very much could be. But at a minimum, the pure tone changes look real.

Dr Subramanian: So what to do now? The patient decided to stop his teprotumumab treatments. Upon stopping, his treatment effect did not regress, but he did not have any additional reduction of his proptosis or improvement in his TED signs and symptoms. His hearing loss did improve to

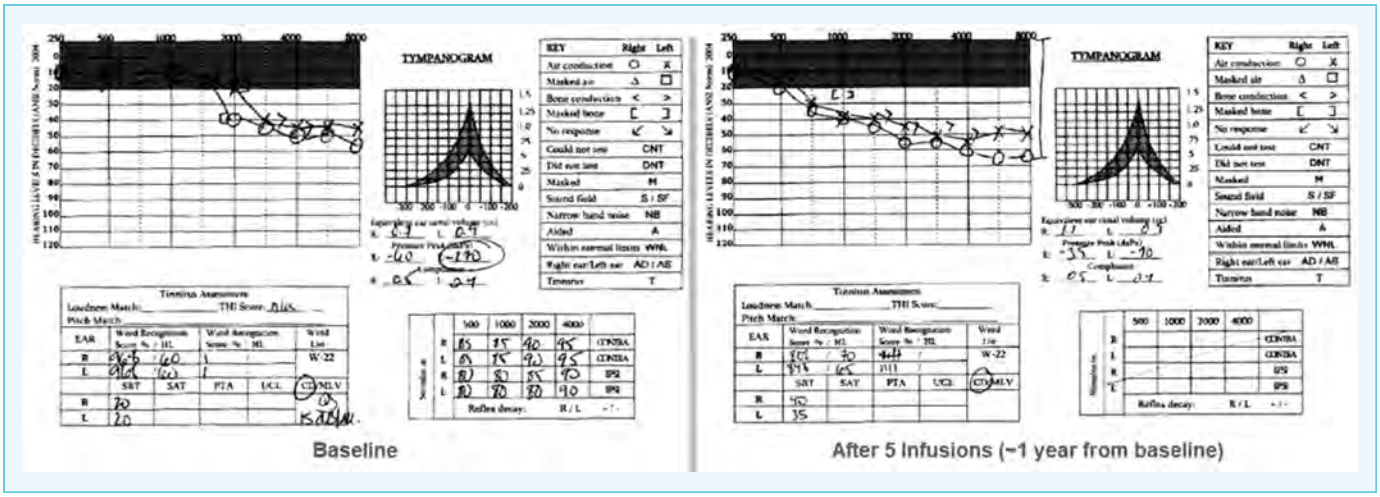


Figure 7. Hearing tests of the patient in Case 1 at baseline and following fifth infusion

some degree; the results on repeat testing in February 2021 were somewhat improved, although they were not back to his baseline level. He remains with some degree of hearing impairment as a result of the treatment.

This was my first case of SNHL in a patient on teprotumumab, and he did have a little bit of pretreatment baseline hearing impairment. Did that make him more susceptible to having hearing loss related to treatment? Data would suggest that perhaps it did.[24] Both the recent studies by Keen and Douglas that we discussed showed that baseline hearing loss was a risk factor for hearing loss with teprotumumab.[18,19]

Case 2: Noise Exposure and Hearing Loss During Teprotumumab Treatment

From the Files of Jennifer Alyono, MD, MS

A 66-year-old man noted gradually progressive hearing loss after completing 8 infusions of teprotumumab. He reported shooting at a gun range without hearing protection.

Dr Alyono: Because IGF-1 is somewhat neuroprotective if it is reduced, the mechanism in cases like this could be that some people are more susceptible to noise-induced hearing loss. This was questioned in this patient. **Figure 8** indicates that at his baseline level, he had some high frequency SNHL, which is the most common pattern we see with both aging and noise-induced hearing loss, and that it worsened after he completed all his infusions.

His word recognition dropped from 100% to 56%. This is concerning because hearing aids can make things louder, but they cannot make things clearer. So if your word recognition drops, that is critical. It is similar to a staticky radio station that is at a low volume—you can turn it up, but you cannot make it less staticky. This type of change is alarming for otologists. Happily, the patient's word recognition improved the next year, although his pure tones did not. But at least he progressed from someone who would hate his hearing aids because they would only amplify garbled speech to someone who might like his hearing aids.

Case 3: Report of Ear Fullness During Teprotumumab Treatment

From the Files of Jennifer Alyono, MD, MS

An 83-year-old woman reports intermittent ear fullness and increasing difficulty communicating with her family during treatment with teprotumumab.

Dr Alyono: This woman did not report hearing loss, only more difficulty communicating with her family. She did not have much change in her pure tones, but she had decreasing word recognitions during this whole time **(Figure 9)**. She went from 88% at baseline to 32% after the sixth infusion, after which she chose to stop receiving teprotumumab. Her word recognition did not improve even 1.5 years after she stopped all the infusions; it was 16% at that time. When you reach this level, hearing aids are not very helpful for many people: a cochlear implant may be the next step.

Case 4: Report of Hearing Loss Following a Second Course of Teprotumumab Treatment

From the Files of César Briceño, MD, MS

A 72-year-old woman with a long history of thyroid disease was initially diagnosed with hypothyroidism, and then became hyperthyroid in 2005 with simultaneous onset of TED. She was treated with radioactive iodine, which she reports helped her "bulging". She was referred by her retina specialist for evaluation of TED in early 2022. She had poor visual acuity at baseline OS (20/800) due to full-thickness, chronic macular hole. She had discomfort, pressure, and concerns about her appearance, which were suspected to be chronic congestive changes. Clinical activity score on presentation in late 2021 was 4 based on conjunctival injection, chemosis, edema of

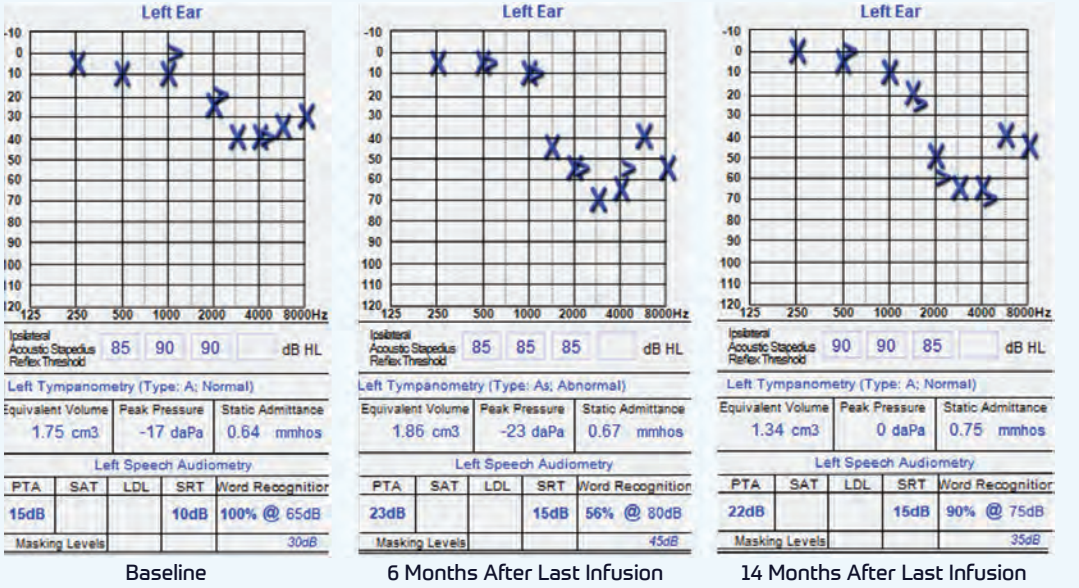
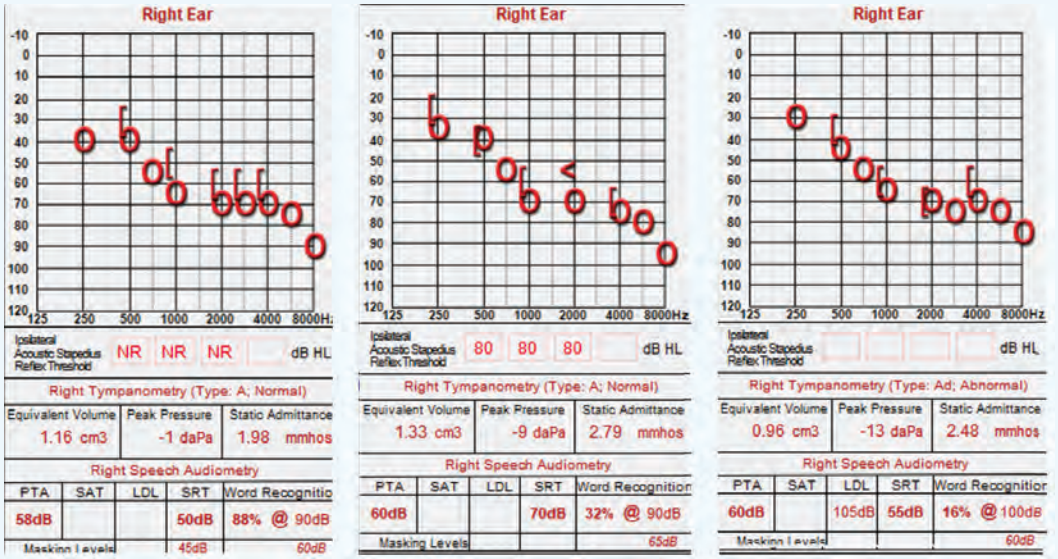


Figure 8. Audiograms of the patient in Case 2 at baseline, 6 months, and 14 months after treatment with teprotumumab

Abbreviations: LDL, loudness discomfort level; PTA, pure-tone average; SAT, speech awareness threshold, SRT, speech reception threshold.

Symbols: X, left ear; >, left bone conduction.



Baseline | After 6th Infusion (treatment stopped) | 1.5 Years After 6th Infusion

Figure 9. Audiograms of the patient in Case 3 at baseline, after infusion 6, and 1.5 years after stopping treatment

Abbreviations: LDL, loudness discomfort level; NR, no response; PTA; pure-tone average; SAT, speech awareness threshold; SRT, speech reception threshold.

Symbols: O, right ear; [, right bone conduction threshold.

the plica, and eyelid edema. She was treated with 1 course of teprotumumab, which was completed in November 2022. A second course of teprotumumab was started in February 2023 owing to residual proptosis and retro-orbital pain OS. This was just starting to improve at the end of the first course of teprotumumab.

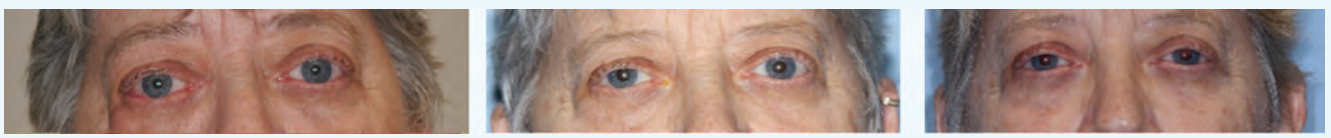
Dr Briceño: The patient tolerated her first course of teprotumumab quite well. She had some diarrhea, which was treated with loperamide, and she had some muscle cramps. I asked about subjective hearing loss, and she had zero complaints. In her baseline audiogram, she had some mild/moderate SNHL at 8000 Hz bilaterally, but she was completely unaware of it and felt she was functioning fine.

Dr Alyono, is that particular type of hearing loss at 8000 Hz clinically significant for most people? Or is that something most people would be asymptomatic to?

Dr Alyono: That would be within the range of an average 72-year-old. There is difficulty with defining what a clinically significant amount of hearing loss is or the threshold at which someone would say a patient's level of hearing loss is a contraindication to getting treated. In the end, you are just balancing the risk/benefit globally. I think some of the difficulty is we do not fully know if the hearing loss with teprotumumab is irreversible. Every one of us is going to have more hearing loss as we age. If you add a little bit more to that along the way, how significant is that going to be? Additionally, does treatment with teprotumumab now predispose to more hearing loss later? Platinum chemotherapeutics, for example, have been shown to increase hearing loss years after people have been treated.

Dr Briceño: That is a good point. When she was close to her final infusion of her first series, she started to notice that her left eye, which is her worse eye, was finally getting better, which caused her to be really sad about having to finish at 8 infusions. She said, "I do not want to have surgery. Do you think we can do this again?" I asked her if she was sure and if she had any complaints about her hearing. She had no hearing complaints and wanted to move forward with another course, during which she had no hearing complaints. She still had no hearing complaints after she finished the second course of teprotumumab in November 2023. She looks good and feels great **(Figure 10)**.

At follow-up after completing her second course, she reported that she had experienced "muffled, stuffy hearing" that lasted for approximately 4 weeks, and then it was entirely gone. Right now, I am awaiting the results of her next audiogram. She told me, "I would do it again. This was amazing. I'm fine. It was only at the end of the second [course], and I would do it again." To me, her case brought up a couple of interesting points. Firstly, she had a delayed response to the drug itself. Therefore, she is someone who is unlike most patients who



Before First Course of Teprotumumab Treatment 2022 | After First Course of Teprotumumab Treatment 2022 | After Second Course of Teprotumumab Treatment 2022

Figure 10. Treatment results of the patient in Case 4 with 2 courses of teprotumumab

start seeing benefits within the second or third infusion and experience a fairly dramatic improvement by the eighth infusion. This patient was in the middle of the road after infusion 8, and it took 16 infusions to get her to where she wanted to be. She is a person with chronic disease, so that may be part of the reason that it took her longer to have a response. Secondly, the AEs took that long to show up, at least subjectively.

MULTIDISCIPLINARY MANAGEMENT OF TEPROTUMUMAB-RELATED HEARING LOSS

Comanagement with an ENT, audiologist, or otolaryngologist is recommended when prescribing IGF-1R inhibitors because of the potential for hearing loss.[2,18] This is especially important at baseline and if symptoms occur during treatment, but it can be beneficial even after treatment.[17]

> *From a multidisciplinary standpoint, I have been fortunate to have ENT specialists to rely on, which is helpful because sometimes getting people in to see an ENT is difficult. I think, to the degree that clinicians can do that—either within their academic institution or within their geographic region—the idea of building your own network that you can rely on results in benefiting the patients.*
>
> *–César A. Briceño, MD*

TAKE-HOME POINTS

- Ototoxicity can be a serious and potentially irreversible AE with teprotumumab
  - Counsel patients on this risk and screen for hearing symptoms at all visits
- Recommend obtaining an audiogram baseline and halfway through the 8-course infusion and after any subjective otologic changes; consider altering treatment depending on the results
- Recommend obtaining an audiogram after the conclusion of treatment if possible

We hope you enjoyed this monograph and learned something new. If you have general questions on this topic, please email them to TED@mededicus.com. Questions will be collated, and responses will be posted quarterly throughout 2024. To see questions and answers, scan the QR code.

Complete the CME posttest online at *https://tinyurl.com/TEDhearingloss*

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See detailed instructions at **Instructions for Obtaining Credit** on page 2.

1. In a prospective case series examining hearing dysfunction after teprotumumab treatment, the symptoms that had the highest resolution rate were:
   a. Ear fullness and muffled conversation sounds
   b. Disequilibrium and reduced word comprehension
   c. Oscillopsia, autophony, and tinnitus
   d. Autophony, ear fullness, and tinnitus

2. A 47-year-old woman who works as a flight attendant was treated with 3 doses of teprotumumab before stopping because of her work schedule in 2021. At that time, she had not seen much improvement in her appearance and had complaints of muffled hearing. Today, she is asking to resume treatment owing to discomfort and concerns about her appearance. Which of the following is the best course of action?
   a. Counsel her that her previous lack of response, otologic symptoms, and occupation make her a poor candidate for treatment
   b. Order an audiogram and schedule an appointment to discuss treatment after the results come back
   c. Begin treatment and have audiometric testing performed halfway through the course and at the last infusion
   d. Discuss the risks of hearing impairment and advise she will need monthly audiograms after treatment is started

3. A 72-year-old man with severe thyroid eye disease has a dramatic improvement in appearance and symptoms after 4 doses of teprotumumab but develops sensorineural hearing loss following the sixth dose. He asks if he should stop treatment. It is most appropriate to counsel him that sensorineural hearing loss:
   a. Has been reported to resolve after treatment but may be permanent
   b. Was rarely reported in studies unless other ototoxic medications were present
   c. Was reversible in the studies assessing hearing loss with teprotumumab
   d. Was commonly reported in older adults and is unrelated to teprotumumab