When TED Talks Listen Up!

An Update on Thyroid Eye Disease.

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When TED Talks Listen Up!

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Disclosures

- Jacob Lang OD, FAAO •
- Speaker; Novartis, Sun Pharma, Allergan
- Consultant; Novartis, Sun Pharma, Allergan, Ocular Therapeutix, Orasis, AOS, and Horizon •

Graves' Disease

- Approximately 25 per 100,000
- Most common cause of HYPERthyroidism
- Autoantibodies against TSHR trigger excessive production of thyroid hormones
- Goal of treatment is to inhibit production of thyroid hormones
 - RAI Therapy
 - Medications
 - Surgery
 - Thyroid supplementation

The condition is named after Irish surgeon Robert Graves, who described it in 1835.



- 16 out of 100,000 women
- 5x LESS likely in men
 - (but men tend to have more severe disease)
- Two peaks of incidence occur in patients at 40–49 and 60–69 years of age
- Smoking increases risk of TED 8 fold
- 20% risk of new or worsening TED after RAI treatment





Thyroid Eye Disease



- Thyroid eye disease (TED) is the most common orbital disease in North America and is frequently associated with Graves' disease.
- Although TED often occurs in patients with hyperthyroidism, it is a distinct disease, and treating the underlying systemic thyroid dysfunction often does not resolve the ocular signs and symptoms.

• At the root of this condition's pathophysiology is the activation of orbital fibroblasts by autoantibodies, which leads to orbital inflammation early on in the disease and subsequent fibrosis.





- Subsequent Ocular Pathologies
 - Dry Eye
 - Exposure / Proptosis
 - Lid Retraction/Lagophthalmos
 - Blink Dynamics/Frictional Forces •
 - Ocular Inflammation
 - Autoimmune Conditions
 - Optic Nerve Compression
 - Inflammation and fibrosis inside a confined space
 - Diplopia
 - EOM infiltration, Inflammation, and Fibrosis















- Up to 50% of patients with Graves' disease will develop TED
- 10% of patients with TED are euthyroid or hypothyroid

Graves'



- TED has long been a disease of "watching and waiting"
- Traditional treatments have been fraught with poor response rates and significant side effects. (steroids, radiation, etc.)
- Surgical intervention is reserved for severe cases involving vision loss and focuses on controlling inflammation, but patients often still require surgical rehabilitation after reaching the fibratic phase



Rundle's Curve Was TED his first name?

• The active phase is typically a self-limited process that lasts an average of <u>one</u> year in nonsmokers and <u>two to three</u> years in smokers



The Most Common Manifestations of TED

Conjunctiva and Cornea^{1,2}

- Chemosis
- Conjunctival redness
- Epiphora ٠
- Photophobia
- Foreign body sensation
- Pain .
- Exposure keratopathy



From Novaes et al. Clin Diabetes Endocrinol. 2016;2:19. Reprinted with permission.4

Proptosis^{2,3}

- Proptosis
 - 62% affected
- Pain/deep ache
- Disfigurement



From Novaes et al. Clin Diabetes Endocrinol. 2016;2:19. Reprinted with permission⁴

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From Bartalena L. Graves' Disease: Complications. https:// www.ncbi.nlm.nih.gov/books/NBK285551/?report=classic Reprinted with permission. Reprinted with permission.⁵

- Eyelid retraction:
 - 91% affected
- Eyelid swelling
- Pain .
- Lagophthalmos

Extraocular Muscle^{2,6}



- Diplopia
 - 51% affected
- Strabismus
- Pain/deep ache





- Physicians view TED as a self-limiting disease,
 - Only 2% of patients consider themselves recovered at the end of this phase



ease, res recovered at the end of this phase

- Current treatment for TED focuses primarily on supportive and palliative care and includes ocular lubrication, prism glasses for diplopia and lifestyle modifications, such as smoking cessation, selenium and vitamin D supplementation and systemic thyroid disease control.
- Once a patient is in the stable phase, some undergo surgical intervention, including orbital decompression, strabismus surgery and eyelid reconstruction.
- Urgent surgery is reserved for severe situations involving compressive optic neuropathy or extensive corneal exposure.



- Unfortunately, often overlooked or under-acknowledged in treatment is the chronic ocular discomfort, visual impairment and morbidity rate commonly associated with TED.
- This disease severely impacts patients emotionally and psychologically, which is also too often under-treated.

"New Normal" for Therapy

- Research revealed a signaling pathway that involves activation of insulin-like growth factor 1 receptors (IGF-1R) in patients with Graves' disease.
- This pathway acts synergistically with thyroid-stimulating hormone receptors and enhances the mechanism of action, increasing orbital tissue inflammation.
- By blocking the IGF-1R, the actions of IGF-1 are inhibited and the inflammatory and proliferative process associated with Graves' ophthalmopathy may be diminished.

Teprotumumab

- Recent FDA approval of Teprotumumab (Tepezza, Horizon Therapeutics), an antigen-specific therapy designed to block IGF-1R and halt the signaling pathway.
- A Phase III trial found that teprotumumab could significantly reduce both proptosis and diplopia in patients with active, moderate-to-severe TED.
- At week 24, 83% of patients (10% of controls) experienced a reduction in proptosis.
- Each secondary outcome had also significantly improved with teprotumumab than with placebo. (Clinical Activity Score, Diplopia, Quality of Life Score)

The NEW ENGLAND JOURNAL of MEDICINE

Teprotumumab for the Treatment of Active Thyroid Eye Disease

R.S. Douglas, G.J. Kahaly, A. Patel, S. Sile, E.H.Z. Thompson, R. Perdok, J.C. Fleming, B.T. Fowler, C. Marcocci, M. Marinò, A. Antonelli, R. Dailey, G.J. Harris, A. Eckstein, J. Schiffman, R. Tang, C. Nelson, M. Salvi, S. Wester, J.W. Sherman, T. Vescio, R.J. Holt, and T.J. Smith

CONCLUSIONS

Among patients with active thyroid eye disease, teprotumumab resulted in better outcomes with respect to proptosis, Clinical Activity Score, diplopia, and quality of life than placebo; serious adverse events were uncommon. (Funded by Horizon Therapeutics; OPTIC ClinicalTrials.gov number, NCT03298867, and EudraCT number, 2017-002763-18.)

ORIGINAL ARTICLE

Teprotumumab

Baseline Bas





Daniel J. Ozzello, Don O. Kikkawa, Bobby S. Korn, Early experience with teprotumumab for chronic thyroid eye disease, American Journal of Ophthalmology Case Reports, Volume 19, 2020

A 50-year-old female with a 3-year history of Graves' disease presented with bilateral exophthalmos greatest on the left side. She was followed for 2 years with stable proptosis measurements (23mm OD, 28mm OS). Her clinical activity score (CAS) was 1 and there were no examination findings reflective of active inflammation. The patient underwent systemic treatment with teprotumumab and despite chronic TED and low CAS, she had notable improvement in proptosis (18mm OD, 22mm OS) and decrease in extraocular muscle volume as noted on orbital imaging.

Teprotumumab Side Effects

- The most common adverse events included muscle spasm, alopecia, nausea and fatigue, the majority of which were mild in severity and resolved after treatment.
- Adverse effects of special interest included
- Hyperglycemia in two patients
- Hearing impairment in five patients (two had hypoacusis, one had deafness, one had autophony and one had mild patulous eustachian tube) in the teprotumumab group, all of which resolved without treatment.

Teprotumumab Side Effects

- Hearing impairment in five patients (two had hypoacusis, one had deafness, one had autophony and one had mild patulous eustachian tube) in the teprotumumab group, all of which resolved without treatment.
 - Hypoacusis is defined as a functional deficit that arises when a person loses some degree of their auditory capacity.
 - Deafness a more complete impairment that inhibits linguistics.

Teprotumumab Side Effects

- Autophony is the unusually loud hearing of a person's own voice.
- With patulous (think open) Eustachian tube, variations in upper airway pressure associated with respiration are transmitted to the middle ear through the Eustachian tube. This causes an unpleasant fullness feeling in the middle ear and alters the auditory perception. Complaints seem to include muffled hearing and autophony. In addition, patulous Eustachian tube generally feels dry with no clogged feeling or sinus pressure.

- Shatters the "watch and wait" mentality
- Challenges practitioners to be on the lookout for this disease so we can treat it earlier and more effectively than ever before.
- It's also encouraging to know there is now something we can offer patients that will alter the course of their disease and improve their quality of life.



Teprotumumab

Signs of TED Might NOT be just "OSD"

- Orbital congestion (not to be mistaken for conjunctivitis)
- Allergic conjunctivitis without any papillary reaction that doesn't improve with allergy drops
- Unexplained changes in vision that are inconsistent with corneal changes from dryness or other pathologies, which can actually be caused by low-grade chronic compressive optic neuropathy
 - Resistance to retropulsion, an unsatisfactory response to a careful motility check and lid lag on down-gaze can help with this diagnosis
 Optic nerve imaging with OCT and visual field testing can be helpful in
 - Optic nerve imaging with OCT and vis these cases

Signs of TED Might NOT be just "OSD"

- Temporal chemosis with injection overlying the extraocular muscles
- associated with dry eye and other corneal disorders



• Chronic ocular ache and pain as opposed to the more common sharp pains

Labs for Eyecare

- TSH
- T3
- T4

- Thyroid-Stimulating Immunoglobulin, (Serum)

TSI

• The majority of TRAb assays detect both TSI and TBAb (Thyroid blocking antibodies) • TSH, T3, T4 are measures of thyroid activity and this has LITTLE relevance with regard to TED

Labs for Eyecare TSI

- IgG Antibody
- Mimics TSH
- Reacts with ocular tissues in TED
 - Thyroid-Stimulating Immunoglobulin, (Serum)
 - The majority of TRAb assays detect both TSI and TBAb (Thyroid blocking antibodies)

• TSH, T3, T4 are measures of thyroid activity and this has LITTLE relevance with regard to TED

- Current Patient Journey
 - Patient-PCP-Endocrinology-Ophthamology-NeuroOphthalmology-Oculoplastics •
- Optometry has an opportunity and an obligation to identify and treat these patients early in their disease.
 - Remember early symptoms of TED
 - •65% DED
 - •51% Diplopia
 - •32% Blurry Vision
 - •13% VF Defects
 - •7% Reduced Color Vision
 - 6-9% Severe Sight Threatening Optic Neuropathy

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Integrated Collaborative Care

Oculoplastic Surgeon Endocrinology PCP

Begin to build your own network within your community. Become a resource for PCP's and Endocrinology.



Patient Journey

Patient and Caregiver Resources

<u>https://drive.google.com/file/d/1k-kaM5uR4AIMNOFzXOvvnB-</u> <u>PjqBY43_H/view?usp=sharing</u>

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Thank You



Thank You



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Disease

chance at recovery.

By Jacob Lang, OD, Nicole Harris, OD, and Sara Tullis Wester, MD



Racing the Rundle Against Thyroid Eye

A new clinical approach to this condition may give patients a fighting



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Thank You