

When
TED Talks
Listen Up!

***An Update on Thyroid
Eye Disease.***

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What makes you suspicious of Thyroid Eye Disease?

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Have you seen a patient with Thyroid Eye Disease in the last 6 months

Yes

No

C

D

None of the above

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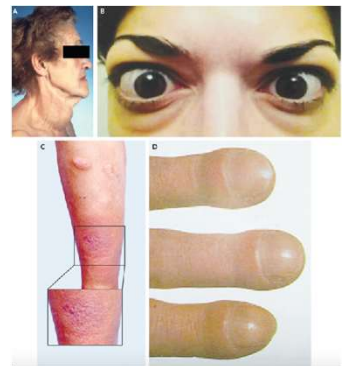
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Financial Disclosures-Jacob Lang, OD, FAAO

- ▶ Oyster Point
- ▶ Allergan,
- ▶ Avellino,
- ▶ Aldeyra,
- ▶ Dompe',
- ▶ Kala,
- ▶ Novartis,
- ▶ AOS,
- ▶ Scope,
- ▶ Sun Pharma,
- ▶ Tarsus,
- ▶ Quidel,
- ▶ Horizon,
- ▶ Aerie,
- ▶ Ocular Therapeutix,
- ▶ Orasis,

Grave's Disease

- Approximately 25 per 100,000
- 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



Thyroid Eye Disease

- 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



Epidemiology of TED

Age-adjusted US incidence



16 cases per 100,000 per person per year (PPPY)



3 cases per 100,000 PPPY

- Two peaks of incidence occur in patients at 40-49 and 60-69 years of age

Thyroid Eye Disease*

*NOT Technology, Entertainment and Design

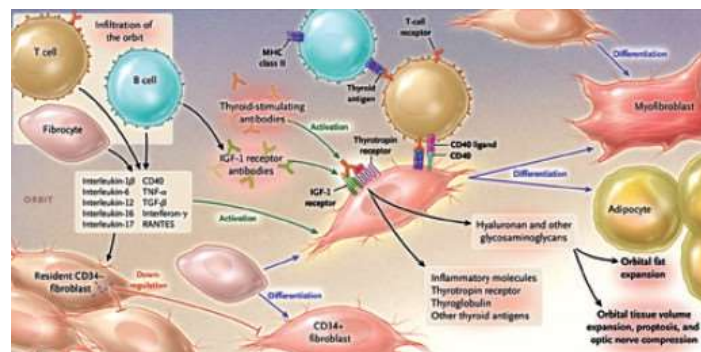
9

- ◆ 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.

Thyroid Eye Disease

NOT Technology, Entertainment and Design

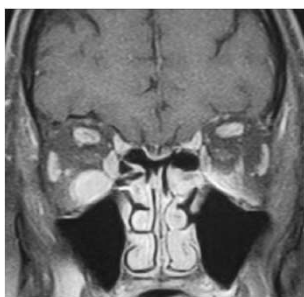
- ◆ At the root of this condition's pathophysiology is the activation of orbital fibroblasts by autoantibodies, which leads to orbital inflammation early on in the disease and subsequent fibrosis.



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Thyroid Eye Disease

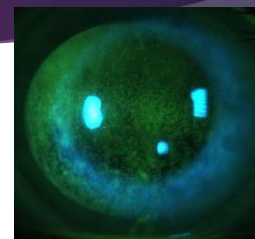
- ◆ At the root of this condition's pathophysiology is the activation of orbital fibroblasts by autoantibodies, which leads to orbital inflammation early on in the disease and subsequent fibrosis.



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Thyroid Eye Disease

- 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



The Most Common Manifestations of TED

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Conjunctiva and Cornea^{1,2}

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



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

Eyelid^{1,3}

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



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

Proptosis^{2,3}

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



Extraocular Muscle^{2,6}

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



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

1. Wang Y, et al. *The Clin Risk Manag.* 2019;15:1305-1318. 2. Patel A, Yang H, Douglas RS. *Am J Ophthalmol.* 2019;208:281-288. 3. Bartley GB, et al. *Am J Ophthalmol.* 1996;121(3):284-290. 4. Novaes, et al. *Clin Diabetes Endocrinol.* 2016;2:19. doi: 10.1186/s40842-016-0037-5. 5. Bartalena L. Graves' Disease: Complications. In: Feingold KR, Anawalt B, Boyce A, et al., editors. *Endotext* [Internet]. <https://www.ncbi.nlm.nih.gov/books/NBK285551/report-classic>. Accessed December 13, 2019. 6. Terwee C, et al. *Eur J Endocrinol.* 2002;146(6):751-757.

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If you suspect TED, what would you do next

PUNT

Treat

Order Imaging and Labs

Watch and Wait

None of the above

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Where would you refer a patient with TED?

PCP

General Ophthalmologist

Neuro-Ophthalmologist

Oculoplastics

Endocrinologist

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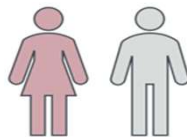
TED Risk Factors



Increases the risk of developing TED by 2- to 8-fold¹⁻³



Risk of developing new onset or worsening of TED is \approx 20% after RAI treatment⁴



Women at higher risk but men have elevated risk for more severe TED^{5,6}



Odds of TED increase by 17% with each decade of age progression³



TRAb levels may correlate with prognosis⁷

RAI, radioactive iodine; TRAb, thyroid autoantibodies.

1. Prummel MF, et al. JAMA. 1993;269(4):479-482. 2. Manji N, et al. J Clin Endocrinol Metab. 2006;91(12):4873-4880. 3. Khong JJ, et al. J Clin Endocrinol Metab. 2016;101(7):2711-2720. 4. Ponto KA, et al. Thyroid. 2010;20(7):785-793. 5. Perros P, et al. Clin Endocrinol (Oxf). 1993;38(4):367-372. 6. Bartley GB. Trans Am Ophthalmol Soc. 1994;92:477-588. 7. Roos JCP, et al. Eye. 2019;33:212-217.

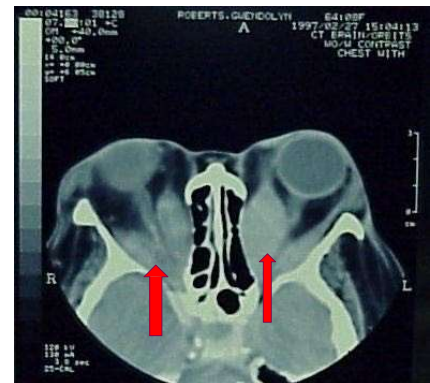
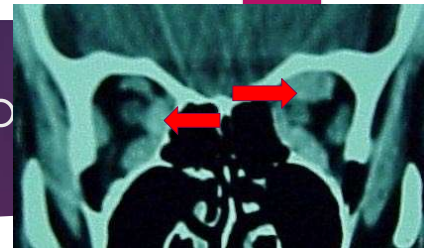
Case Report 1

- 52 year old female with history of Graves disease treated with radioactive iodine 12 months ago noted increased redness and “bug-eyed” over the last 3-4 months
- Denies double vision, nor pain, does feel eyes are very dry and vision not as good. Eyes do not close at night
- Meds: Synthroid and artificial tears 4 times a day.
- Best corrected 20/20 OU
- Color plates 12/14 OU
- IOP 17/18, however 25/27 in upgaze
- Superficial punctate staining on the inferior cornea OU,
- 1-2+ injection of vessels over horizontal recti muscles
- Hertels 24/25 with base of 100, lagophthalmus, superior and inferior scleral show
- Normal optic nerve and fundus



Photos courtesy of Scott Sigler, MD

CT and post-surgical lid correction



Photos courtesy of Scott Sigler, MD

Case 1



	LEFT Eye	Right Eye
Proptosis (mm)	29	27
Diplopia	1	1
CAS	7	5

CFB: change from baseline; CAS: Clinical Activity Score
Photos provided with permission from patients of Dr. Douglas

Douglas RS, et al. N Engl J Med. 2020;382(4):341-352..

Case 2



	RIGHT Eye	LEFT Eye
Proptosis (mm)	24	24
Diplopia	0	0
CAS	5	5

CFB: change from baseline; CAS: Clinical Activity Score
Photos provided with permission from patients of Dr. Douglas

Douglas RS, et al. N Engl J Med. 2020;382(4):341-352..

Case 3



	RIGHT Eye	Eye LEFT
Proptosis (mm)	25	24
Diplopia	1	1
CAS	6	6

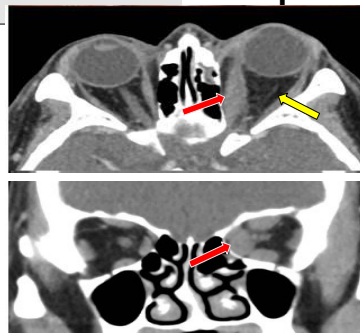
CFB: change from baseline; CAS: Clinical Activity Score
 Photos provided with permission from patients of Dr. Douglas

Douglas RS, et al. N Engl J Med. 2020;382(4):341-352..

Case 4



	RIGHT Eye	Eye LEFT
Proptosis (mm)	23	28
Diplopia	NA	NA
CAS	1	1



RED: EOM
 YELLOW: Orbital Fat

EOM: extraocular muscle
 Ozzello DJ, et al. Am J Ophthalmol Case Rep. 2020;19:100744.



CASE PRESENTATION

65 y/o female with 4 months of eyelid swelling & redness

Diagnosed as allergy vs inflammation

- ▶ Treated with oral steroids x 8 weeks

She developed double vision

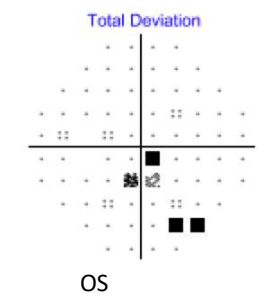
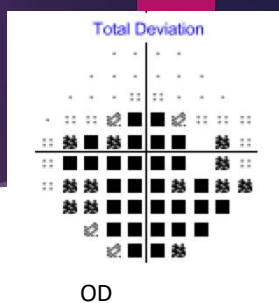
- ▶ Diagnosed with TED
- ▶ Treated with IV methylprednisolone 500 mg/week x 6 weeks then 250 mg

Developed loss of color vision



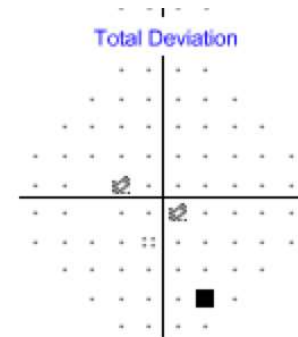
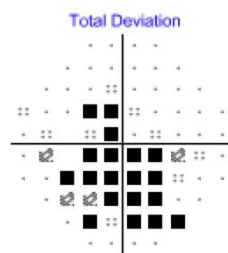
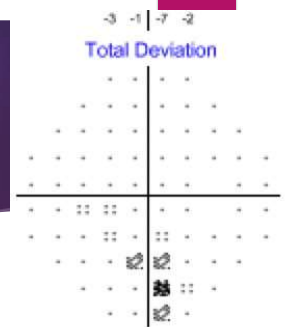
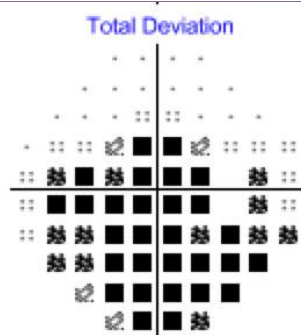
Eye Exam

- ▶ Vision:
 - ▶ 20/80 OD 20/60 OS
- ▶ IOP: 28 OD, 26 OS
 - ▶ Steroid response
- ▶ EOM: -2 upgaze OD
- ▶ Pupils: 1+ RAPD OD
- ▶ Color Vision 0/14 OD
 - ▶ 14/14 OS



Compressive Optic Neuropathy

- ▶ Orbital decompression
OD & IV steroids
 - ▶ VA OD: 20/80 → 20/30
- ▶ Active inflammation OS
 - ▶ Treated with orbital XRT OS
- ▶ Developed CON OS
 - ▶ + APD OS
- ▶ IV steroids 1g qd x 3
- ▶ Orbital decompression OS
 - ▶ VA OD: 20/30 → 20/25



Next Steps

- ▶ Restrictive strabismus
- ▶ Eyelid retraction
- ▶ Treated with:
 - ▶ Strabismus surgery
 - ▶ Bilateral upper lid retraction repair



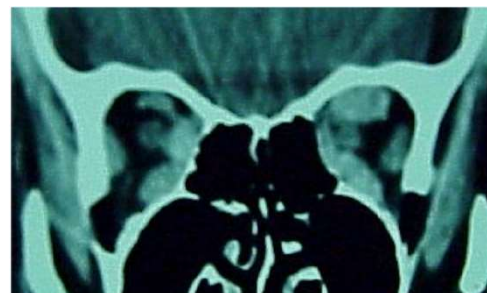


“I'M SLOW”

- ◆ Inferior rectus
- ◆ Medial,
- ◆ Superior,
- ◆ Lateral
- ◆ and then Oblique.

- ◆ Fibrotic Restriction

- ◆ Inability to look up when the eye is adducted



Grade*	Lid retraction	Soft tissues	Proptosis†	Diplopia	Corneal exposure	Optic nerve status
Mild	<2 mm	Mild involvement	<3 mm	Transient or absent	Absent	Normal
Moderate	≥2 mm	Moderate involvement	≥3 mm	Inconstant	Mild	Normal
Severe	≥2 mm	Severe involvement	≥3 mm	Constant	Mild	Normal
Sight threatening	—	—	—	—	Severe	Compression

*Mild TED: Patients whose features of TED have only a minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment.

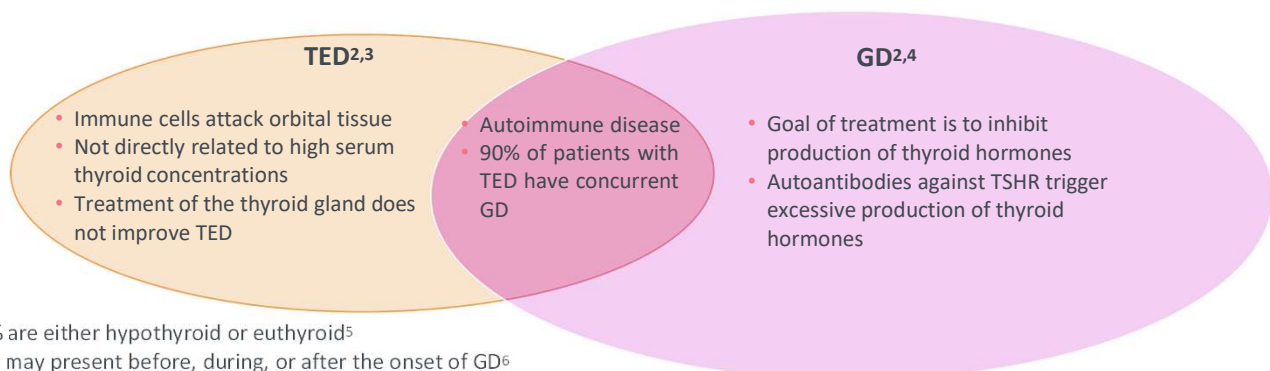
Moderate-to-severe TED: patients without sight-threatening TED whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Sight-threatening TED: patients with dysthyroid optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.

†Proptosis refers to the variation compared to the upper limit of normal for each race/sex or the patient's baseline, if available.

Ross DS, et al. *Thyroid*. 2016; 26(10):1343-1421

TED Is the Most Common Extrathyroidal Manifestation of Graves' Disease

Up to 50% of patients with Graves' disease (GD) will develop TED¹



TSHR, thyroid-stimulating hormone receptor.

1. Piantanida E, et al. *J Endocrinol Invest*. 2013;36(6):444-449. 2. Thyroid eye disease (TED or Graves' eye disease). <https://www.umkelloggeye.org/conditions-treatments/thyroid-eye-disease>. Accessed February 14, 2019. 3. Gwinup G, et al. *JAMA*. 1982;247(15):2135-2138. 4. Menconi F, et al. *Autoimmun Rev*. 2014;13(4-5):398-402. 5. Bartley GB, et al. *Am J Ophthalmol*. 1996;121(4):426-434. 6. Eckstein AK, et al. *Br J Ophthalmol*. 2009;93(8):1052-1056.

TED

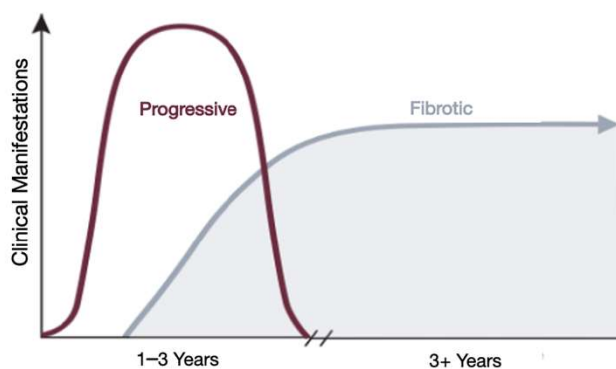


- ◆ TED has long been a disease of “watching and waiting”
- ◆ Traditional treatments have been fraught with poor response rates and significant side effects.
- ◆ Surgical intervention is reserved for severe cases involving vision loss and focuses on controlling inflammation, but patients often still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

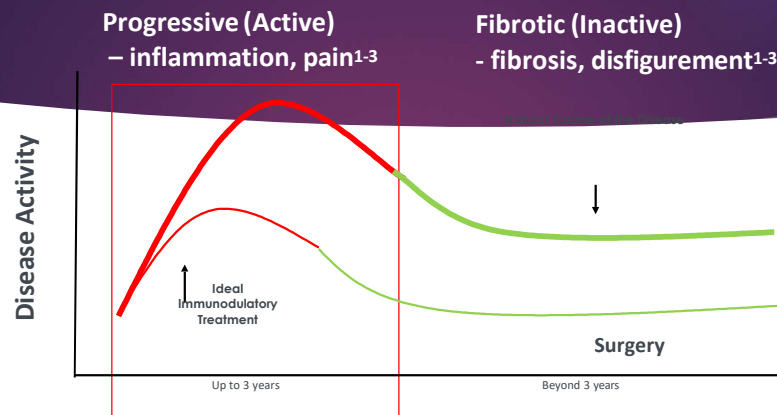
Rundle's Curve

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- ▶ The active phase is typically a self-limited process that lasts an average of **one** year in nonsmokers and **two to three** years in smokers



Limited Window for Treatment During Active TED^{1,2}



**Once TED is inactive, medical therapy may not help.
Surgical intervention may be the only option, and, in some cases, it is also unsuccessful²⁻⁵**

1. Bothun ED, et al. Clin Ophthalmol. 2009;3:543-551. 2. Barrio-Barrio J, et al. J Ophthalmol. 2015;2015:249125. 3. Dickinson AJ, et al. In: Wiersinga WM, Kahaly GJ, eds. Basel: Karger; 2017:1-25. 4. Bartalena L, et al. Eur Thyroid J. 2016;5(1):9-26. 5. Rootman DB, et al. Ophthalmic Plast Reconstr Surg. 2017;33(4):289-293.

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



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Labs for Eyecare

- ◆ TSH
- ◆ T3
- ◆ T4

TSI

- ◆ Thyroid-Stimulating Immunoglobulin, (Serum)
- ◆ The majority of TBAb 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

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Labs for Eyecare

- ◆ IgG Antibody
- ◆ Mimics TSH
- ◆ Reacts with ocular tissues in TED

- ◆ Thyroid-Stimulating Immunoglobulin, (Serum)
- ◆ The majority of TBAb 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

TED Treatment

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- ◆ 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.



Quality of Life

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- ◆ 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.

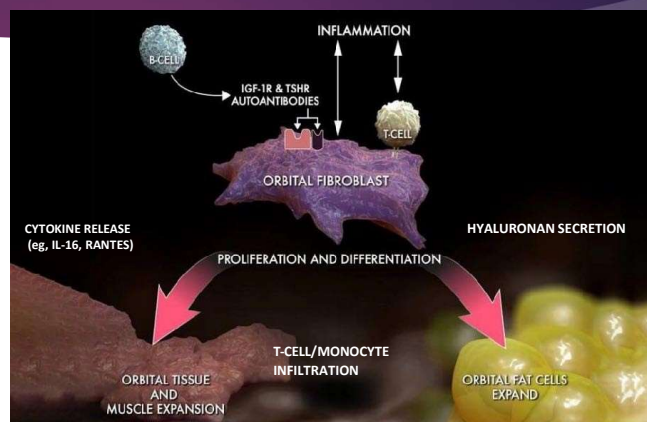
“New Normal” for Therapy

- 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.

TED is Driven by Autoantibody Activation of Insulin Growth Factor-1 Receptor (IGF-1R)

Orbital fibroblasts are the principal cells that drive the inflammation and expansion of orbital soft tissue, muscle, and fat¹⁻⁴

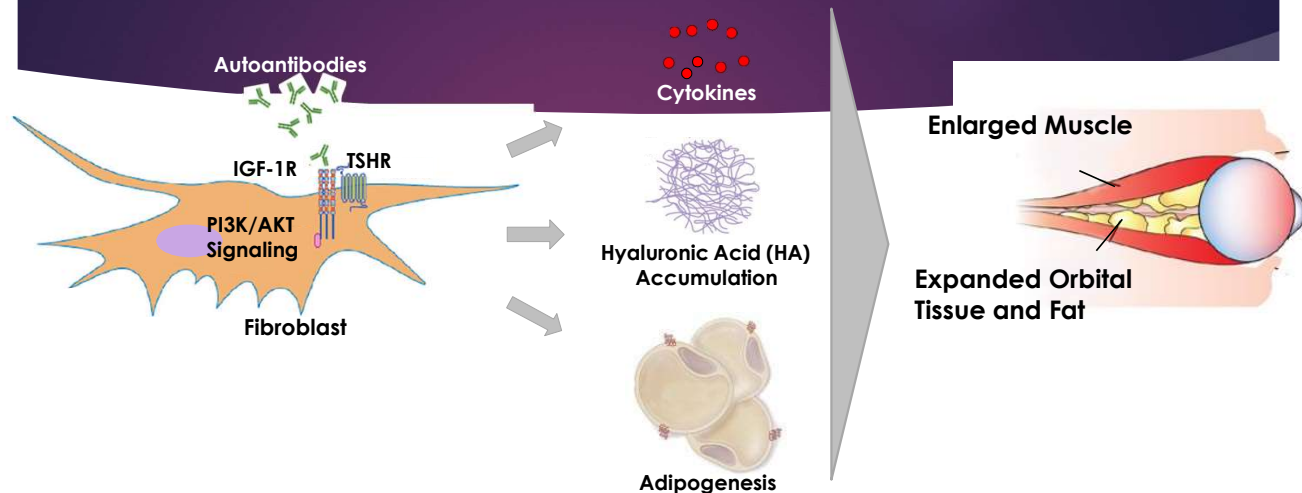
- IGF-1R and TSHR form a receptor-signaling complex and colocalize in orbital fibroblasts⁵
- IGF-1R is overexpressed in TED orbital fibroblasts⁵
- Activation of IGF-1R stimulates release of inflammatory cytokines and production of hyaluronan^{6,7}



IGF-1R, insulin-like growth factor-1 receptor; IL-16, interleukin-16; RANTES, regulated on activation, normal T cell expressed.

1. Smith TJ, et al. Thyroid. 2008;18(9):983-988. 2. Smith T. Pharmacological Rev. 2010;62(2):199-236. 3. Bahn RS. N Engl J Med. 2010;362(8):726-738. 4. Shan SJ, et al. J Neuroophthalmol. 2014;34(2):177-185. 5. Tsui S, et al. J Immunol. 2008;181:4397-4405. 6. Pritchard J, et al. J Immunol. 2003;170:6348-6354. 7. Smith TJ, et al. J Clin Endocrinol Metab. 2004;89:5076-5080.

IGF-1R is Central to Pathogenesis of TED



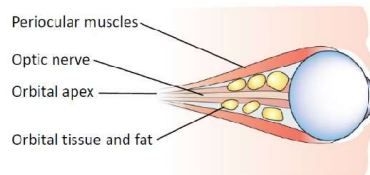
- ▶ IGF-1R is necessary for downstream signaling and structural changes driving disease

Smith TJ and Janssen J 2018 Endo Rev. DOI: 10.1210/er.2018\00066, Iyer S et al Prac Res Clin Endo Metab. 26:281, Douglas 2019 Eye 33:183

Inflammation, Tissue Expansion, and Eye Muscle Changes Lead to the Clinical Manifestations of TED

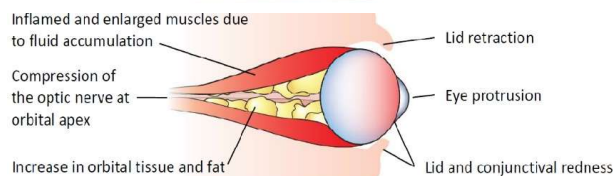
Activation of the IGF-1R/TSHR signaling complex on orbital fibroblasts, triggers the inflammatory response, leading to tissue expansion and remodeling in the eye¹⁻⁴

Healthy Eye and Orbital Tissue



- Eye is well protected by lid
- Thin periocular muscles
- Optic nerve can easily pass through apex
- Orbit contains a small amount of tissue and fat

In Presence of TED



1. Pritchard J, et al. J Immunol. 2003;170(12):6348-6354. 2. Smith TJ, Hoa N. J Clin Endocrinol Metab. 2004;89(10):5076-5080. 3. Sorisky A, et al. J Clin Endocrinol Metab. 1996;81(9):3428-3431. 4. Valyasevi RW, et al. J Clin Endocrinol Metab. 1999;84(7):2557-2562.

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)

ORIGINAL ARTICLE

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.)



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

American Journal of Ophthalmology Case Reports

journal homepage: www.elsevier.com/locate/ajoc



Early experience with teprotumumab for chronic thyroid eye disease

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ARTICLE INFO

Keywords:
Thyroid eye disease (TED)
Proptosis
Clinical activity score (CAS)
Teprotumumab
Inactive disease
Quiescent disease
Fibrotic disease

ABSTRACT

Purpose: To report the first case of a patient with chronic thyroid eye disease (TED) treated with teprotumumab.
Observations: 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.
Conclusion and importance: This case report suggests that teprotumumab may be used in patients with chronic TED and low CAS. Improvement in the proptosis and reduction in extraocular muscle volume suggest that teprotumumab may alter disease course even in patients with inactive or quiescent TED.

Teprotumumab

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B Clinical Photographs of a Patient in the Teprotumumab Group

Baseline

24 Wk after Initial Dose



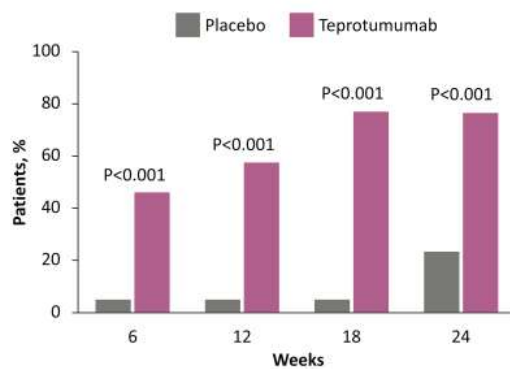
Teprotumumab

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B Clin



Figure 2 | Achievement of primary endpoint



I Dose

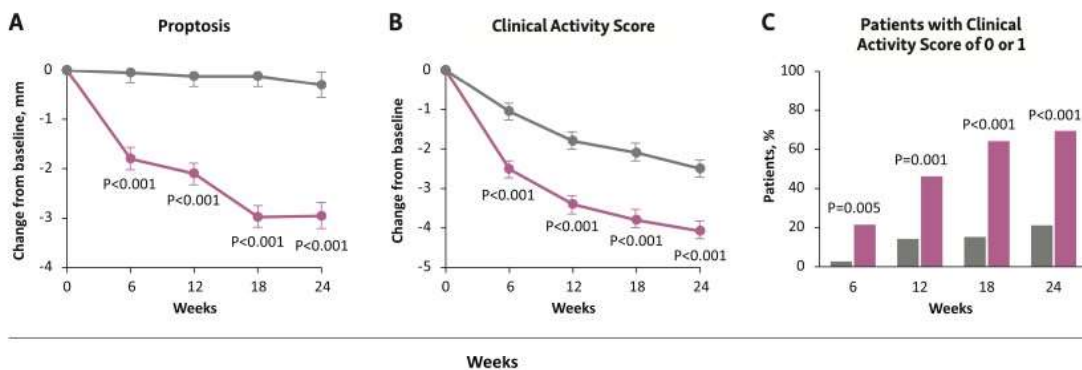


Teprotumumab

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D Clin

Figure 3 | Results for proptosis, CAS, and percent of patients achieving CAS ≤1



Teprotumumab

Table 1 | NO SPECS Classification

Class	Grade
0	No physical signs or symptoms
I	Only signs (eyelid retraction)
II	Soft-tissue involvement (0: absent, a: minimal, b: moderate, c: marked)
III	Proptosis (0: absent, a: minimal, b: moderate, c: marked)
IV	Extraocular muscle signs (0: absent, a: limitation in extremes of gaze, b: evident restriction, c: fixation of globe[s])
V	Corneal involvement (0: absent, a: stippling, b: ulceration, c: clouding, necrosis, perforation)
VI	Sight loss (optic nerve compression) (0: absent, a: visual acuity 0.63–0.5, b: visual acuity 0.4–0.1, c: visual acuity <0.1 to no light perception)

Figure based on NO SPECS classification developed by Sidney C. Werner, first published in the *American Journal of Ophthalmology* in October 1969.

Table 2 | Clinical Activity Score

	Clinical Activity Score
1	Painful feeling behind globe
2	Pain on attempted gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Chemosis
6	Inflammatory eyelid swelling
7	Inflammation of caruncle or plica
8	Increase of ≥ 2 mm in proptosis in last 1–3 months
9	Decrease in visual acuity in last 1–3 months
10	Decrease in eye movements of $\geq 8^\circ$ in last 1–3 months

Figure based on Clinical Activity Score developed by Maarten Ph. Mourits and first published in *Clinical Endocrinology* in August 1989.

For initial CAS, items 1–7 are tallied at one point each for a final CAS based on a 7-point scale. On follow-up visits, the final three items are added for a CAS out of 10 points.

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
- ◆ May worsen **IBD symptoms**
- ◆ **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.

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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.

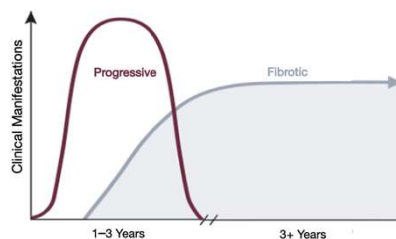
52

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.

Teprotumumab

- ▶ This shatters the “watch and wait” mentality and 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.



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What symptoms would make you suspicious of TED

Itching

Eye Pain

Dry, Sand, Grit

Double Vision

None of the above

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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 these cases

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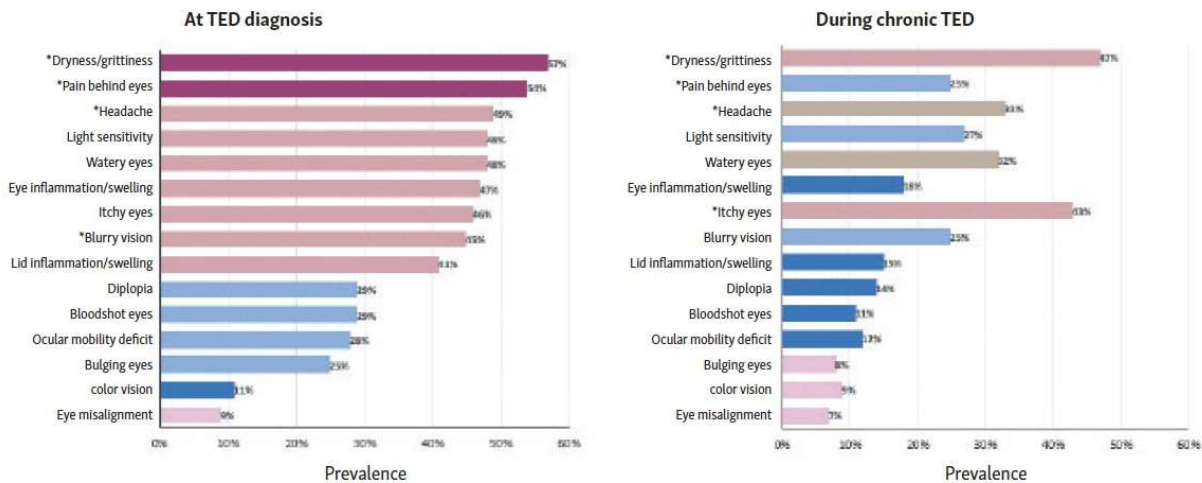
TED vs OSD

- ◆ Temporal chemosis with injection overlying the extraocular muscles
- ◆ Chronic ocular ache and pain as opposed to the more common sharp pains associated with dry eye and other corneal disorders



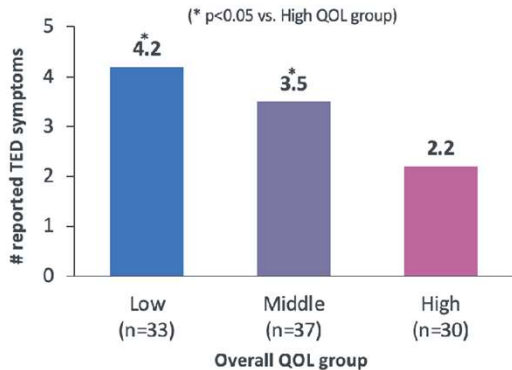
Signs of TED

Might NOT be just "OSD"



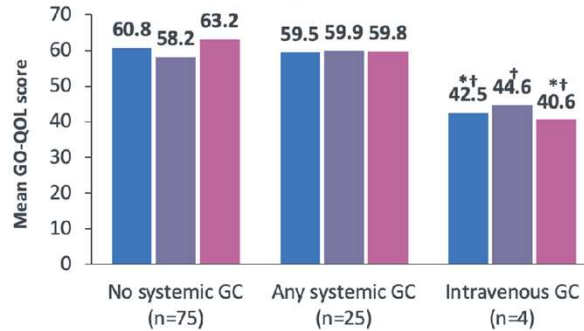
QOL in Chronic TED Patients is Impacted by Clinical Features and Active Phase Treatment Choice

Higher number of signs and symptoms correlates with reduced QOL score in chronic TED



IV glucocorticoid use during active phase associated with reduced QOL score in chronic TED

(* p<0.05 vs. no systemic glucocorticoids; † p<0.05 vs. oral glucocorticoids only)



GO-QOL, Graves' Ophthalmopathy Quality of Life questionnaire
 Low QOL = GO-QOL ≤50; Middle QOL = GO-QOL >50 and <75; High QOL = GO-QOL ≥75
 Cockerham KP, et al. Ophthalmol Ther. 2021; Epub ahead of print.

OSD & TED

Change in Lacrimal Gland Volume and Tear Production Following Treatment with Teprotumumab

Shoaib Ugradar¹, Jane S. Kim², Erin Zimmerman³, Jenna Braun⁴, Tunde Mester⁴, Yao Wang⁴

¹Oculoplastics, UCLA, Los Angeles, California, United States, ²Division of Eye Plastic, Orbital, and Facial Cosmetic Surgery, Kellogg Eye Center, University of Michigan, Ann Arbor, Michigan, United States, ³UCLA, Los Angeles, California, United States, ⁴Oculoplastics, Cedars Sinai Hospital, Los Angeles, California, United States

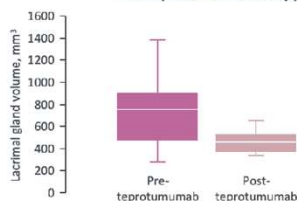
***Abstract presented at the American Society of Ophthalmic Plastic & Reconstructive Surgery (ASOPRS) Fall Scientific Symposium, November 11-12, 2021; New Orleans, LA.**

Teprotumumab is Associated with Reduced Lacrimal Gland Volume and Increased Tear Production

- Dry eye is a common cause of discomfort in TED¹
- Lacrimal gland enlargement in TED correlated with subjective tearing²

- Prospective, longitudinal study of 20 TED patients who received 8 infusions of teprotumumab³
 - Primary endpoints: lacrimal gland volume, tear production (Schirmer's test)
 - **Teprotumumab significantly reduced TED-related expansion of the lacrimal gland and increased tear production in patients with acute and chronic TED**

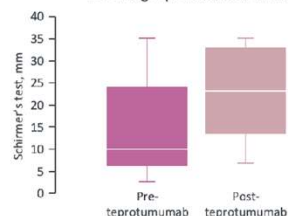
Change in lacrimal gland volume before and after teprotumumab therapy



Lacrimal gland volume (study orbit) decreased from $751 \pm 349 \text{ mm}^3$ at baseline to $418 \pm 134 \text{ mm}^3$ after treatment ($p < 0.01$)

Tear volume increased from $14.5 \pm 10.5 \text{ mm}$ at baseline to $22 \pm 11 \text{ mm}$ after treatment

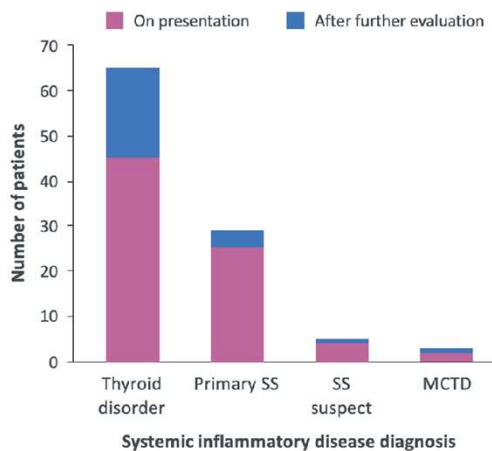
Change in Schirmer's test in the study orbit following teprotumumab therapy



Dry Eye and TED

- **Dry eye** prevalence reported to range from 5.1 to 29%¹⁻⁴
- **Thyroid disease** identified as a **significant risk factor / comorbid condition**¹⁻⁴

- **2-year retrospective study**
 - 539 new patients
 - 32 suspected TED based on history and / or exam
 - 21 found to have echographic TED
 - 18 (86%) female
 - 8 hypothyroid, 2 Graves
 - Average 3 prior ophthalmologists seen



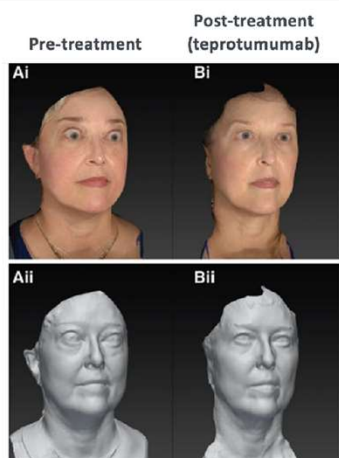
Gupta et al. Am J Ophthalmol 2009;147:919-923.
Heinrich et al. Cornea 2014;33:819-825.

TED is a Condition of the Eye, But Also the Face

In addition to orbital soft tissue expansion, TED is associated with expansion of soft tissue in other regions of the face, including the brow, temples, and mid and lower face

Teprotumumab reduced mean soft tissue volume across facial regions

(n=23 patients with mean TED duration of 29 months)



59-year-old female with 10-month history of TED and expansion of facial soft tissue

Ugrader S et al. *Plast Reconstr Surg Glob Open.* 2021;9:e3809.

A Growing Body of Evidence Continues to Support the Use of TEPEZZA in Chronic TED

Case Study*	Patients	Key Results
1) Ozzello – AJO – 2020	1	Proptosis reduction of 5 mm and 6 mm in the right and left eye respectively after 3 infusions
2) Ugradar – Eye – 2020	4	4 non-inflammatory TED patients experienced mean proptosis reduction of 2.6 mm
3) Davis – NANOS – 2021 (Poster)	1	Proptosis reduction of 5-6 mm from baseline after completing treatment
4) Diniz – OPRS – 2021	6	71% overall proptosis response rate (proptosis reduction ≥ 2 mm)
5) Ozzello – Orbit – 2021	9	78% of study participants experienced proptosis reduction of ≥ 2 mm in at least one eye
6) Ugradar – Eye – 2021	31	90% of study participants experienced clinically significant improvement (≥ 2 mm) in proptosis

*Studies ordered chronologically

AJO: American Journal of Ophthalmology, OPRS: Ophthalmic Plastic and Reconstructive Surgery, NANOS: North American Neuro-Ophthalmology Society, TRCO: The Royal College of Ophthalmologists.

Note: Data from separate clinical trials may not be directly comparable due to differences in trial protocols, endpoints, conditions and patient populations

1. Ozzello DJ, et al. *Am J Ophthalmol Case Rep.* 2020 May 15;19:100744. doi: 10.1016/j.ajoc.2020.100744. 2. Ugradar S, et al. *Eye (Lond)*. 2020 Nov 21. doi: 10.1038/s41433-020-01297-w. 3. Davis R, et al. NANOS 2021 Feb annual meeting abstract. <https://collections.lib.utah.edu/arc/87278/sigs0771>. 4. Diniz SB, et al. *Ophthalmic Plast Reconstr Surg.* 2021 Mar 8. doi: 10.1097/IOP.0000000000001959. 5. Ozzello DJ, et al. *Orbit.* 2021 Jun 1:1-8. doi: 10.1080/01676830.2021.1933081. 6. Ugradar S, et al. *Eye (Lond)*. 2021 Jul 9. doi: 10.1038/s41433-021-01593-z.



www.nature.com/eye

ARTICLE OPEN

Check for updates

Teprotumumab for the treatment of chronic thyroid eye disease

Shoaib Ugradar¹, Julia Kang², Andrea L. Kossler³, Erin Zimmerman¹, Jenna Braun⁴, Andrew R. Harrison⁵, Swaraj Bose⁴, Kimberly Cockerham^{2,3} and Raymond S. Douglas⁴

Case Series: Real-World Experience with Teprotumumab in Chronic TED

Design

Case series of 31 consecutive patients with chronic TED (mean time since diagnosis: 7 years) treated with teprotumumab (Ugradar et al. Eye. 2021)

Patients showed marked improvement in proptosis, CAS, and diplopia with teprotumumab treatment

Key results

90% of study orbits had clinically significant improvement (≥ 2 mm) in proptosis

84% of fellow orbits also had clinically significant improvement

Significant reduction in fat & muscle volume

Of 15 patients who had diplopia at baseline,

67% had clinically significant improvement in diplopia

47% had complete resolution of diplopia

Despite the dormant appearance of chronic TED, orbital fibroblasts continually turnover hyaluronic acid and other ECM macromolecules once a week to maintain tissue integrity. Therefore, interrupting the IGF-1R pathway may reduce the downstream signaling that leads to tissue expansion in chronic TED

Ugradar S, et al. Eye. 2021.

Clinical Experience with Teprotumumab for Chronic TED

- Patient selection
 - 68-year-old Black male with a 9-year history of TED
 - Previous treatment with steroids, bilateral orbital radiation, bilateral orbital decompression, and strabismus surgery
 - Progressively worsening proptosis
 - Exophthalmometry: 32 mm OD, 32.5 mm OS
 - CAS of 3
- After 8 infusions of teprotumumab, the patient saw clinically significant reductions in proptosis and reached a CAS of 0
 - Exophthalmometry: 26 mm OD, 28 mm OS
 - Reduction of 6 mm and 4.5 mm, respectively

Before teprotumumab treatment



After teprotumumab treatment



CAS, clinical activity score; OD, right eye; OS, left eye.
Ugradar S, et al. Eye. 2021;19:100744.

Images above, as published in Eye, are licensed under a Creative Commons Attribution 4.0 International License

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Patient and Caregiver Resources

- ▶ https://drive.google.com/file/d/1k-kaM5uR4AIMNOFzXOvvnB-PjqBY43_H/view?usp=sharing
- ▶ www.accessdata.fda.gov/drugsatfda_docs/label/

Thyroid Eye Disease (TED) & Graves' Disease RESOURCE GUIDE

FOR PATIENTS
& CAREGIVERS

Future

- ▶ <https://clinicaltrials.gov/ct2/show/NCT04583735?term=teprotumumab&draw=2&rank=8>
- ▶ ClinicalTrials.gov Identifier: NCT04583735

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Tepro is effective when treating _____TED

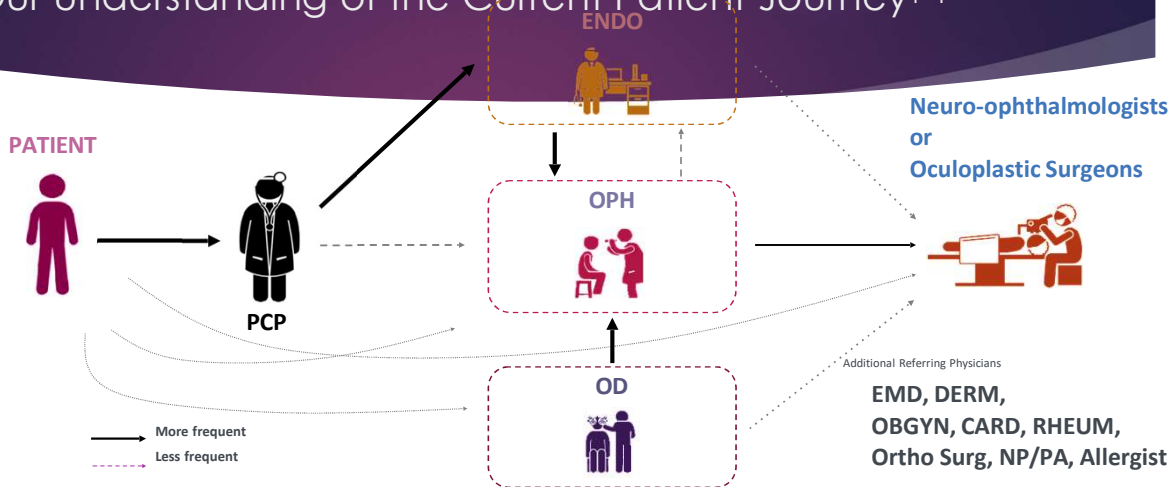
Active, Early

Longstanding,
Chronic

All of the Above

Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app

Our Understanding of the Current Patient Journey¹⁻⁴



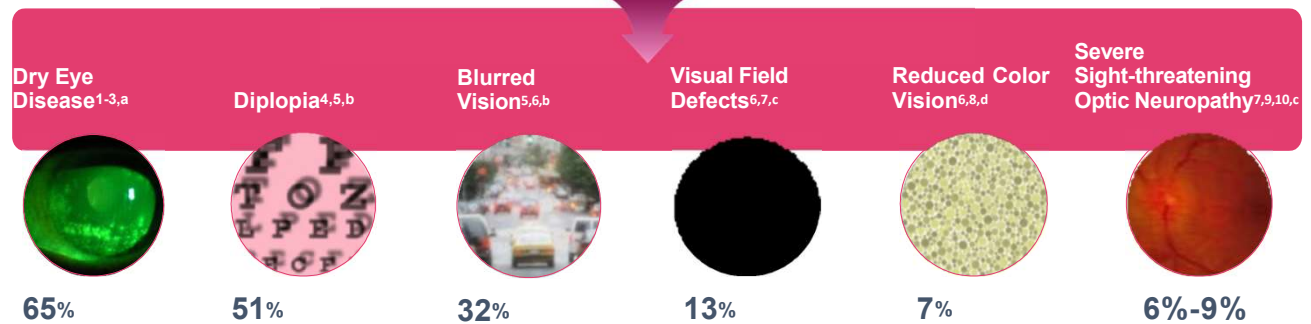
CARD, cardiology; DERM, dermatology; EMD, emergency medicine; ENDO, endocrinology; NP, nurse practitioner; OBGYN, obstetrics-gynecology; OD, optometrist; OPH, ophthalmology; Ortho Surg, orthopedic surgery; PA, physician assistant; PCP, primary care physician; RHEUM, rheumatology.

1. Bartalena L, et al. Eur Thyroid J. 2016;5(1):9-26. 2. Estcourt S, et al. Eur J Endocrinol. 2009;161:483-487. 3. Data on file: TED Qualitative Patient Physician Assessment Draft Report 10-31-2018. 4. Data on file. Thyroid eye disease market landscape study. March 15, 2018.

TED Is Associated With Significant Vision-threatening Impairments

Consequences of TED can be devastating and can include:

Vision impairment in patients with TED



^aFrom Pflugfelder SC. <https://www.reviewophthalmology.com/article/studies-yield-a-deeper-understanding-of-dry-eye>. Reprinted with permission.³ From VSRN Vision Surgery Rehab Network website. <http://www.visionrehab.org/image-gallery/>. Reprinted with permission.⁵ From Fernandez E, et al. *Ann Thyroid Res*. 2016;2:63-65. Reprinted with permission.⁷ From de Oliveira HM, et al. <https://arxiv.org/ftp/arxiv/papers/1502/1502.03723.pdf>. Reprinted with permission.⁸

1. Ismailova DS, et al. *Orbit*. 2013;32(2):87-90. 2. Seltzer JH, et al. *Clin Ophthalmol*. 2015;9:57-62. 3. Pflugfelder SC. Review of ophthalmology website. <https://www.reviewophthalmology.com/article/studies-yield-a-deeper-understanding-of-dry-eye>. Accessed September 27, 2019. 4. Terwee C, et al. *Eur J Endocrinol*. 2002;146(6):751-757. 5. VSRN Vision Surgery Rehab Network website. <http://www.visionrehab.org/image-gallery/>. Accessed September 27, 2019. 6. McKeag D, et al. *Br J Ophthalmol*. 2007;91(4):455-458. 7. Fernandez E, et al. *Ann Thyroid Res*. 2016;2:63-65. 8. de Oliveira HM, et al. Cornell University arxiv.org website. <https://arxiv.org/ftp/arxiv/papers/1502/1502.03723.pdf>. Accessed September 27, 2019. 9. Barley GB. *Trans Am Ophthalmol Soc*. 1994;92:477-588. 10. Neigel JM, et al. *Dysthyroid optic neuropathy*. *Ophthalmology*. 1988;95(11):1515-1521.

Integrated Collaborative Care

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



Patient and Caregiver Resources

- ▶ https://drive.google.com/file/d/1k-kaM5uR4AIMNOFzXOvvnB-PjqBY43_H/view?usp=sharing
- ▶ www.accessdata.fda.gov/drugsatfda_docs/label/

Thyroid Eye Disease (TED) & Graves' Disease RESOURCE GUIDE

FOR PATIENTS & CAREGIVERS

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Would you feel comfortable writing an Rx for an infusion?

Yes

No

Infusion Schedule

- ▶ Partner with local infusion center
- ▶ Schedule
 - ▶ Infusion 1: 90 minutes 0.5 dose
 - ▶ Infusion 2: 90 minutes full dose
 - ▶ Infusions 3-8: full dose over 60 minutes

Thank You

Keys to Unlocking Thyroid Eye Disease

A Curated Scientific Guidebook



Access this guidebook online by scanning this with your phone.

thyroid eye



Thank You

Jacob Lang OD, FAAO,
Dipl. ABO



drjakelang@gmail.com

 @ SeeOneTeachOne