THYROID EYE DISEASE:
Managing a Condition with Grave Consequences

This continuing medical education activity is provided by

VINDICO medical education

This activity is supported by an educational grant from Horizon Therapeutics USA, Inc.

Pathophysiology of TED

Increased pressure in the "cone"

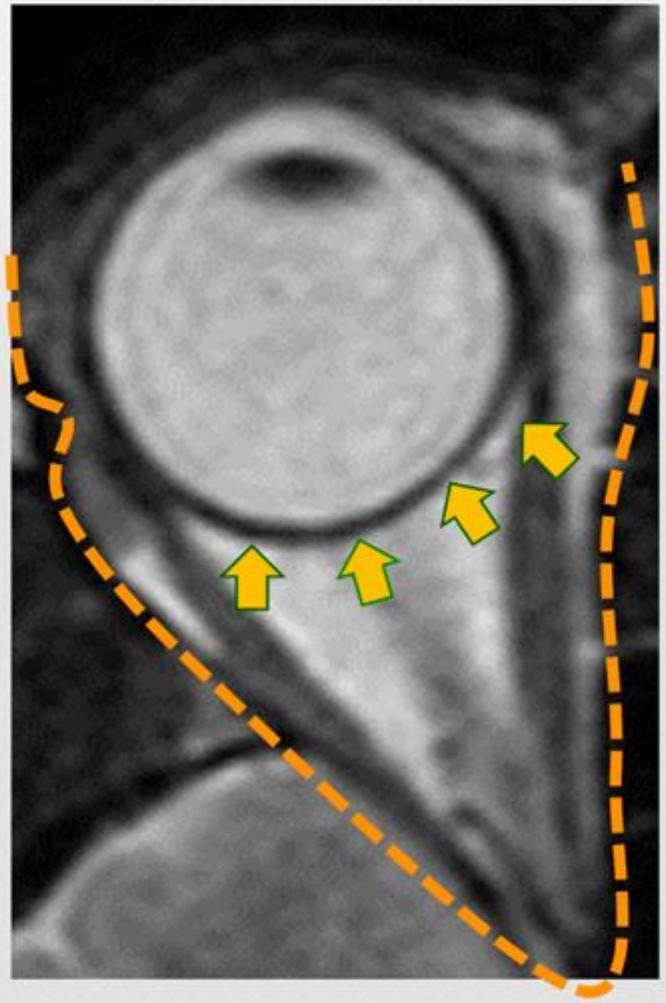
Expansion of muscle bellies

Expansion of fat

Impedance of posterior venous outflow

Cone edema

Venous flow reversal



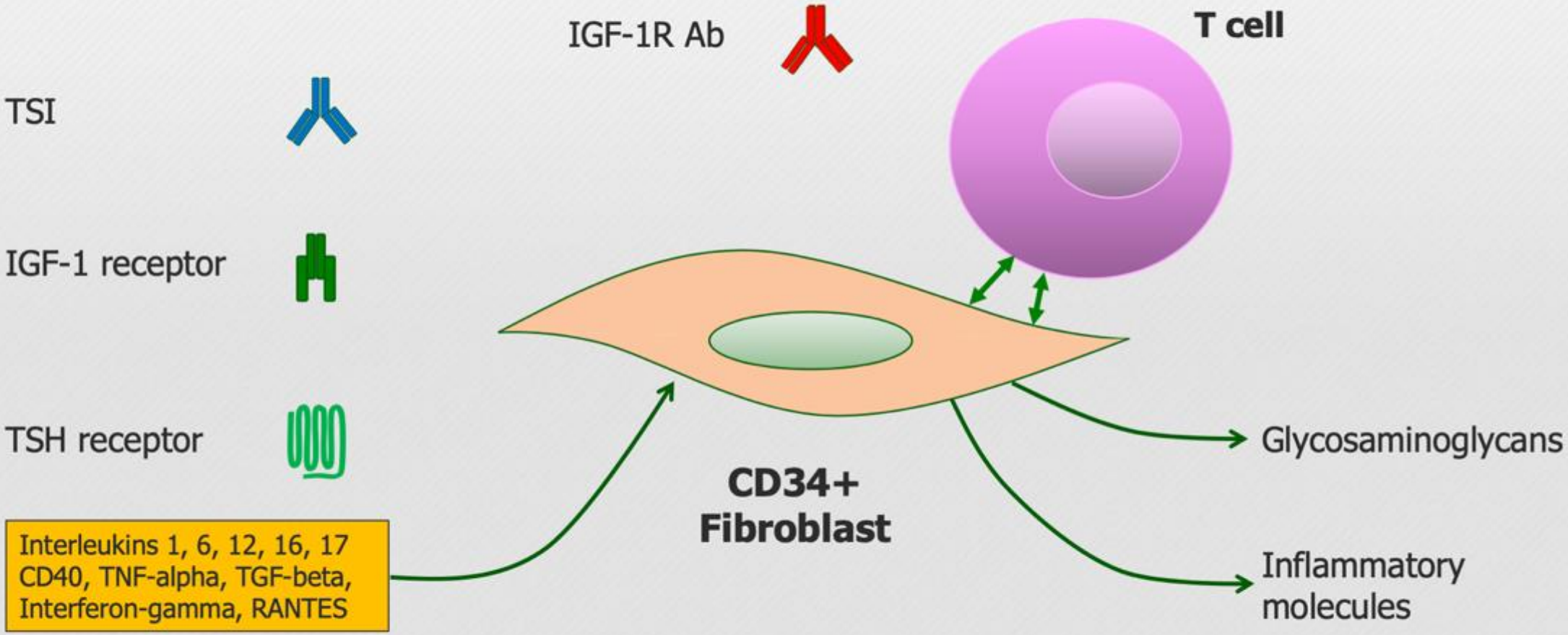
Loss of muscle contractility

Loss of muscle compliance

Increasing stiffness

Meyer P, et al. *Eye (Lond)*. 2019;33(2):244-253.

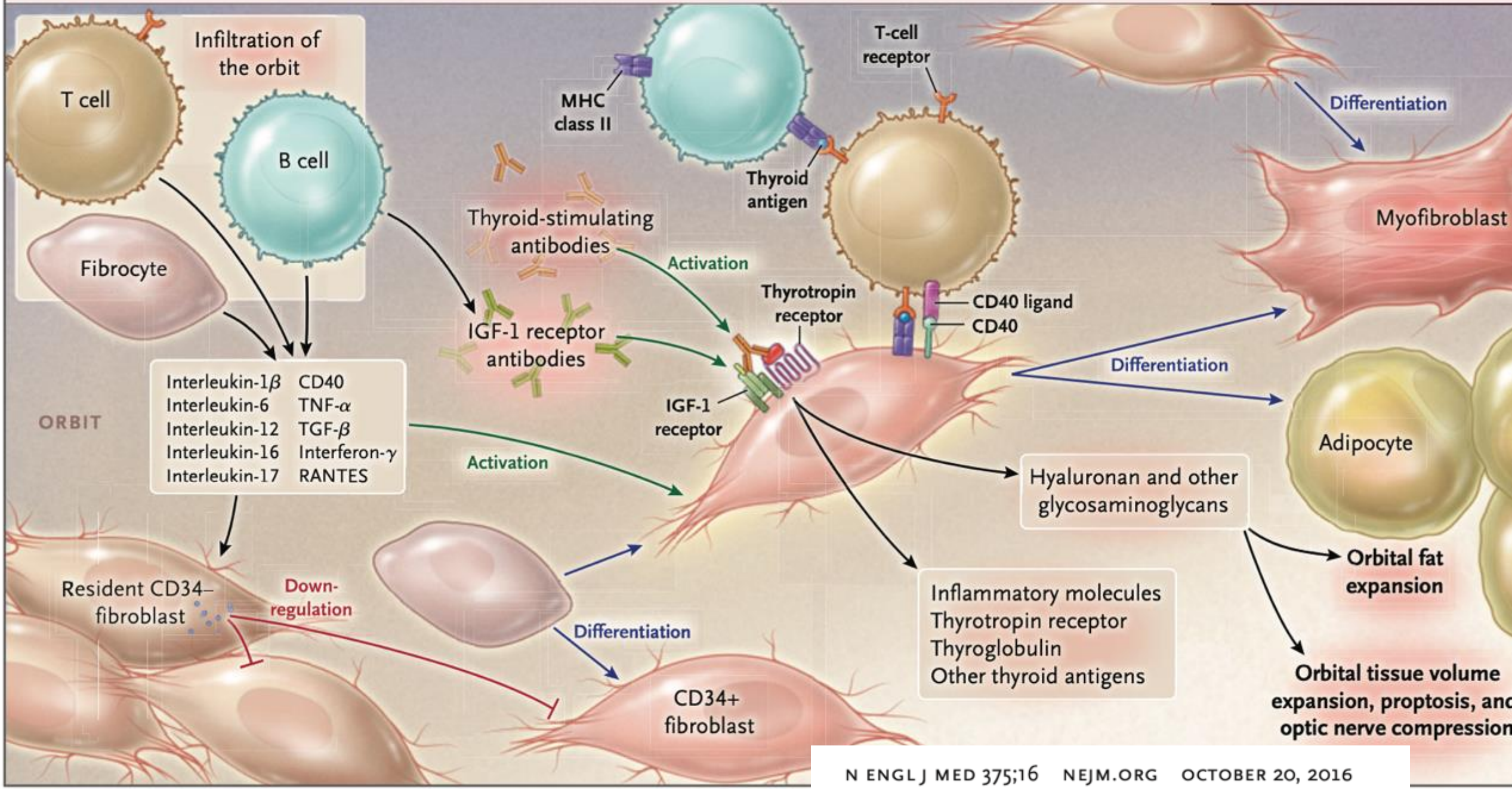
Pathogenesis of TED



DC = cluster of differentiation; IGF = insulin-like growth factor; TSH = thyroid-stimulating hormone; TSI = thyroid-stimulating immunoglobulins; TNF = tumor necrosis factor.

Smith T, et al. *N Engl J Med.* 2016;375(16):1552-1565.
Smith TJ. *F1000Res.* 2018;7:134.
Pritchard J, et al. *J Immunol.* 2003;170(12):6348-6354.

B Theoretical Model of the Pathogenesis of Thyroid-Associated Ophthalmopathy



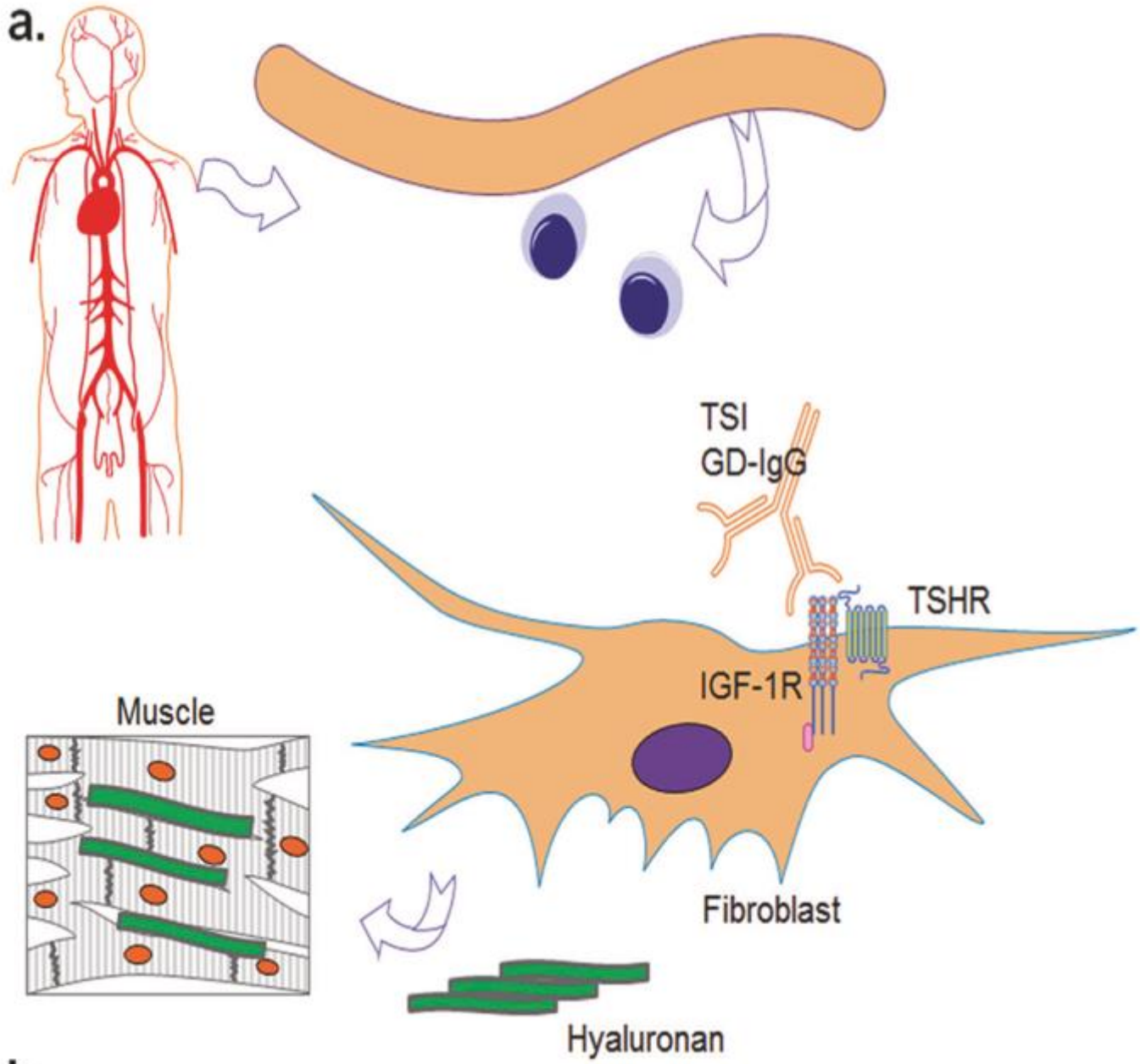


Fig. 2 **a** Pathogenic autoantibodies stimulating the orbital fibroblasts resulting in production of hyaluronan and giving rise to symptoms of thyroid eye disease. **b** Teprotumumab (an IGF-1R antagonist) blocks the stimulatory effects of pathogenic autoantibodies on the orbital fibroblasts TSI thyroid stimulating immunoglobulins, GD-IgG Graves' disease immunoglobulins, TSHR thyroid stimulating hormone receptor, IGF-1R insulin-like growth factor-1 receptor

TED: Epidemiology

- Women (2:1 to men)
- More severe in men
- *Severity:* European (+++), Asian (+)
- Genetics
- Orbital anatomy

Stan MN, et al. *Thyroid*. 2010;20(7):777-783.

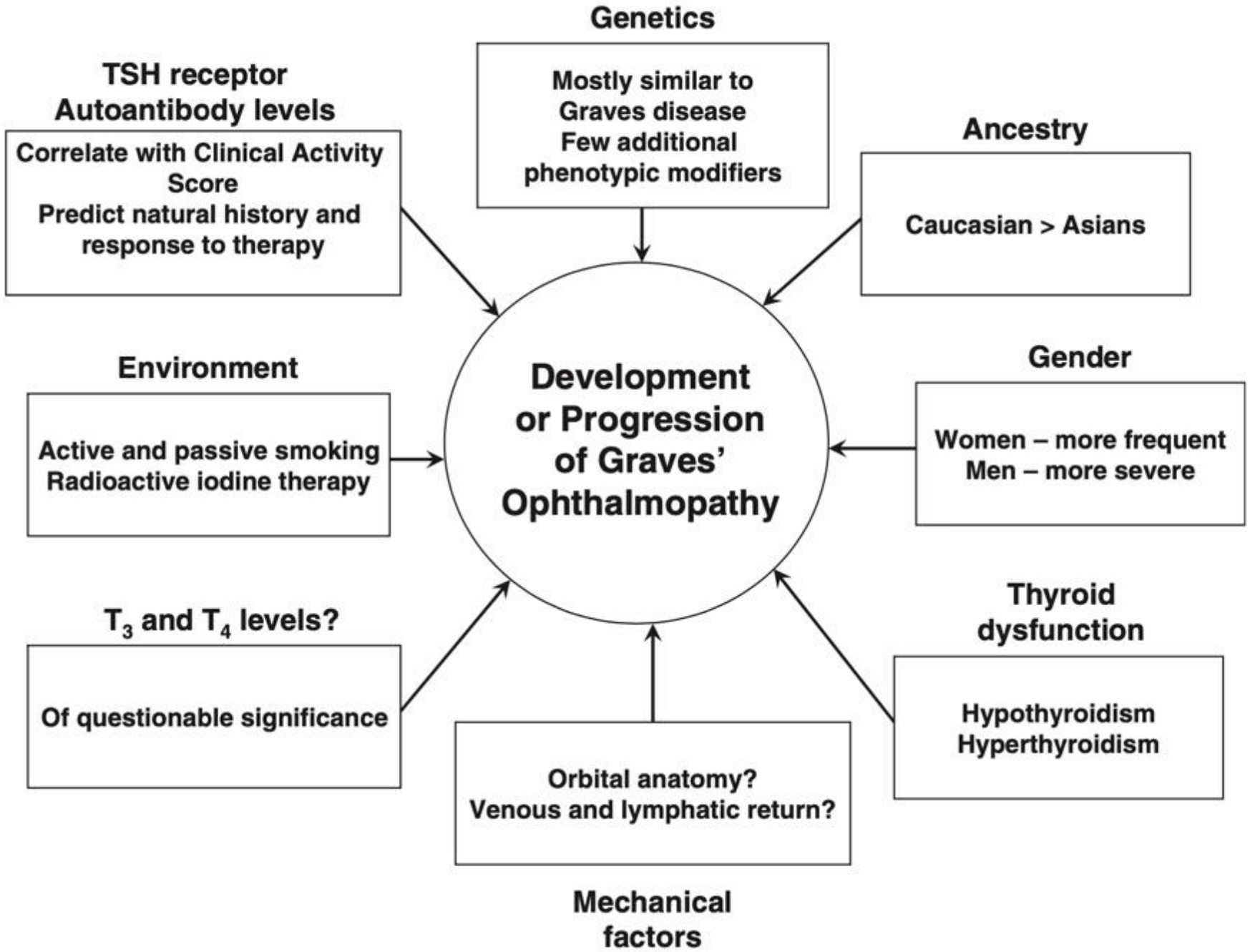


FIG. 1. Risk factors for the development or progression of Graves' ophthalmopathy. TSH, thyrotropin; T3, triiodothyronine; T4, thyroxine.

THYROID
Volume 20, Number 7, 2010

DOI: 10.1089/thy.2010.1634

TED: Epidemiology *(continued)*

- TED occurs in 25% to 50% of patients with Graves disease and up to 30% of patients with TED have evidence of Hashimoto disease[1]
- Most patients have hyperthyroidism, some have spontaneous hypothyroidism, and 5% have spontaneous euthyroidism
- Most often bilateral but can be asymmetrical
- In 80% of patients with Graves' disease or TED, the other condition will develop within 18 months[2]
- Risk of recurrence of TED is 5% to 15% and can happen years later[3]

TED = thyroid eye disease.

1. Li Z, et al. *Curr Opin Ophthalmol*. 2018;29(6):528-534; 2. Wiersinga WM, et al. *Thyroid*. 2002;12(10):855-680; 3. Patel P, et al. *Ophthalmic Plast Reconstr Surg*. 2015;31(6):445-448.

TED: Presenting Symptoms

Clinical Finding	Frequency
Eyelid retraction	90%
Proptosis	60%
Ocular misalignment	40%

- Periorbital erythema and edema
- Chemosis
- Increased intraocular pressure
- Exposure keratopathy
- Compressive optic neuropathy
- *Lid retraction and stare are nonspecific and can be seen in thyrotoxicosis from any cause*

Smith T, et al. *N Engl J Med.* 2016;375(16):1552-1565.

TED: Psychological Impact

- Patients with moderate to severe TED show significantly greater emotional distress especially when proptosis is present[1]
- Patients with TED (who are euthyroid at the time of assessment) score worse on measures of depression, anxiety, and well-being than patients with other chronic diseases[2]

1. Farid M, et al. *Arch Ophthalmol*. 2005;123(4):491-496; 2. Coulter I, et al. *Eur J Endocrinol*. 2007;157(2);127-131.

TED: Risk Factors

- **TSH-receptor antibodies**
  - TSI levels correlate with disease activity[1]
  - TSI levels seem to correlate with response to treatment
  - Some studies were contradictory because of different assay methods

1. Stan MN, et al. *Thyroid*. 2010;20(7):777-783.

TED: Risk Factors *(continued)*

- **Smoking**
  - Smokers are twice as likely to develop TED
  - TED is ~4x more likely to develop/worsen in smokers after radioactive iodine
  - Cigarette smoke extract and hypoxia increase production of glycosaminoglycans by orbital fibroblasts
  - Smoking is the *strongest* modifiable factor in TED

1. Stan MN, et al. *Thyroid.* 2010;20(7):777-783.

TED: Risk Factors *(continued)*

- Selenium deficiency is associated with increased severity[1]
- High cholesterol/LDL appears to be associated with TED
  - Patients receiving statin treatment are less likely to develop TED[2]
- Cases resembling TED have been associated with immune checkpoint inhibitors[2]

LDL = low-density lipoprotein.

1. Khong JJ, et al. *Clin Endocrinol (Oxford)*. 2014;80(6):905-910; 2. Li Z, et al. *Curr Opin Ophthalmol*. 2018;29(6):528-534.

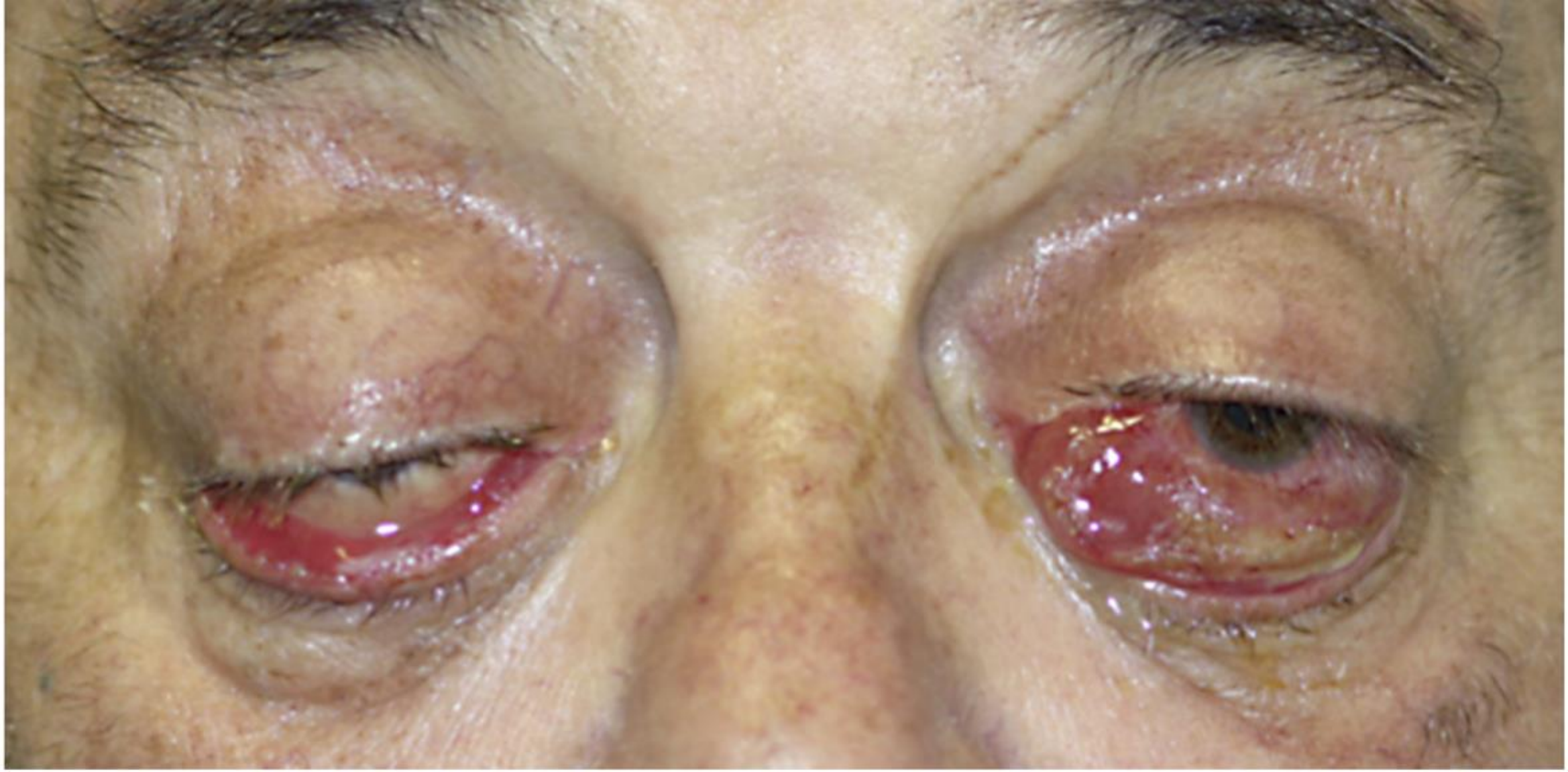


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Fig. 1. Initial presentation of the patient with nivolumab-associated inflammatory ophthalmopathy.

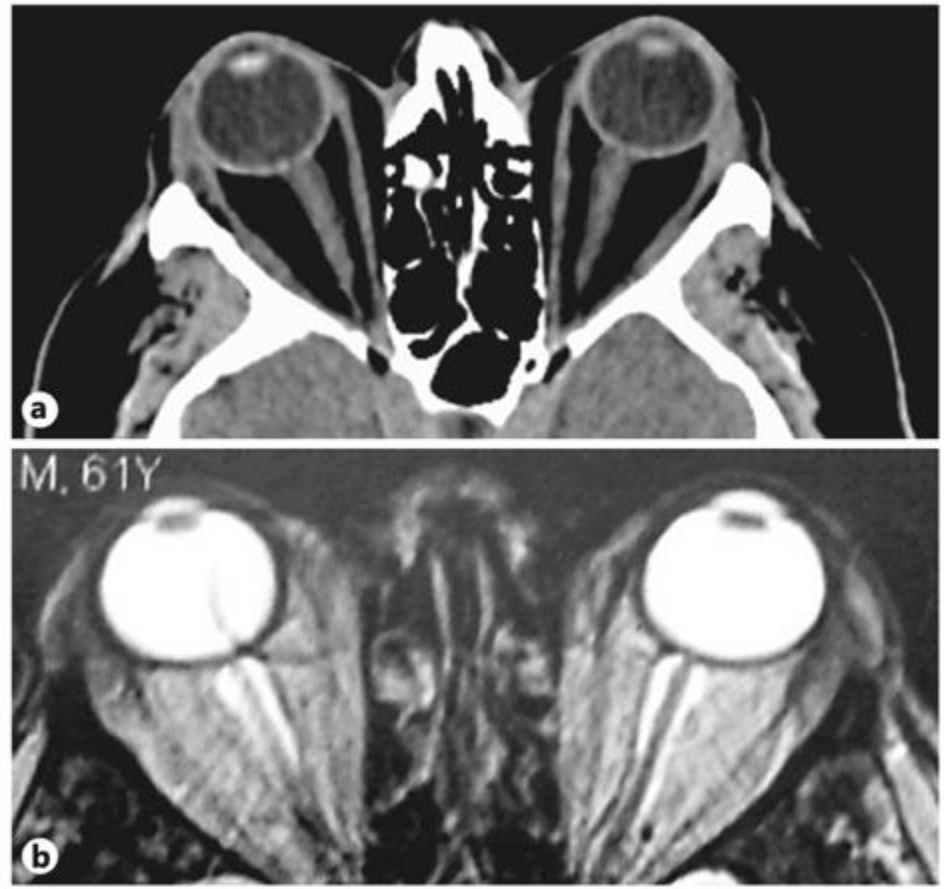
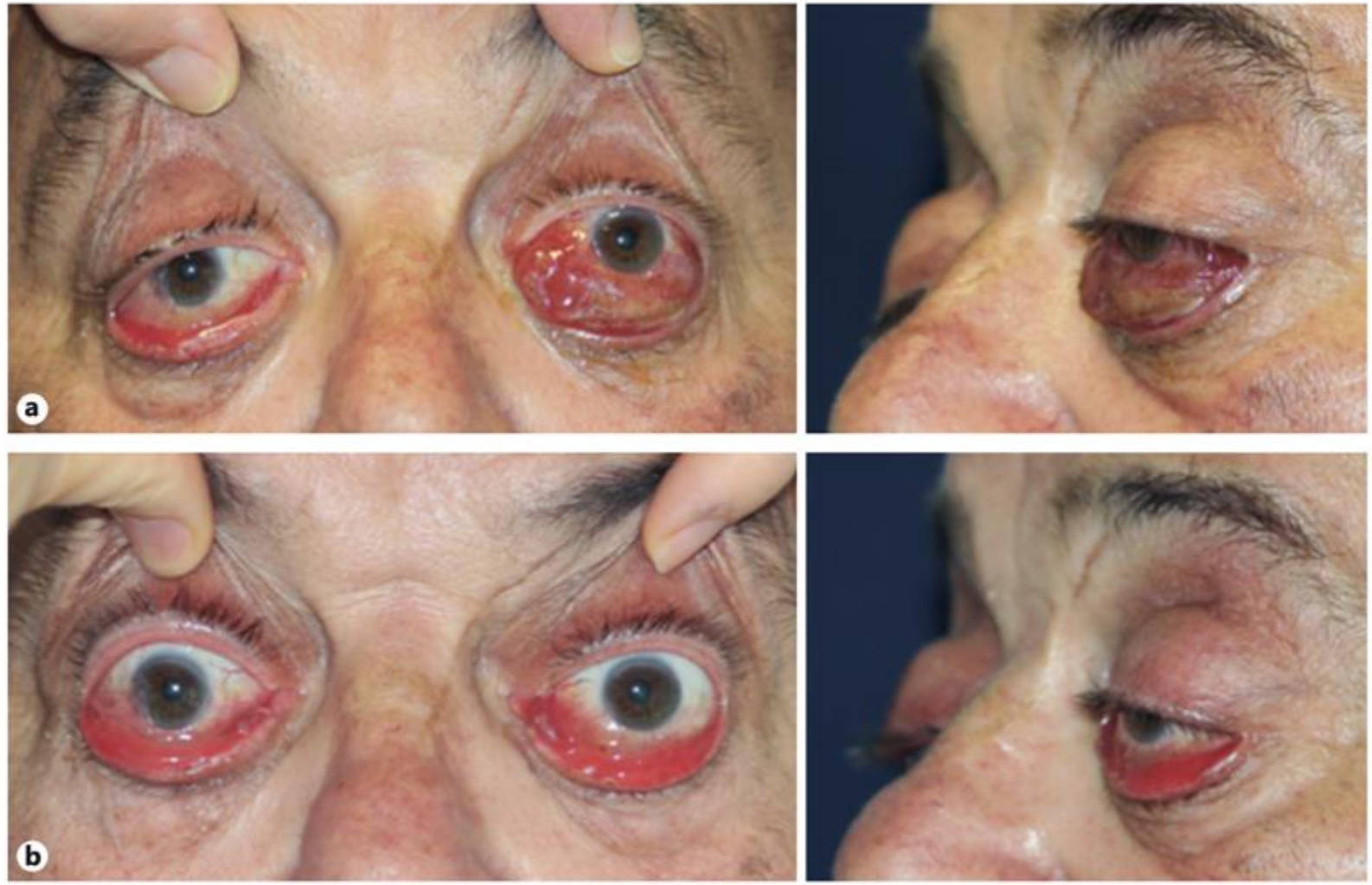


Fig. 2. a Axial CT scan showing severe exophthalmos after nivolumab treatment, with severe proptosis of both orbits with fat tissue augmentation and no extra-ocular muscle involvement. **b** Axial T2-weighted MR images confirmed exophthalmos with inflammatory edema of the retro-ocular fat tissue.



Color version available online

Fig. 3. Severe ophthalmopathy at diagnosis (**a**) and after 3 weeks of treatment (**b**) with weekly high-dose glucocorticoids (methylprednisolone 1 g × 2 and 500 mg × 1).

TED: Risk Factors *(continued)*

- **Radioactive iodine**
  - The risk for TED after radioactive iodine therapy is 15% to 40%
  - Radioactive iodine therapy appears to be related to antigen release from the thyroid gland and subsequent enhancement of the autoimmune response
  - Insufficiently treated hypothyroidism occurring after this therapy may worsen TED

1. Stan MN, et al. *Thyroid*. 2010;20(7):777-783; 2. Bartalena L, et al. *N Engl J Med*. 1998;338(2):73-78

Assessment of TED Activity

- **Clinical activity score (CAS: 1-7)[a]**
  - Pain (globe, eye movement)
  - Redness (lids, conjunctiva)
  - Swelling (lids, conjunctiva, caruncle)
- **Comparison**
  - Proptosis, movement, acuity (1-3)

[a] Active = CAS≥3

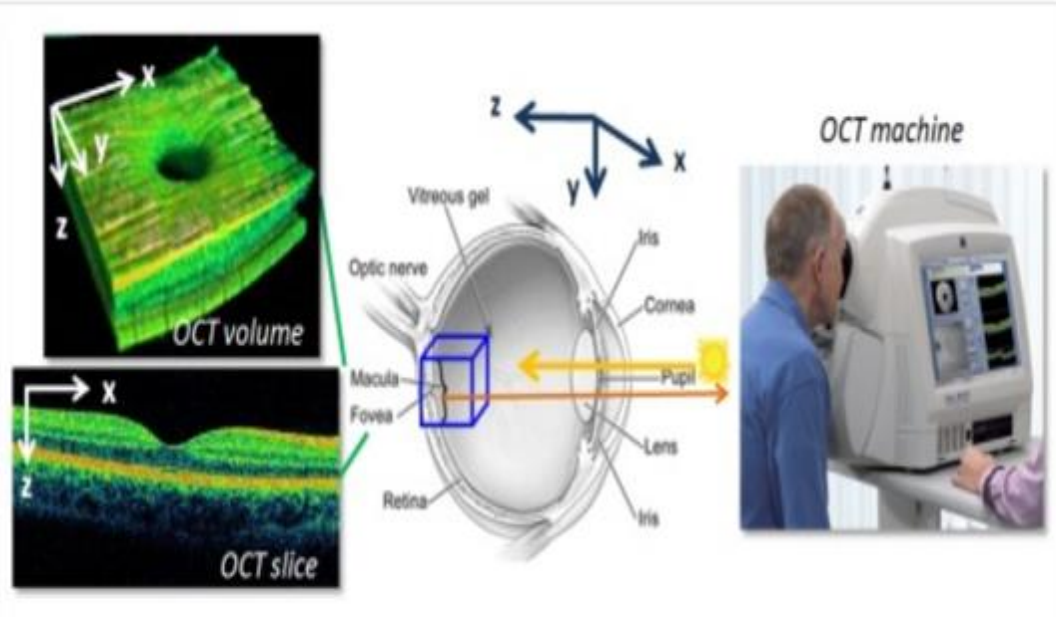
Mourits MP, et al. *Br J Ophthalmol.* 1989;73(8):639-644.

Imaging Assessment

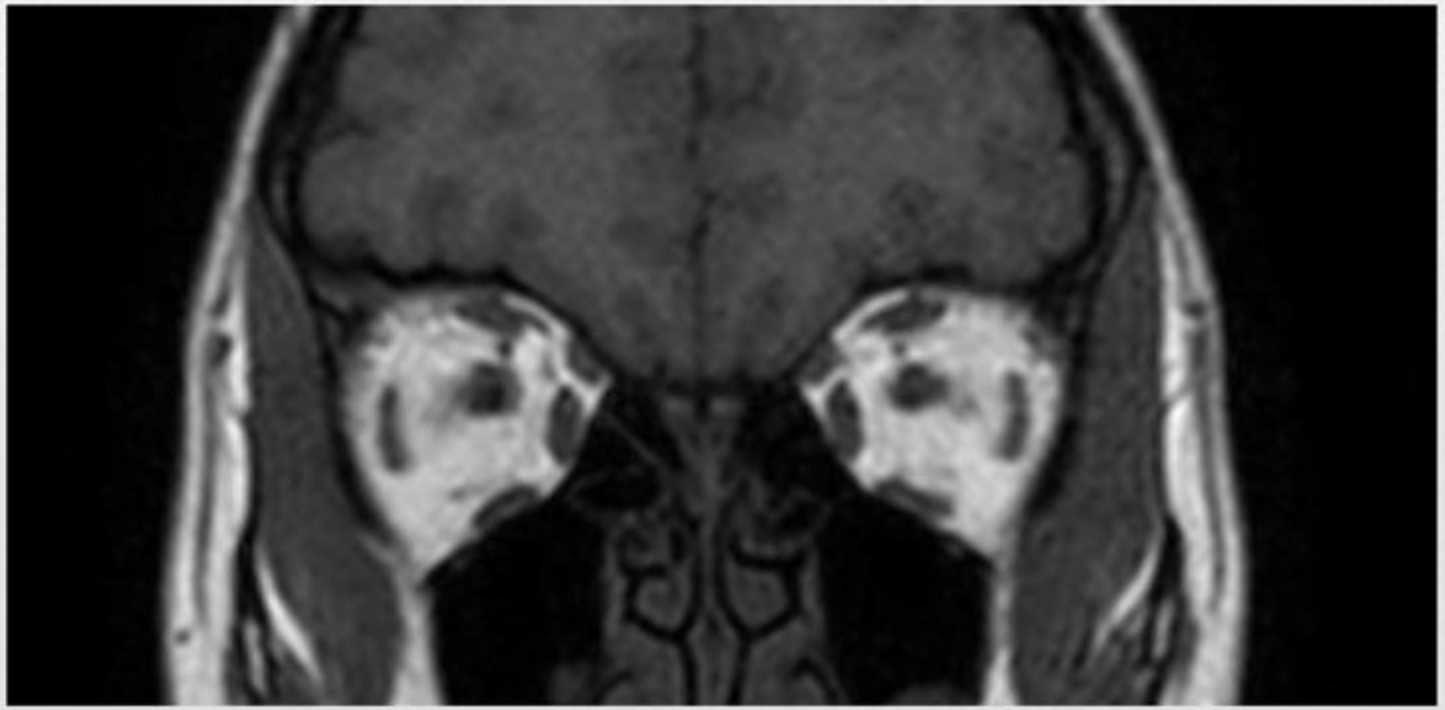
- Magnetic resonance imaging
  - Muscle, fat, nerve, vessels, orbit
- Optical coherence tomography
  - Choroidal thickness, optic nerve, rectus muscle size
- Doppler ultrasonography
  - Internal carotid, ophthalmic artery, central retinal artery
- Possible role for technetium scan

Roos JCP, et al. *Curr Opin Ophthalmol.* 2019;30(5):401-440.

Optical Coherence Tomography (OCT)



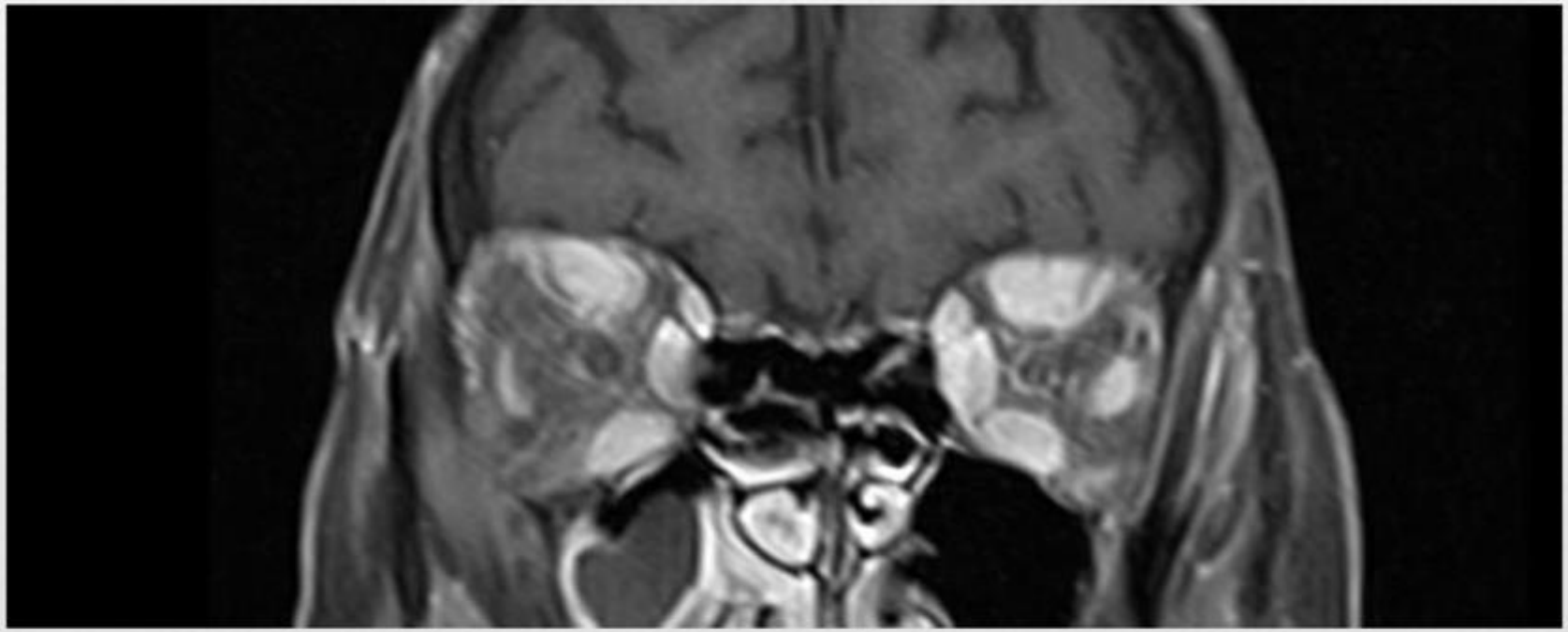
OCT is a noninvasive imaging technology used to obtain high resolution cross sectional images of the retina which is especially important for conditions such as macular degeneration and diabetic retinopathy. This procedure is similar to ultrasound technology except the imaging is performed by light rather than sound. This enables the measurement of the retinal nerve fiber thickness for glaucoma and other neurological conditions.



No TED

T1 Coronal

Image courtesy of Christian Nasr, MD.



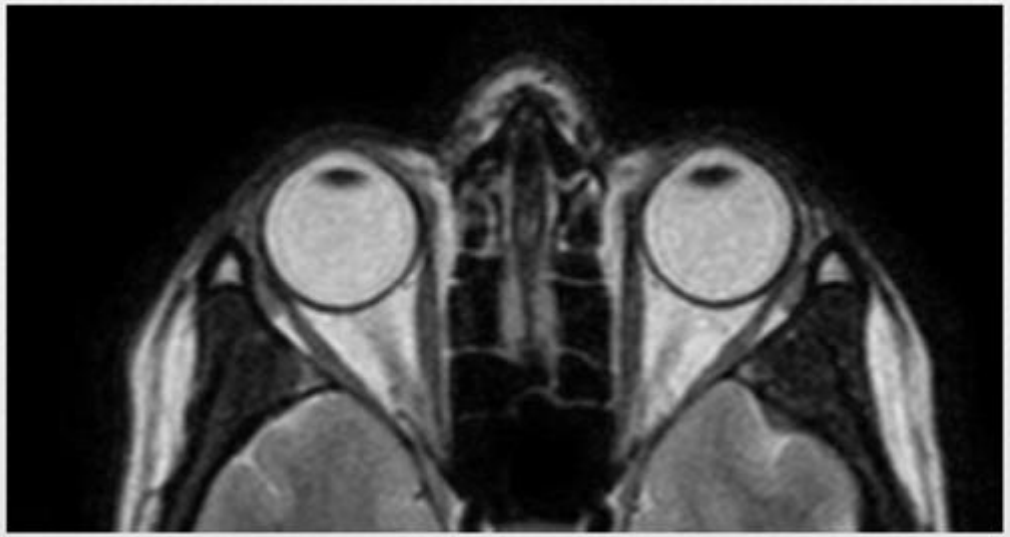
TED

T1 coronal postcontrast

Image courtesy of Christian Nasr, MD.

No TED

Axial T2



TED

Axial T1 postcontrast

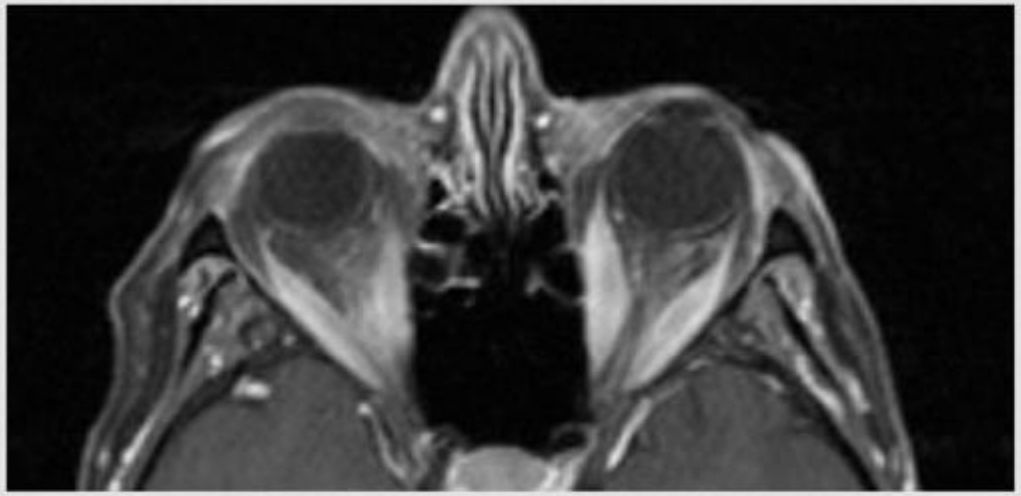
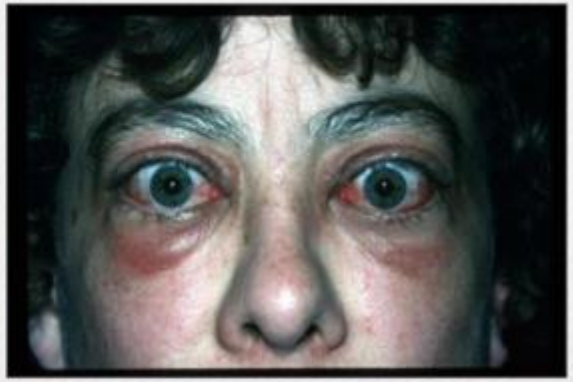
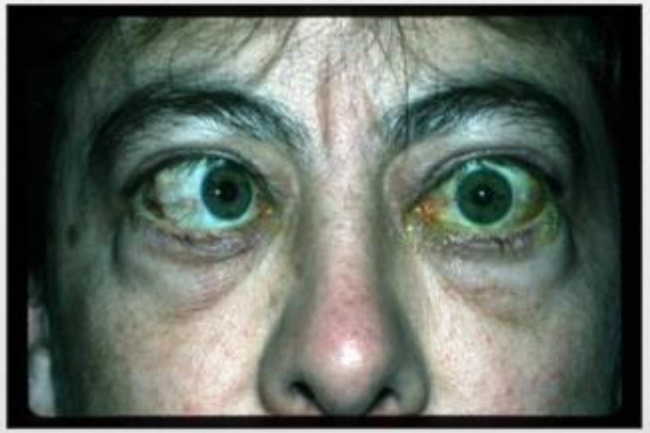


Image courtesy of Christian Nasr, MD.



Active



Inactive

Disease

Inflammation → Fibrosis

18 to 24 months

5 to 7 years

Time

Image and permission courtesy of
Raymond Douglas, MD, PhD.

Grading Disease Severity

- **Sight-threatening**
  - CON, corneal ulcer threatening breakdown
- **Moderate to severe**
  - Diplopia
  - Exophthalmos >3 mm
  - Retraction >2 mm
  - Moderate to severe soft tissue involvement
- **Mild**
  - Retraction <2 mm
  - Exophthalmos <3 mm
  - Corneal exposure responds to lubrication

CON = compressive optic neuropathy.
Gillespie EF, et al. *Curr Neurol Neurosci Rep.* 2012;12(3):318-324.

What Conventional Treatments Exist?

EUGOGO Recommended Regimen

- The currently recommended regimen for IV glucocorticoid therapy is a cumulative dose of 4.5 g of methylprednisolone, divided into 12 weekly infusions
  - 6 weekly infusions of 0.5 g, followed by
    6 weekly infusions of 0.25g

Bartalena L, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy (EUGOGO) Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J.* 2016;5(1):9-26.

Studies Using the Recommended EUGOGO IV Steroid Regimen

Author, year	N (Week 12)	Study Design and Patient Population	Baseline Proptosis	Adverse events (AEs)
Kahaly 2005	35	Randomized, single-blind; euthyroid; TED duration <6 months	23.75 ± 2.14	8 AEs were reported in 6 patients, of which palpitations were the most common.
Aktaran 2007	25	Prospective randomized, single-blind; euthyroid; TED duration <6 months	22.2 ± 2	Weight gain was the most commonly reported AE. 12% of patients had palpitations and hot flashes on the day of treatment.
Bartalena 2012	54	Randomized, double-blind; euthyroid; mean TED duration 12.4 months	22.2 ± 3	Mild AEs were reported in 18 patients. Major AEs were reported in 3 patients: major depression, occurrence of diabetes mellitus requiring therapy and profound muscle weakness
Xing 2014	54	No immunosuppressives or radiotherapy in the previous 3 months; median TED duration 7 months	22.10 ± 2.76	Not reported
Yang 2015	31	Retrospective; euthyroid; no previous treatment for TED except local measures; median TED duration 7 months	23.04 ± 3.8	Mild AEs were observed in 14 patients. A major AE occurred in 1 patient who developed diabetes mellitus, requiring use of hyperglycemic medication.
Zhu 2014	38	Prospective randomized; no immunosuppressives or radiotherapy in the previous 3mth; mean TED duration 13.6 months	22.06 ± 3.17	Weight gain and hypokalemia were the most common AEs.
He 2017	15	Prospective randomized controlled; euthyroid; no previous IV methylprednisolone; median TED duration 7 months	17.2 ± 2.1	17 patients experienced AEs, of which weight gain and hidrosis were most common. No severe AEs occurred.
Kahaly 2018	73	Randomized, open-label; euthyroid; No immunosuppressives or corticosteroids in the previous 3 months; mean TED duration 15 months	21.27 ± 3.68	29 (19 grade 1 and 10 grade 2) treatment related AEs were reported in 20% of patients.
Li 2020	20	Prospective; euthyroid; No immunosuppressives, orbital radiotherapy or surgery; mean TED duration 8 months	18.9 ± 2.42	Weight gain was most common AE. Mild increase in BP and blood glucose was observed in a low proportion during therapy. No other severe AEs were recorded.

Zhu, et al. *JCEM.* 2014;99(6):1999-2007; Kahaly, et al. *Lancet Diabetes Endocrinol.* 2018;6(4):287-298; Kahaly, et al. *JCEM.* 2005;90(9):5234-5240; Bartalena, et al. *JCEM.* 2012;97(12):4454-63; He, et al. *Endocrine J.* 2017;64(2):141 – 149; Yang, et al. *Ophthal Plast Reconstr Surg.* 2014;30:157-161; Aktaran, et al. *Int J Clin Pract.* 2007;61(1):45-51; Xing, et al. *Br J Ophthalmol.* 2015;99:1686 – 1691; Li, et al. *J Endocrinol Invest.* 2020:doi 10.1007/s40618-020-01322-5.

Observed Proptosis Changes

Author, year	N at BL	N at week 12	Mean proptosis at BL (mm)	Mean proptosis at week 12 (mm)	Mean change in proptosis at week 12 (mm)
Kahaly 2005	35	35	23.75	21.5	-2.25
Aktaran 2007	25	25	22.2	21	-1.2
Bartalena 2012	54	54	22.2	21.8	-0.4
Xing 2014	54	54	22.10	21.42	-0.68
Yang 2014	32	31	23.04	23.66	0.62
Zhu 2014_ 12 week	39	38	22.06	20.81	-1.25
He 2017	18	15	17.2	16	-1.2
Kahaly 2018	81	73	21.27	21.15	-0.12
Li 2020	20	20	18.9	16.9	-2
Weighted mean change from baseline					**-0.76**

Zhu, et al. *JCEM.* 2014;99(6):1999-2007; Kahaly, et al. *Lancet Diabetes Endocrinol.* 2018;6(4):287-298; Kahaly, et al. *JCEM.* 2005;90(9):5234-5240; Bartalena, et al. *JCEM.* 2012;97(12):4454-63; He, et al. *Endocrine J.* 2017;64(2):141 – 149; Yang, et al. *Ophthal Plast Reconstr Surg.* 2014;30:157-161; Aktaran, et al. *Int J Clin Pract.* 2007;61(1):45-51; Xing, et al. *Br J Ophthalmol.* 2015;99:1686 – 1691; Li, et al. *J Endocrinol Invest.* 2020:doi 10.1007/s40618-020-01322-5.

GORMAN SCORE

Diplopia Score	
0	No diplopia
1	Intermittent, ie, diplopia in primary position of gaze, when tired or when first awakening
2	Inconstant, ie, diplopia at extremes of gaze
3	Constant, ie, continuous diplopia in primary or reading position

Observed Diplopia Changes (Gorman Score)

Author, year	N at BL	N at week 12	Mean diplopia at BL	Mean diplopia at week 12	Mean change in diplopia at week 12
He 2017	12	12	1.5	1.3	-0.2
Aktaran 2007	11	11	1.7	1	-0.7
Kahaly 2018	52	52	1.79	1.15	-0.64
Kahaly 2005	26	26	2.9	1.8	-1.1
Zhu 2014_12 week	28	28	2.04	1.75	-0.29
Xing 2014	35	35	2.14	1.63	-0.51
Li 2020	13	13	1.77	1.46	-0.31
Weighted mean change from baseline					**-0.58**

Zhu, et al. *JCEM.* 2014;99(6):1999-2007; Kahaly, et al. *Lancet Diabetes Endocrinol.* 2018;6(4):287-298; Kahaly, et al. *JCEM.* 2005;90(9):5234-5240; Bartalena, et al. *JCEM.* 2012;97(12):4454-63; He, et al. *Endocrine J.* 2017;64(2):141 – 149; Yang, et al. *Ophthal Plast Reconstr Surg.* 2014;30:157-161; Aktaran, et al. *Int J Clin Pract.* 2007;61(1):45-51; Xing, et al. *Br J Ophthalmol.* 2015;99:1686 – 1691; Li, et al. *J Endocrinol Invest.* 2020:doi 10.1007/s40618-020-01322-5.

Discussion: Side Effect Profile of Glucocorticoids

System Affected	Side Effects
Musculoskeletal	Osteoporosis, avascular necrosis of bone, myopathy
Endocrine and metabolic	Hyperglycemia, Diabetes mellitus, dyslipidemia, weight gain, cushingoid features, growth suppression, adrenal suppression
Gastrointestinal	Gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis
Cardiovascular	Hypertension, coronary heart disease, ischemic heart disease, heart failure
Dermatologic	Dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss
Neuropsychiatric	Mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium
Ophthalmologic	Cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy
Immunologic	Suppression of cell-mediated immunity, predisposition to infections, reactivation of latent infections

Oray M, et al. *Expert Opin Drug Saf.* 2016;15(4):457-465.

Steroids – Bottom Line

- Steroids do NOT reverse the underlying alterations of orbital tissue
- They do NOT reverse proptosis or strabismus
- Substantial side effects, but only masks symptoms?

Bartalena L, et al. *J Clin Endocrinol Metab*. 2012;97(12):4454-63.

Rituximab (RTX)

- Chimeric mouse-human monoclonal antibody against CD20 antigen on B lymphocytes
- Deplete B cells, interferes with production of cytokines and B-cell antigen presentation, decreases autoreactive T cells
- Approved for other autoimmune conditions (RA and systemic lupus erythematosus)

Rituximab [Prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5367s5388lbl.pdf. Accessed January 9, 2020.

Rituximab (RTX)

- Conflicting results from trials (2015-2017) for treatment of moderate to severe TED
  - One RCT: intraorbital RTX is as effective and safe as IV glucocorticoid (GC)[1]
  - Two RCTs: IV RTX more effective than GC[2,3]
  - One RCT: IV RTX no effect over saline[4]
- Several reports of development of dysthyroid optic neuropathy[4,5]

RCT = randomized controlled trial; TED = thyroid eye disease.

1. Savino G, et al. *Endocrine*. 2015;48(1):241-7.
2. Salvi M, et al. *J Clin Endocrinol Metab.* 2015;100(2):422-31.
3. Li J, et al. *Pharmacology*. 2017;99(3-4):144-52.
4. Stan MN, et al. *J Clin Endocrinol Metab*. 2015;100(2):432-41.
5. Krassas GE, et al. *Clin Endocrinol (Oxf)*. 2010;72(6):853-5.

Long-term Efficacy Comparisons – Steroids and Rituximab

Drug Treatment	Response		*P*
Methylprednisolone IV	Low Dose (n = 53)	High Dose (n = 52)	
Proptosis mean baseline (mm)	23.3	22.5	
Proptosis Δ 12 weeks (mm)	−0.8	−0.6	NS
CAS median baseline	4	5	
CAS Δ 12 weeks	−1.8	−2.7	.01
Rituximab	PBO (n = 12)	Rituximab (n = 13)	
Proptosis mean baseline (mm)*	23.2	24.4	
Proptosis Δ 24 weeks (mm)*	−0.4	+0.3	NS
CAS mean baseline	5.3	4.9	
CAS Δ 24 weeks	−1.5	−1.3	NS
*, averaged values from both eyes; NS, not significant			

- Methylprednisolone –12 weekly IV infusions (EUGOGO protocol)
  - Cumulative dose: low = 2.25 g, high = 7.47 g
- Rituximab – 2 infusions separated by 2 weeks (ie, standard RA protocol)
  - Each infusion dose = 1 g

CAS = clinical activity score; EUGOGO = European Group on Graves' Orbitopathy; RA = rheumatoid arthritis.

Bartalena L, et al. *J Clin Endocrinol Metab*. 2012;97(12):4454-63.
Stan MN, et al. *J Clin Endocrinol Metab*. 2015;100(2):432-441.

Tocilizumab

- Humanized monoclonal antibody against IL-6 receptor
- **2014:** Prospective nonrandomized study showed efficacy in TED refractory to IV steroids[1]
- **2018:** Multicenter, RCT showed efficacy in glucocorticoid-resistant TED; however, small study (n=32) and composed with heterogenous group of patients who had pretreatment with other immunosuppressive agents[2]
- Subcutaneous tocilizumab demonstrated efficacy in 2 patients[3]

IL = interleukin; IV = intravenous.

1. Perez-Moreiras JV, et al. *Ophthalmic Plast Reconstr Surg*. 2014;30(2):162-7.
2. Perez-Moreiras JV, et al. *Am J Ophthalmol*. 2018;195:181-90.
3. Cooperman T, et al. *Ophthalmic Plast Reconstr Surg*. 2019;35(3):e64-e66.

Mycophenolate Mofetil (MMF)

- Inhibits the proliferative responses of T and B lymphocytes, recruitment of leukocytes, modulates chemotaxis
- MMF targets rapamycin (mTOR) pathways, having direct effect on orbital fibroblasts
- **2017:** Improvement in CAS, diplopia, and proptosis with MMF versus steroids[1]
- **2018:** Better efficacy in patients with MMF + IV steroids compared with IV steroids alone[2]

mTOR = mammalian target of rapamycin.

1. Ye X, et al. *Clin Endocrinol (Oxf)*. 2017;86(2):247-55.
2. Kahaly GJ, et al. *Lancet Diabetes Endocrinol*. 2018;6(4):287-98.

Azathioprine

- Antimetabolite with similar mechanism to MMF
- **RCT (2018):** all patients received oral steroids; post hoc analysis showed reduction in relapse rate after steroid withdrawal[1]
- Less well tolerated than MMF

1. Rajendram R, et al. *Lancet Diabetes Endocrinol*. 2018;6(4):299-309.

Innovation: TED-specific Treatment

- Molecular targeting of antigen

Insulin-like Growth Factor-1 Receptor

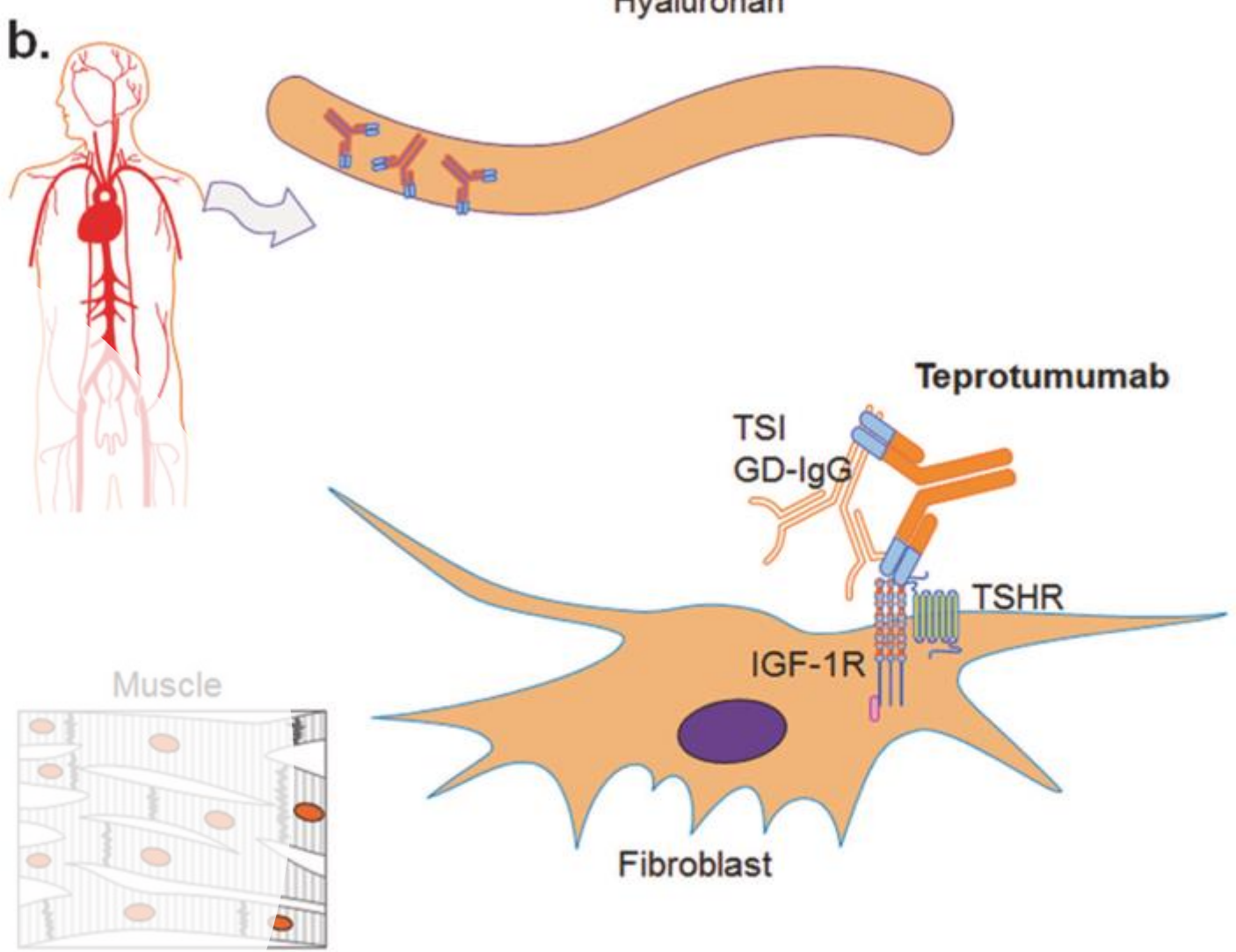
- Overexpressed on Graves' disease (GD) fibroblasts and immune cells
- Signaling of fibroblasts and immune cells mimics pathologic findings
- Antibodies to these receptors in GD patients

Smith TJ, et al. *Best Pract Res Clin Endocrinol Metab*. 2012;26(3):291-302.

Teprotumumab: Mechanism of Action

- Fully human monoclonal antibody inhibitor of IGF-1R
- Targeted binding to IGF-1R of the IGF-1R/TSHR signaling complex
- Blocks autoantibodies from attacking orbital cells
- Turns off IGF-1R/TSHR signaling at disease source
- Reduces inflammation + prevents excessive cell growth and hyaluronan build up behind eye

Douglas RS. *Eye (Lond)*. 2019;33(2):183-90; Smith TJ, Hegedüs L. *N Engl J Med*. 2016;375(16):1552–1565.




NDC-75987-130-15
TEPEZZA
(teprotumumab-trbw)
for Injection
500 mg/vial
For Intravenous Infusion Only
Reconstitute and Further Dilute Prior to Use
Single-dose vial. Discard unused portion.
Rx Only
TEPEZZA
(teprotumumab-trbw)
for injection
500 mg/vial
For Intravenous Infusion Only

How is Tepezza (teprotumumab-trbw) taken?

The standard dosage is:[1]

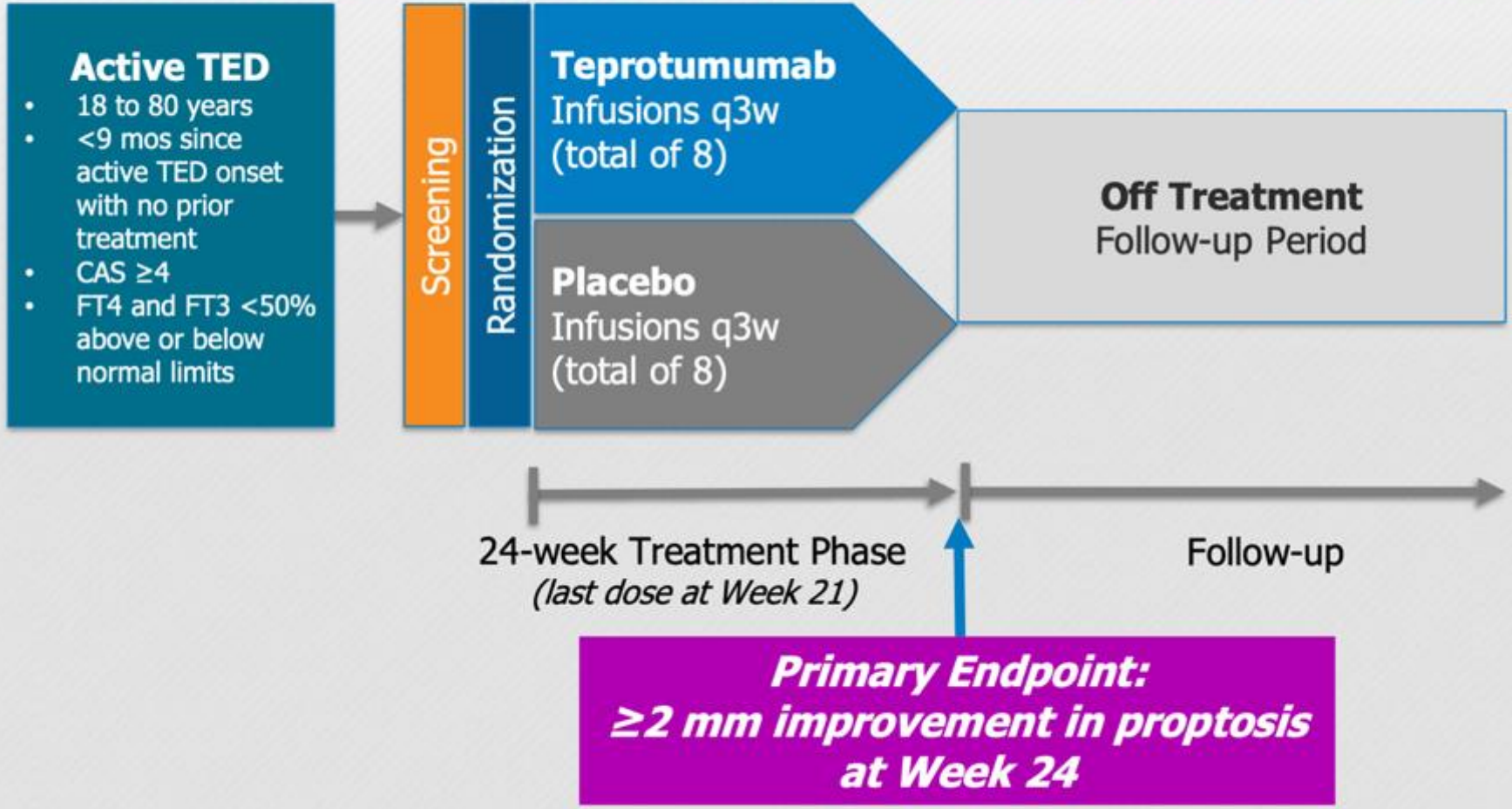
- 10 mg/kg body weight for the first dose
- Followed by 20 mg/kg body weight every three weeks for 7 additional infusions

A dose of Tepezza (teprotumumab-trbw) is given as an intravenous infusion (drip) into a vein.[1]

Complete information about Tepezza (teprotumumab-trbw) dosage and administration can be fo
official prescribing information listed in our references section.[1]

Teprotumumab for the Treatment of Active Thyroid Eye Disease

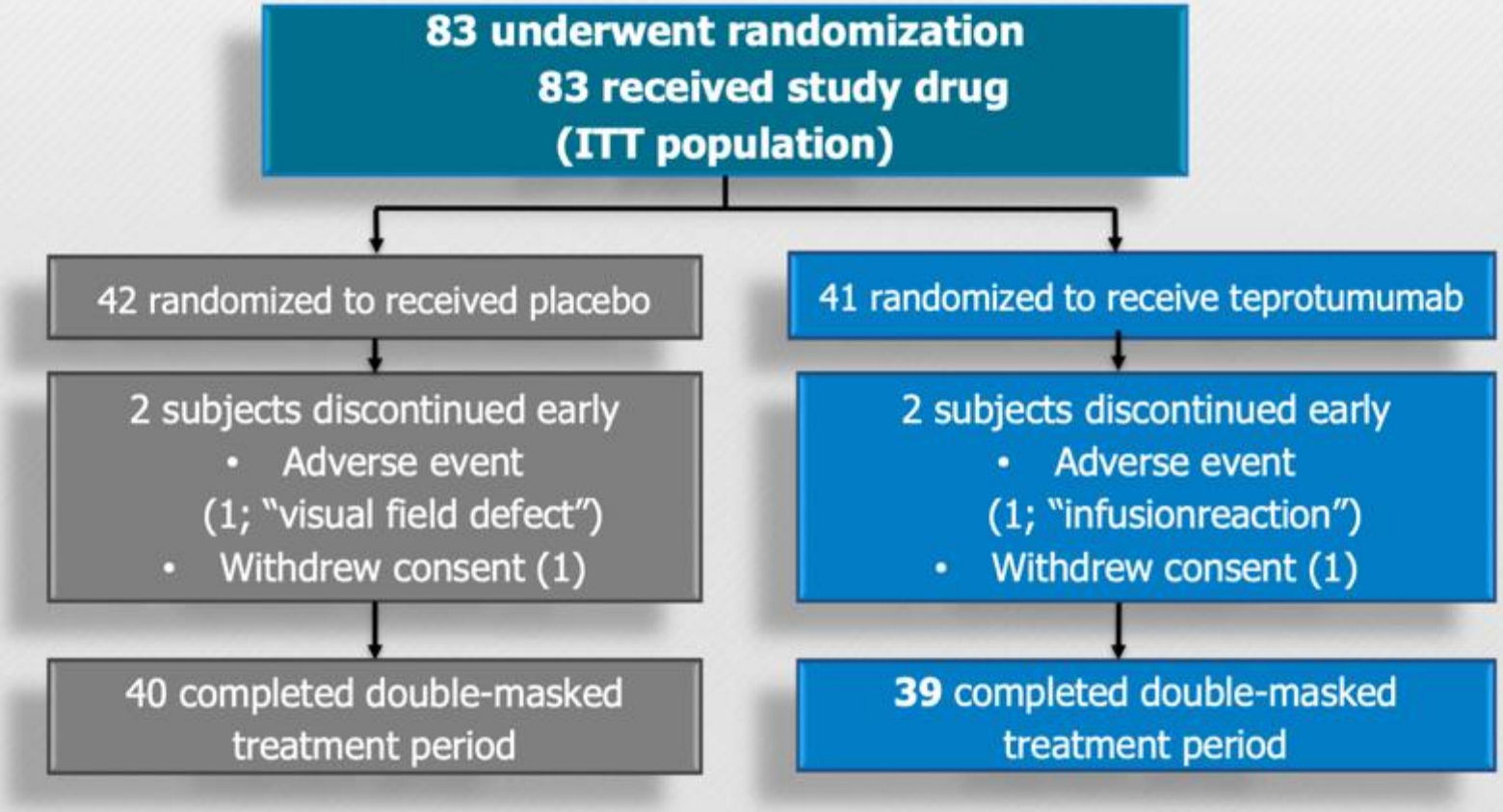
Phase 3, 24-Week Randomized, Double-masked, Placebo-controlled Trial



FT3 = free triiodothyronine; FT4 = free thyroxine.

NCT03298867: Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis With Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (**OPTIC**). Data From: Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

Subject Disposition



ITT = intent-to-treat.
Adapted from Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

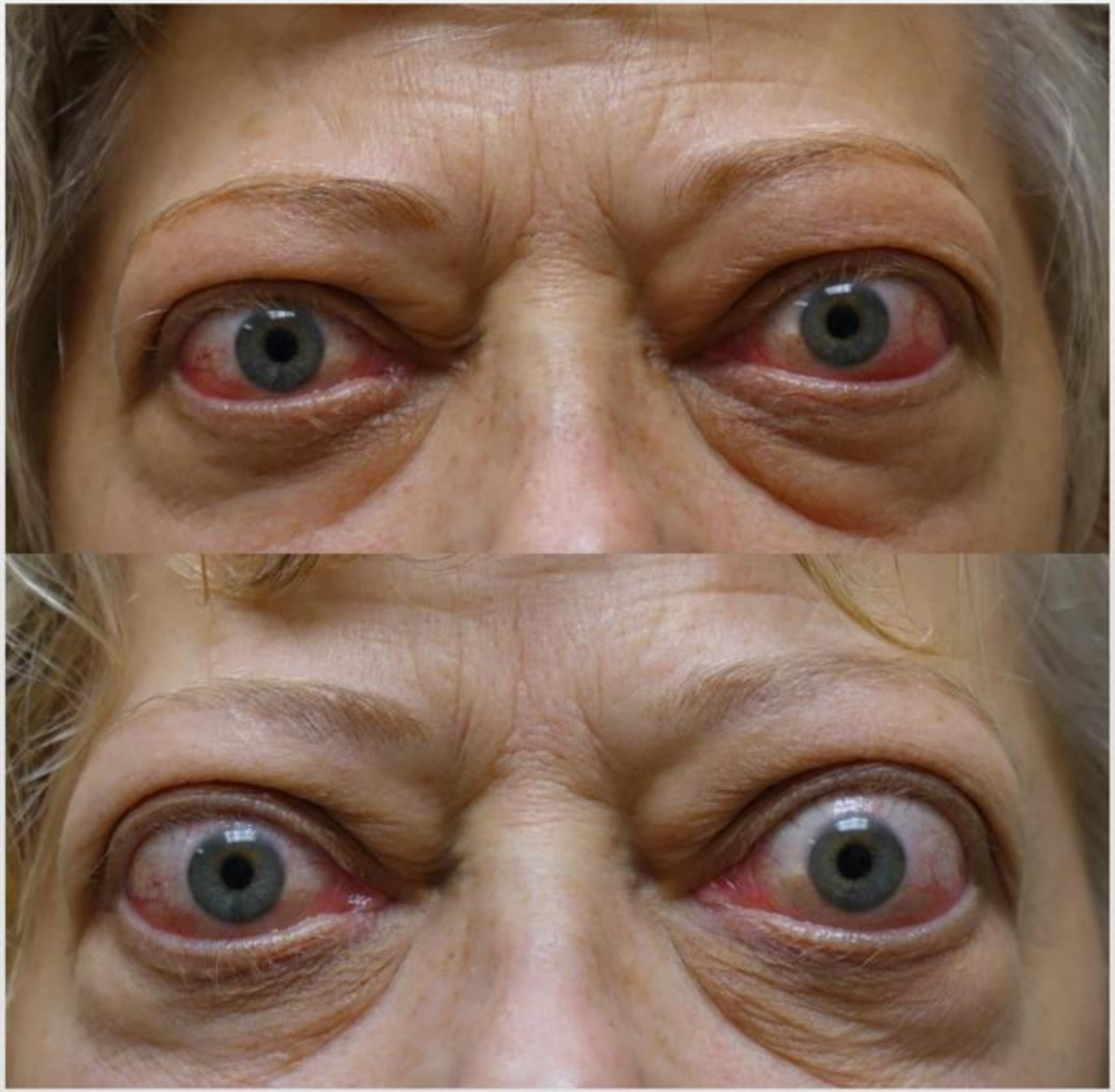
Summary of Results

The primary outcome of proptosis responders (% of patients with ≥2-mm reduction in proptosis from baseline) was *significantly greater* with teprotumumab than placebo

- All secondary endpoints were also met ($P \leq .001$)
  - Overall responder rate at Week 24 (primary endpoint in the phase 2 study)
  - Percent of participants with a CAS value of 0 or 1 at Week 24
  - Percent of patients with a change from baseline of at least 1 grade in diplopia (double vision)
  - Mean change in proptosis from baseline through week 24
  - Mean change in Graves' ophthalmopathy quality of life score from baseline through week 24

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

OPTIC Trial



Placebo Patient

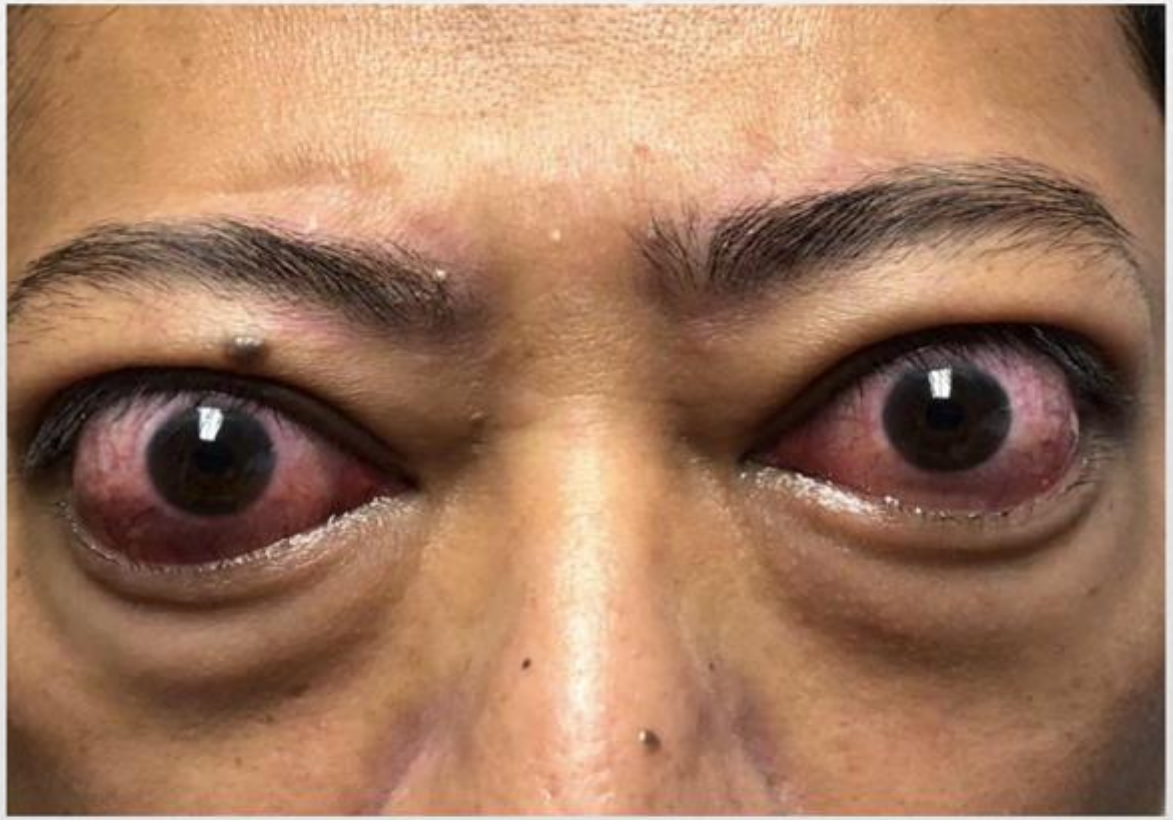
Pretreatment

Week 24

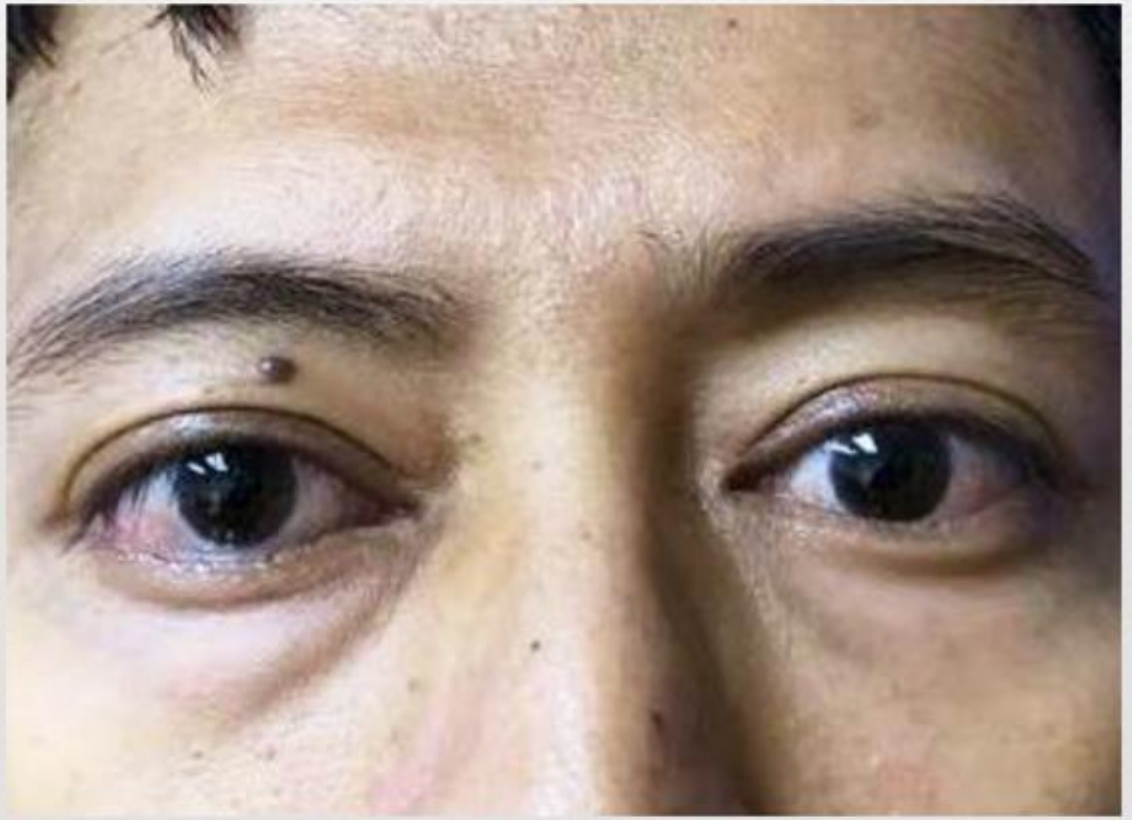
Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352. Used with permission.

OPTIC Trial

Teprotumumab



Pretreatment

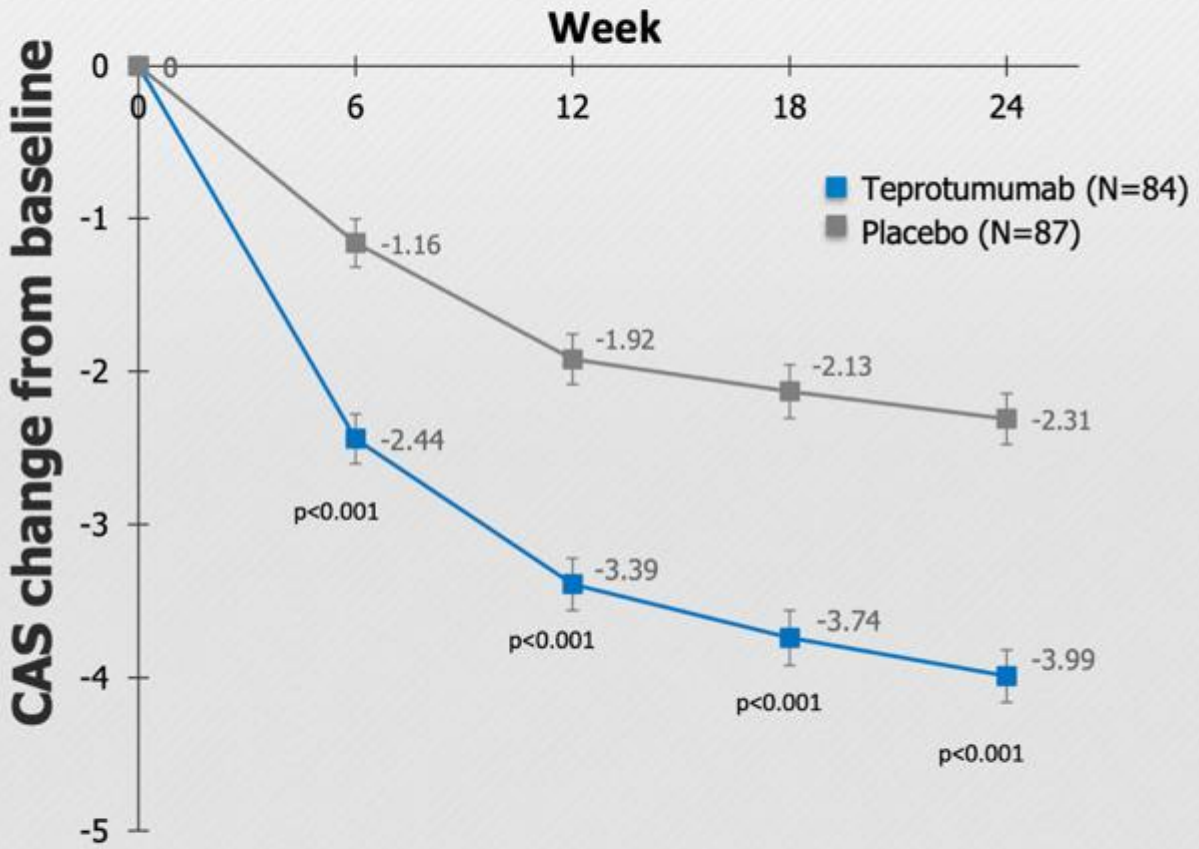


Week 24

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

OPTIC Trial

Clinical Activity Score Reductions



Clinical Activity Score (CAS)

1	Spontaneous orbital pain
2	Gaze evoked orbital pain
3	Eyelid swelling that is considered to be due to active GO
4	Eyelid erythema
5	Conjunctival redness that is considered to be due to active GO
6	Chemosis
7	Inflammation of caruncle *OR* plica

For each item present, 1 point is given

Disease Inactivation: 61.9% of teprotumumab-treated patients had absent TED activity (CAS of 0 or 1) vs 21.8% of placebo-treated patients at week 24 (*P*<.001)

GO = Graves' ophthalmopathy

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352;
Image from Kahaly GJ, et al. *Thyroid.* 2019;29(Suppl 1). https://www.liebertpub.com/doi/pdf/10.1089/thy.2019.29085.abstracts.

Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix, including the following terms: baseline score, tobacco use status (nonuser, user), treatment group, visit, and visit-by-treatment and visit-by-baseline-score interactions; least square mean ± standard error

Proptosis Response (Reduction of ≥2 mm)

Primary Outcome

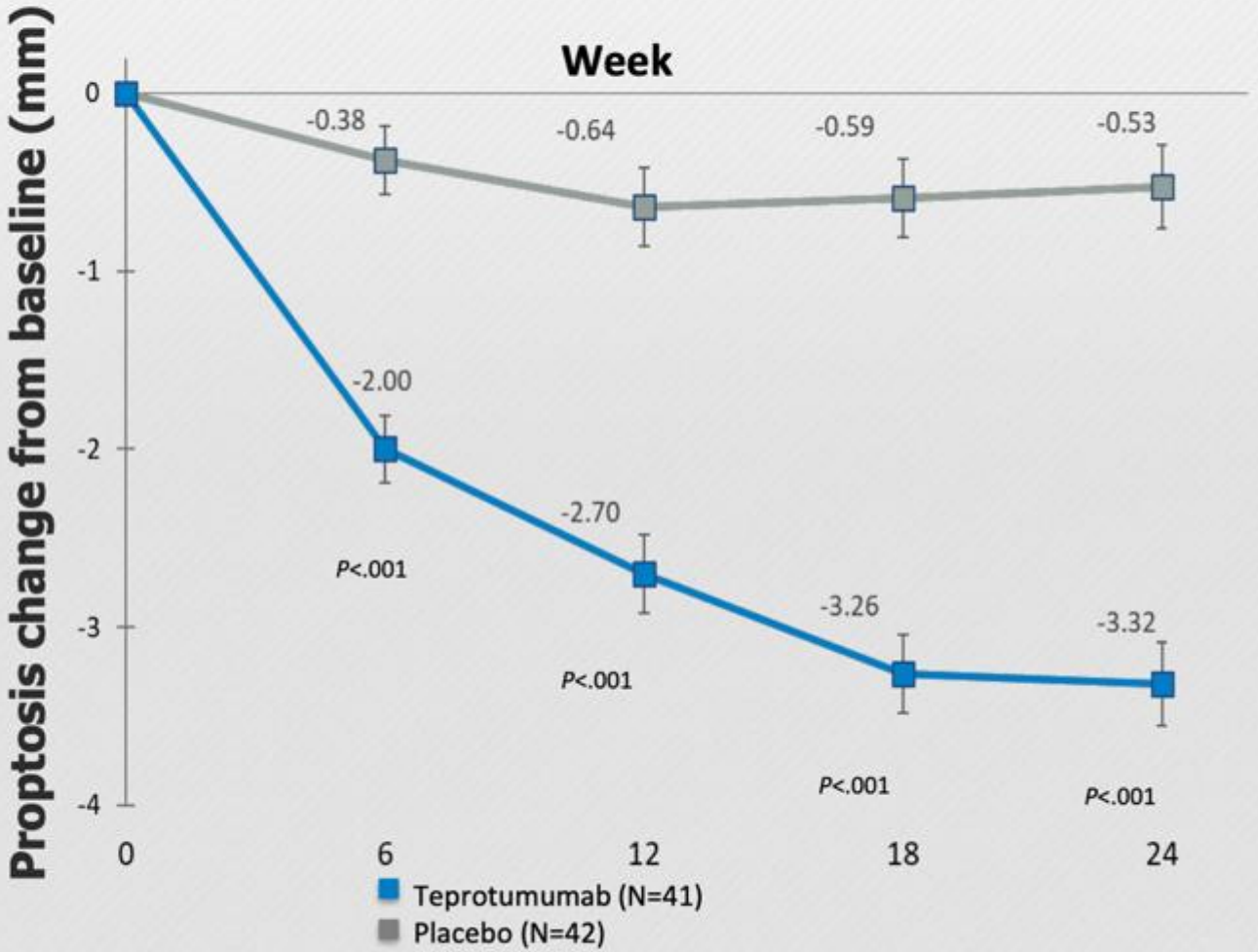
‡Stratified Difference in Response Rates. Estimates from the 2 strata (tobacco user, tobacco nonuser) are combined with Cochran-Mantel-Haenszel weights.

Number needed to treat (NNT) of 1.36

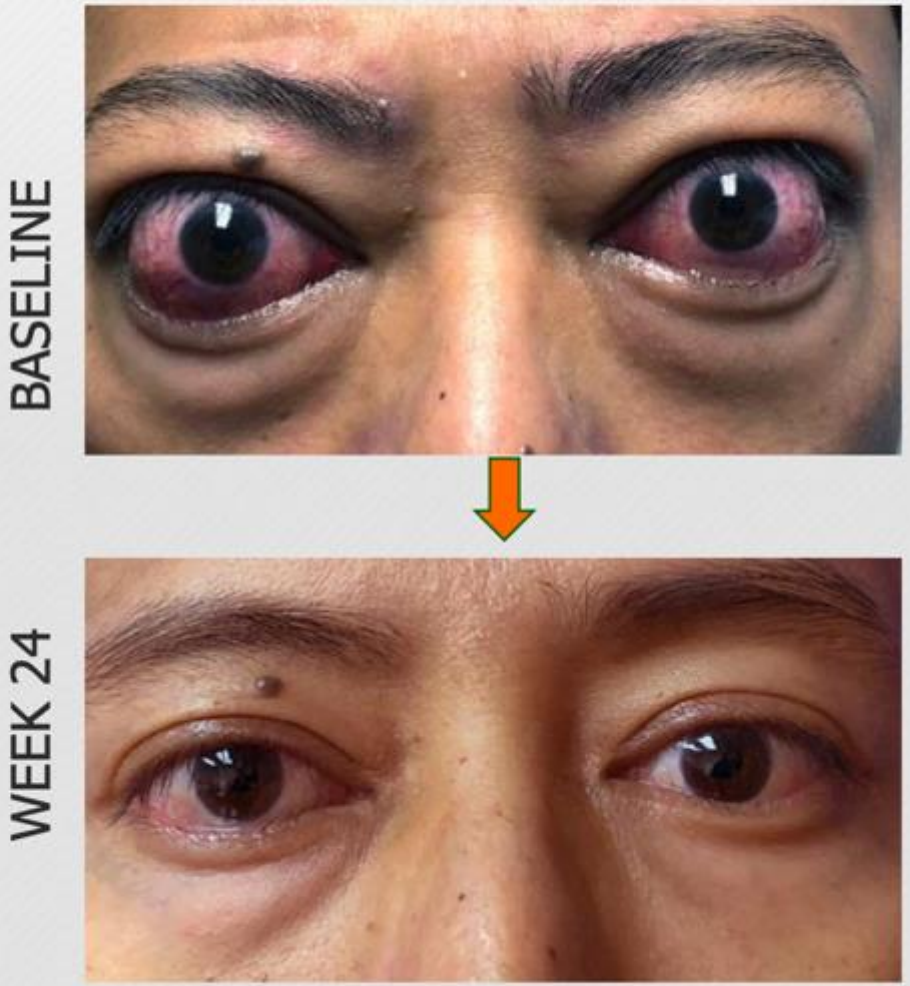
Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352. Used with permission.

OPTIC Trial

Proptosis Reductions



Teprotumumab



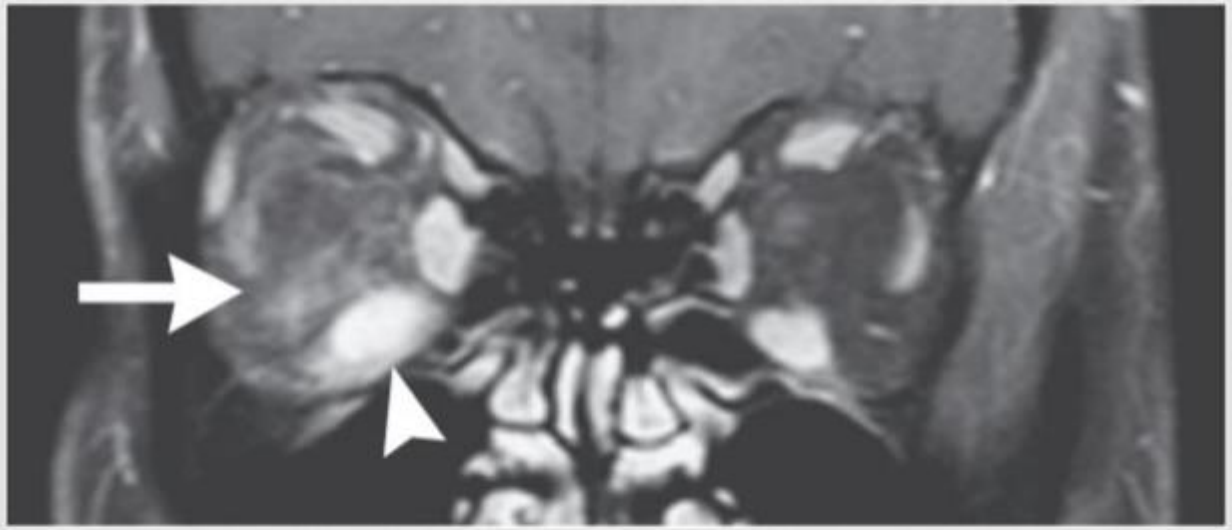
Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix, including the following terms: baseline score, tobacco use status (nonuser, user), treatment group, visit, and visit-by-treatment and visit-by-baseline-score interactions; least square mean ± standard error.

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

Magnetic Resonance Imaging (MRI): Muscle and Orbital Fat Effects in a Teprotumumab-Treated Patient

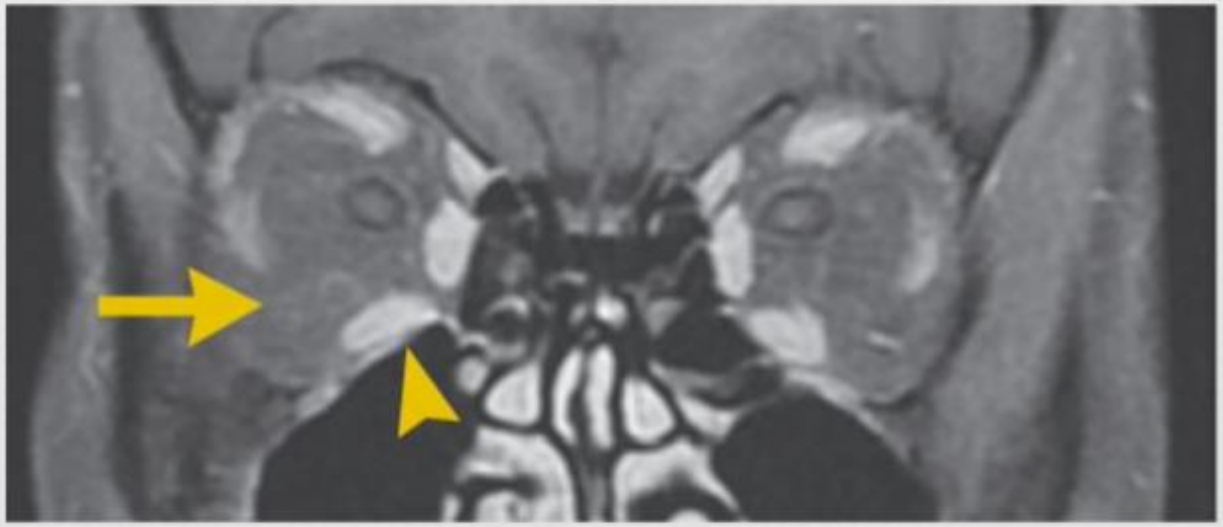
OPTIC Trial

Pretreatment



- At baseline, the MRI showed marked enhancement of the inferior rectus muscle (white arrowhead) and orbital fat (white arrow), findings indicative of inflammation and edema.

24 Week after Initial Dose

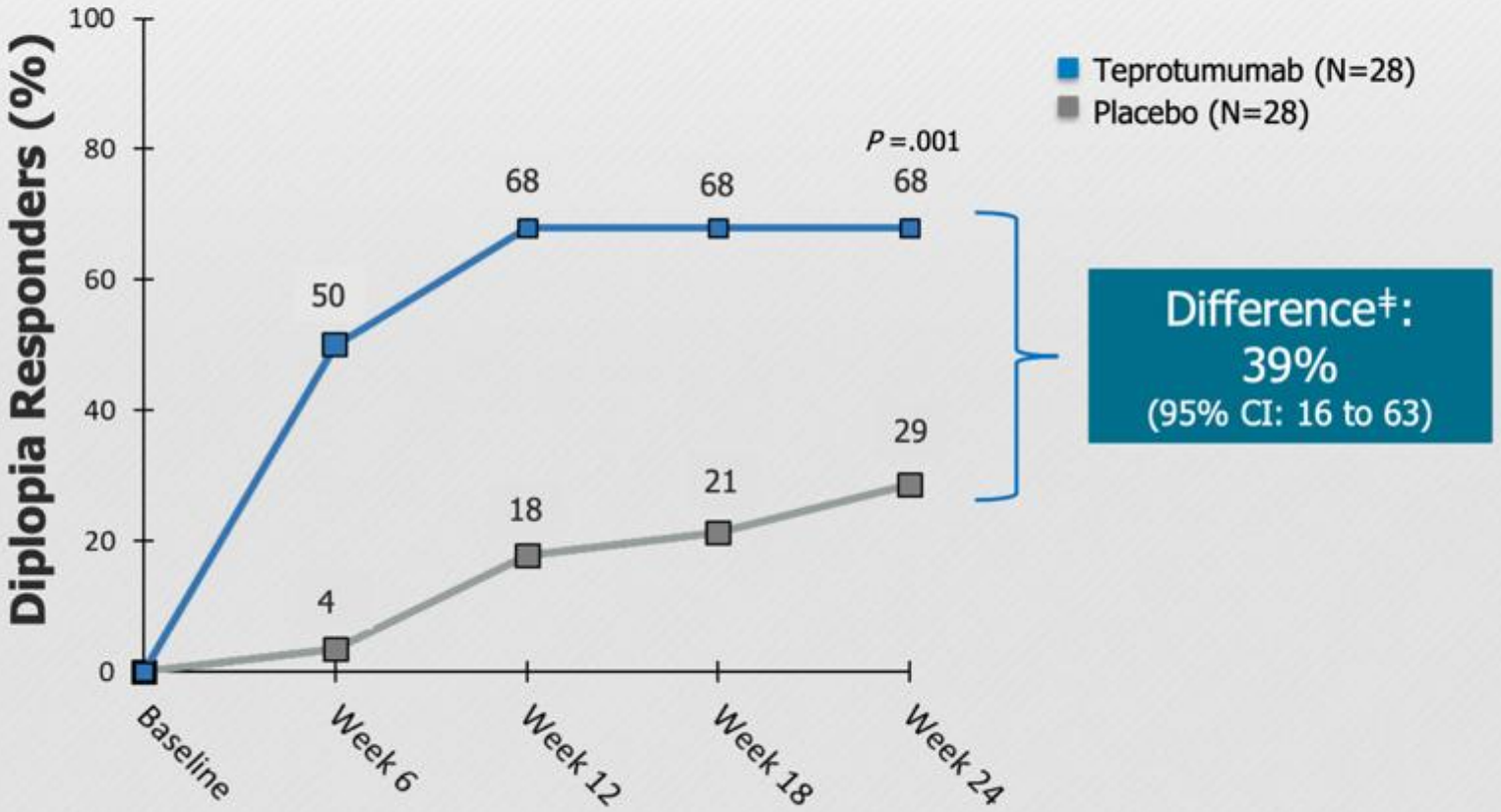


- At week 24, the MRI showed resolution of the enhancement of the inferior rectus muscle (yellow arrowhead) and orbital fat (yellow arrow).
- The size of the inferior rectus muscle was reduced by 49% according to volumetric analysis (yellow arrowhead), and the volume of the medial rectus muscle was reduced by 41%.

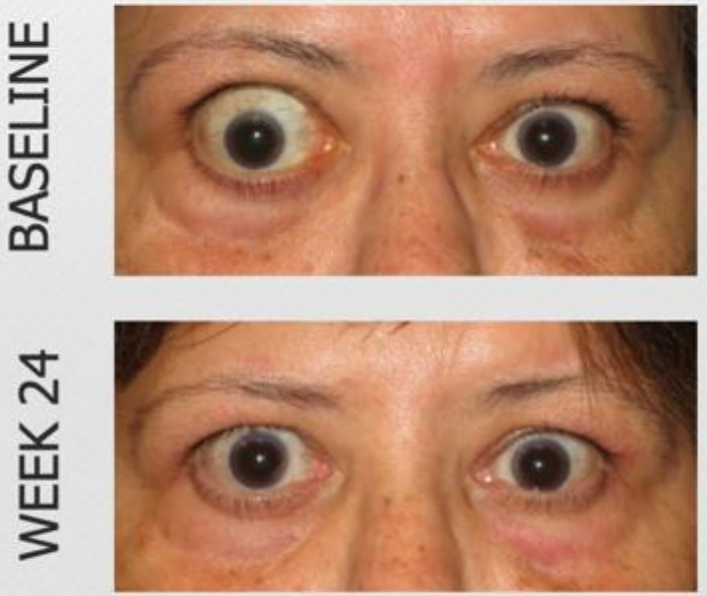
Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352. Used with permission.

Diplopia Responders: ≥1 Grade Improvement in Those With Baseline Diplopia

OPTIC Trial



Teprotumumab



Diplopia Score

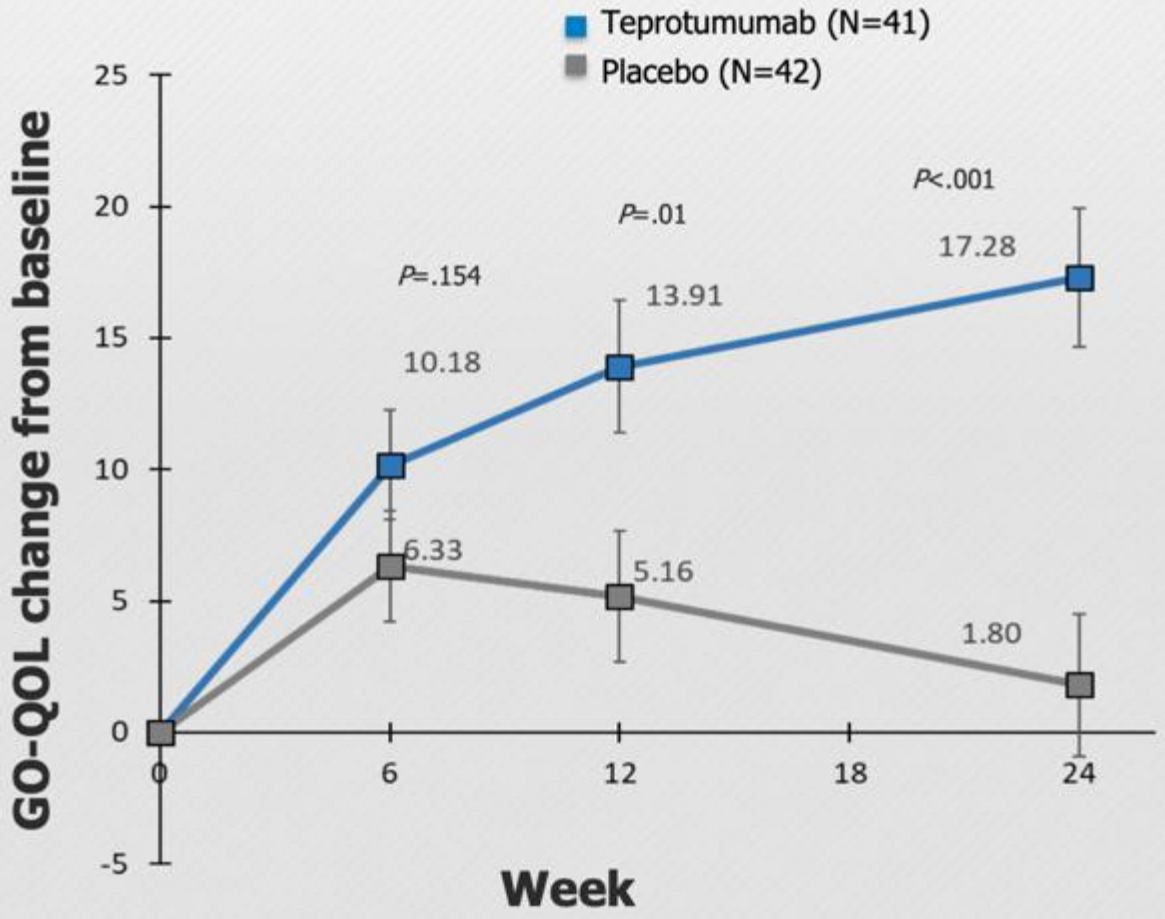
0	No diplopia
1	Intermittent, ie, diplopia in primary position of gaze, when tired or when first awakening
2	Inconstant, ie, diplopia at extremes of gaze
3	Constant, ie, continuous diplopia in primary or reading position

Note: 28 patients in each group had diplopia at baseline.
‡Stratified difference in response rates. Estimates from the 2 strata (tobacco user, tobacco nonuser) are combined with Cochran-Mantel-Haenszel weights.

Image and permission courtesy of Raymond Douglas, MD, PhD.

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

GO-QOL Improvements – Overall



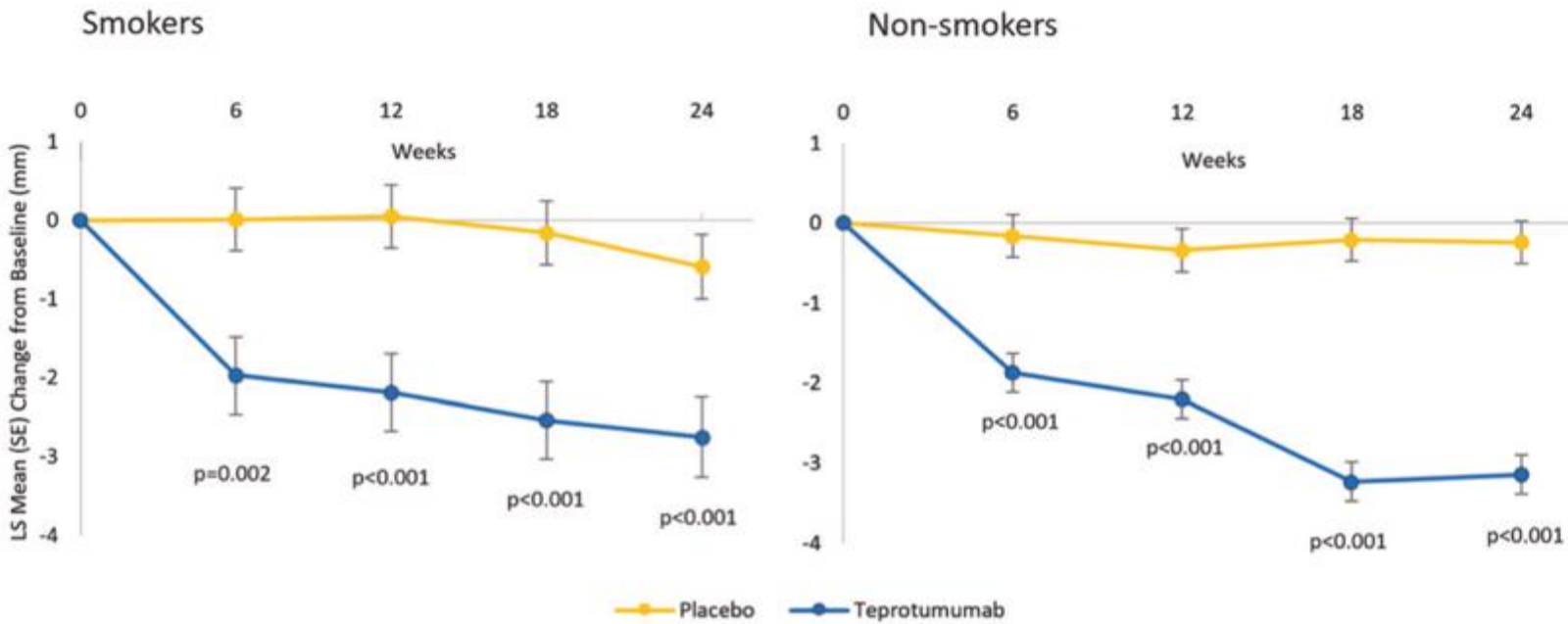
Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model with an unstructured covariance matrix including the following terms: baseline score, tobacco use status (nonuser, user), treatment group, visit, and visit-by-treatment and visit-by-baseline-score interactions; least square mean ± standard error.

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

Drivers of decreased QOL:

- TED activity[1-4] and ocular pain[1,5]
- Disease severity[2-4,6,7]:
  - Proptosis[4, 8-10] and asymmetric proptosis (≥3 mm difference between eyes)[4]
  - Diplopia[1, 3-5, 11]
  - Blurred vision[1]

1. Kahaly GJ, et al. *Clin Endocrinol (Oxf).* 2005;63(4):395-402. 2. Choi YJ, et al. *Eye (Lond).* 2012;26(4):544-51. 3. Lin IC, et al. *J Formos Med Assoc.* 2015;114(11):1047-54. 4. Villagelin D, et al. *Front Endocrinol (Lausanne).* 2019;10:192. 5. Kahaly GJ, et al. *Thyroid.* 2002;12(3):237-9. 6. Park JJ, et al. *Br J Ophthalmol.* 2004;88(1):75-8. 7. Delfino LC, et al. *Arch Endocrinol Metab.* 2017;61(4):374-81. 8. Bartalena L, et al. *Endocr Rev.* 2000;21(2):168-99. 9. Gerding MN, et al. *Thyroid* .1997;7(6):885-9. 10. Tehrani M, et al. *Eur J Ophthalmol.* 2004;14(3):193-9. 11. Bradley EA, et al. *Ophthalmology.* 2006;113(8):1450-4.



Teprotumumab, N	11	11	11	9	29	29	28	29
Placebo, N	17	16	16	15	25	25	25	24

Fig. 8 Reduction in Proptosis in smokers and non-smokers

Safety Profile

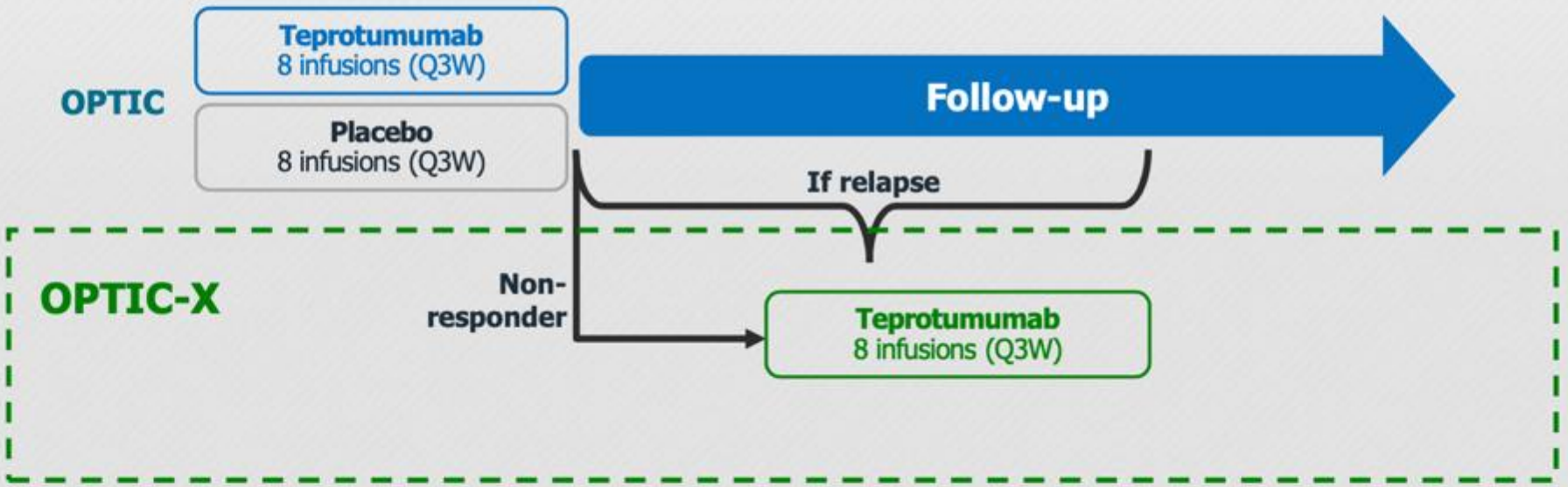
Treatment-emergent Adverse Events Occurring in >5% of Patients:

Number of patients (%)	Placebo (n=42)	Teprotumumab (n=41)
Muscle Spasm	4 (10)	13 (32)
Alopecia	5 (12)	8 (20)
Nausea	4 (10)	6 (15)
Fatigue	1 (2)	5 (12)
Diarrhea	5 (12)	4 (10)
Headache	4 (10)	4 (10)
Dry skin	0 (0)	4 (10)
Dysgeusia	0 (0)	4 (10)
Stomatitis	1 (2)	3 (7)
Amenorrhoea	0 (0)	3 (7)
Dizziness	0 (0)	3 (7)
Cough	3 (7)	2 (5)
Abdominal pain upper	3 (7)	2 (5)
Influenza	3 (7)	1 (2)

Majority of treatment-emergent adverse events were mild to moderate in intensity and no nonserious events led to discontinuation

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

OPTIC-X and OPTIC 48-Week Follow-Up



Treatment of Graves' Orbitopathy to Reduce Proptosis With Teprotumumab Infusions in an Open-Label Clinical Extension Study (OPTIC-X)
ClinicalTrials.gov Identifier: NCT03461211

Summary of OPTIC-X and OPTIC 48-Week Off Treatment Results

- 89 percent of OPTIC placebo patients achieved clinically significant proptosis reduction when treated with teprotumumab in OPTIC-X
- Of the small number of patients who received a full course of teprotumumab in OPTIC and were non-responders (five), two achieved a ≥2mm proptosis reduction with an additional course of teprotumumab
- Durability, the majority of teprotumumab proptosis responders at Week 24 of OPTIC maintained response at Week 72, which was nearly a year off treatment
- Of the the small number of teprotumumab patients who relapsed during off-treatment follow-up in OPTIC, >60 percent experienced ≥2mm proptosis improvement with additional teprotumumab treatment in OPTIC-X
- There were no new safety concerns in either OPTIC-X or 48-week OPTIC follow-up period, even with the additional teprotumumab treatment in OPTIC-X

OPTIC Week 24 non-responders: Patients who did not achieve at least a 2mm proptosis improvement from baseline at Week 24 of OPTIC.
Relapse is defined as patients who lost at least 2mm of their Week 24 proptosis improvement during the 48-week off-treatment period even if proptosis improvement was substantially better than at OPTIC baseline, or patients who had a substantial increase in the number of inflammatory signs or symptoms without worsening proptosis.
ClinicalTrials.gov Identifier: NCT03461211; Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.

Efficacy Comparison – Decompression Surgery

Recent reports suggest comparable reductions in proptosis

Study	n (Pts.)	n (Eyes)	Change in Proptosis (mm)	Comment
Rootman et al. 2016 (UCLA) Retrospective	169	319	–3.8	33% Patients postoperatively developed strabismus requiring further surgery
Wu et al. 2016 (U Michigan) Retrospective	356	420	–3.8	Strabismus leading to binocular diplopia the most common complication
OPTIC Study Week 24*			–3.3	No evidence of strabismus complication – in contrast, marked improvement in subjective diplopia
*Data are mean reductions from baseline for patients with values at Week 24				

Note: decompression surgery is performed on inactive TED – does not constitute a direct comparison for active disease

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

Conclusions

- Steroids do NOT reverse the underlying alterations of orbital tissue or reverse proptosis or strabismus and have substantial side effects
- *Other therapies used for TED:* Rituximab, tocilizumab, mycophenolate mofetil, azathioprine
- *Teprotumumab*
  - Phase 3, placebo-controlled study of teprotumumab demonstrated a significant reduction in proptosis
  - These results confirm that teprotumumab is highly effective in reducing proptosis, supporting a positive benefit/risk profile in the treatment of TED, with apparent disease-modifying activity
  - Teprotumumab is FDA approved for thyroid eye disease

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-352.
Teprotumumab. Prescribing Information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761143s000lbl.pdf

Case 1: 22-year-old Woman
History of Present Illness

22-year-old who developed concomitant TED and hypothyroidism in 2018

- Started immediately on levothyroxine
- No relevant ocular past history
- No family history of Graves' disease or other autoimmune diseases
- Reports of bilateral eye protrusion and periorbital pain
- Denies increased tearing, blurry vision, or diplopia

Image and permission courtesy of Raymond Douglas, MD, PhD.

TED = thyroid eye disease.

Initial Physical Examination

Eyes

- Full motility/no strabismus
- CAS 2/7 OU
- Mouritz 24 mm/25 mm
- Full visual field

Laboratory results (on FT4 replacement)

- Serum TSH, 0.03 µIU/L
- FT4, 1.13 ng/dL
- Total T3, 93 ng/dL

CAS = clinical activity score; FT = free thyroxine; T3 = triiodothyronine; TSH = thyroid-stimulating hormone.

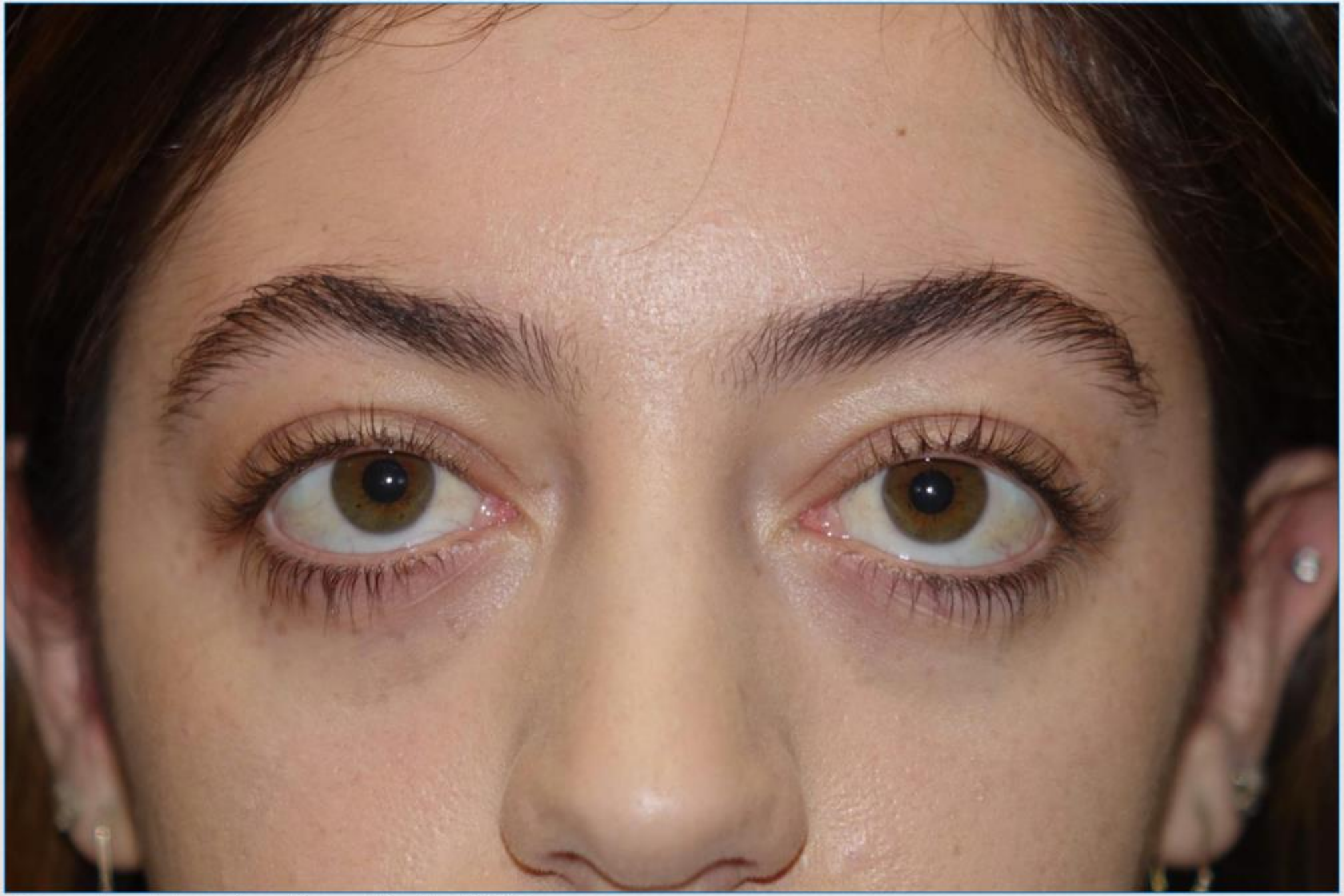


Image and permission courtesy of Raymond Douglas, MD, PhD

Mild conjunctival injection, lid retraction, edema

Lid
retraction

Symmetrical proptosis

Image and permission courtesy of Raymond Douglas, MD, PhD.

Treatments Instituted

Local Eye Care

- Eye lubrication
- Protection from strong light and wind
- Nighttime coverage
- Maintaining euthyroid state
- Avoidance of smoke and irritants
- Vitamin D
- Selenium

Case 1: 22-year-old Woman
Clinical Course

- Patient continues to be clinically euthyroid taking levothyroxine
- Eyes have not progressed
- Comfortable in the absence of systemic steroids
- Continues daily activities without problems
- May be interested in cosmetic intervention in the future
- Reproductive concerns

Case 2: 53-year-old Woman
History of Present Illness

53-year-old woman who developed Graves' disease with hyperthyroidism and debilitating TED

- Eye symptoms began in August 2019 with eyelid swelling
- Graves' disease was diagnosed in October 2019 based on lid retraction and marked, right-sided proptosis
- Initial complaints: diplopia, right-sided discomfort, periocular pain
- No previous relevant ocular history
- No family history of Graves' disease, or other autoimmune disorders
- Physical exam: asymmetrical proptosis, conjunctivititis
- Initial (untreated) labs: TSI 369 IU/L, TSH < 0.01 µIU/mL, FT4 2.2 ng/dL

Image and permission courtesy of Raymond Douglas, MD, PhD.

TSI = thyroid-stimulating immunoglobulins.

Disease Course

- **Thyroid**
  - Hyperthyroidism treated with methimazole
  - Rapidly improved thyrotoxicosis symptoms
  - *December 30, 2019 (on Methimazole):* TSI 488 IU/L, TSH < 0.01 uIL/mL, FT4 1.1 ng/dL

- **Eyes**
  - Serial examinations showed worsening injection, no changes in vision
  - Increasing diplopia in up-and-right gaze but orthotropic in primary gaze
  - High-dosage intravenous steroids failed

Next Options for Therapy

- Another course of steroids with or without orbital radiotherapy?

- Watch and wait for progression to cease, followed by staged remedial surgeries?

Case decision update:

- Patient and her physician elected teprotumumab
- Teprotumumab therapy initiated
- Standard infusion protocol (10 mg/kg body weight initial dose then 20 mg/kg every 3 weeks)

Baseline

CAS 7/7 on a scale of 1 to 7.

Hertel exophthalmetry 27/18 mm

CAS = clinical activity score.
Image and permission courtesy of Raymond Douglas, MD, PhD.

Week 9

Hertel 23/18 mm
CAS 2/7, 1/7

Week 3

Hertel 24/18 mm
CAS 4/7, 1/7

Baseline

Hertel 27/18 mm
CAS 7/7, 1/7

Images and permission courtesy of Raymond Douglas, MD, PhD.

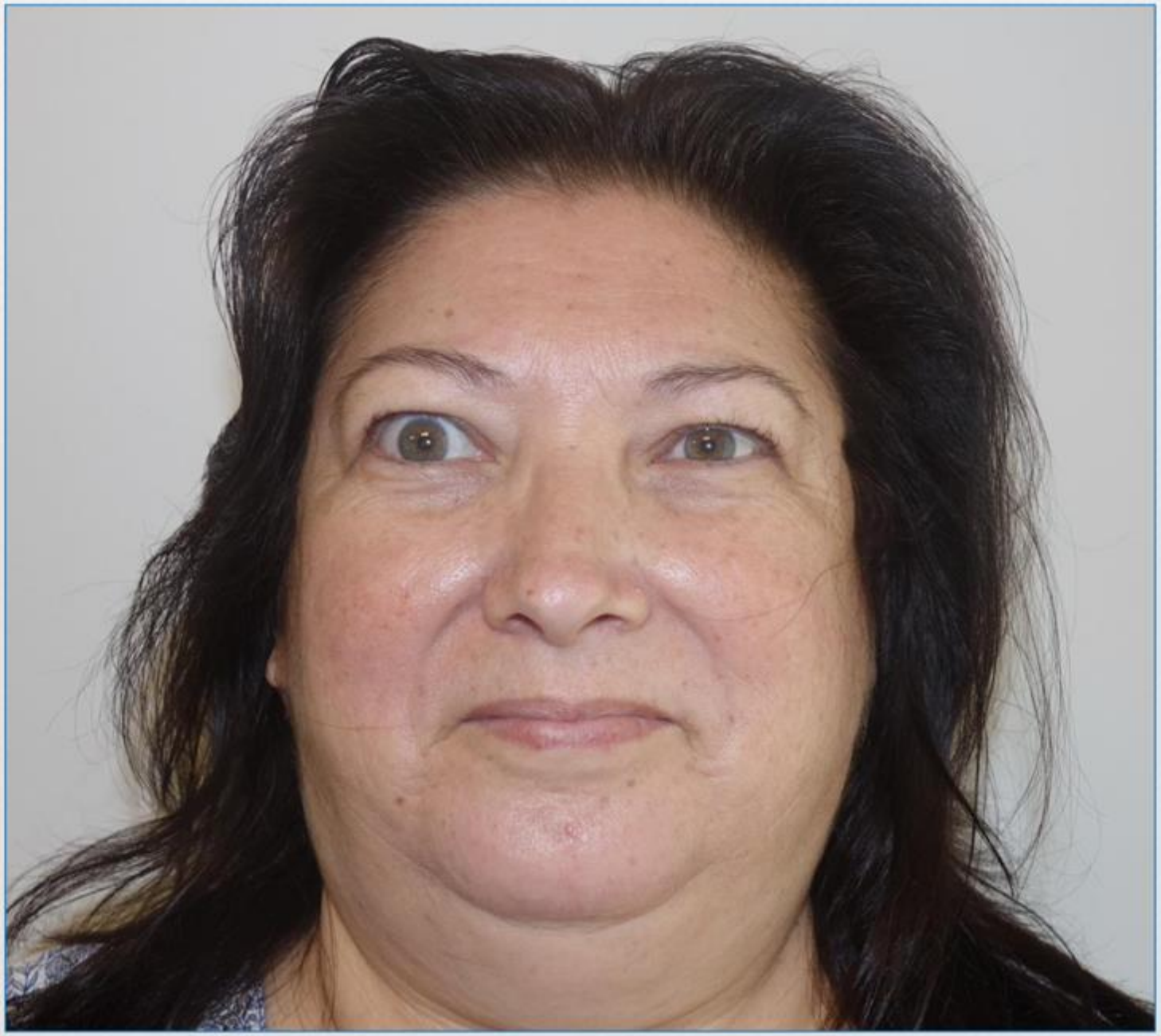
Week 15

CAS 1/7 OD 0/7 OS

Hertel 21.5/18 mm

No motility deficit

Image and permission courtesy of Raymond Douglas, MD, PhD.



Week 21

CAS 1/7 OD 0/7 OS

Hertel 19/18 mm

No motility deficit

Image and permission courtesy of Raymond Douglas, MD, PhD.

Case 2: 53-year-old Woman
Clinical Course Summary

- The patient improved dramatically following teprotumumab
- CAS and proptosis improved; diplopia resolved
- Drug was well tolerated; no side effects were noted
- Clinical euthyroid state maintained on methimazole
- Upcoming decisions concerning definitive thyroid therapy
  - To be made by patient, endocrinologist, and ophthalmologist
  - Given severe TED, will probably avoid RAI
  - Could elect surgical thyroidectomy or remain on methimazole

Summary of Cases

- These 2 cases demonstrate the wide spectrum of disease
- 50% to 60% of TED cases remain mild and self-limited
- Patients with mild, well-tolerated disease can be managed successfully with periodic monitoring and local measures
- Moderate to severe TED may require more aggressive treatment
- Patient 2 was successfully treated with teprotumumab after failure of high-dosage intravenous steroids

Thank you for joining us!