

Thyroid Eye Disease

Erik M. Happ, MD
Chair, Department of Ophthalmology
Allegheny General Hospital
Pittsburgh, PA

Disclosure

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Thyroid Eye Disease (TED)

- AKA....
 - Dysthyroid Orbitopathy (DO), Thyroid Associated Ophthalmopathy (TAO), Graves Ophthalmopathy (GO)...All the same
- Highest association with Graves Disease
 - 25-50% Patients with Graves develop TED
 - Hypothyroidism, Hashimoto's thyroiditis, Euthyroidism
 - 50% of Euthyroid patients will develop Graves in 5 years

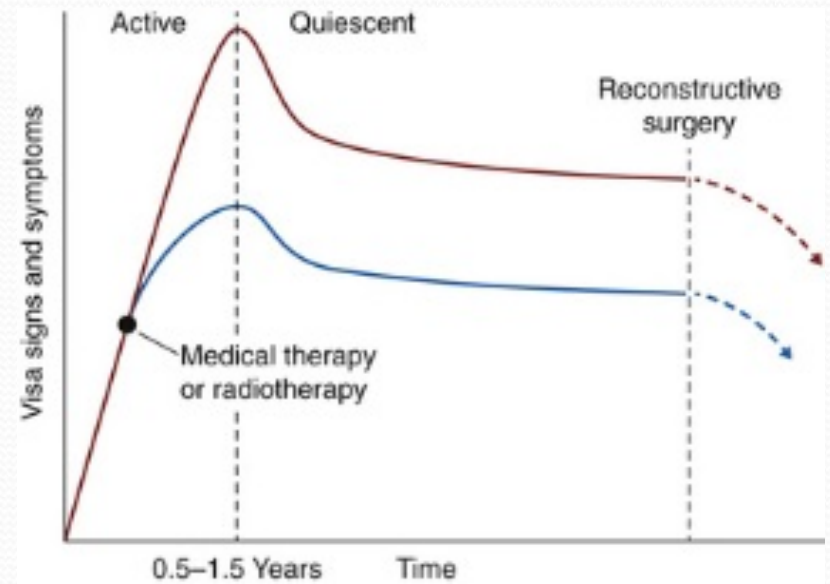
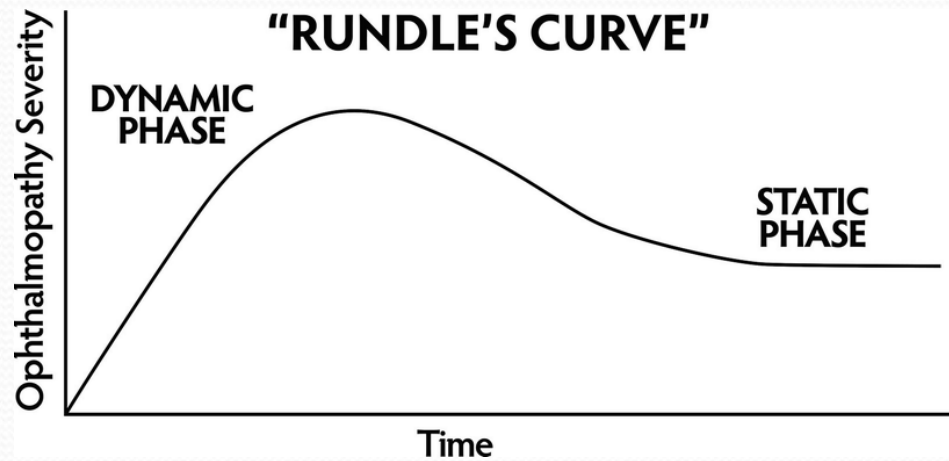
Facts about TED

- Underlying “cross link”
 - TSH like receptor on fibroblasts, adipose cells
 - IGF-1R (more later)
- Orbital disease course runs independent of thyroid status (vice versa)
- Women 6x more common than men
- Cigarette smoking increases risk and worsens disease course

Phases of TED

- Active phase
 - 6 mos to 5 years
 - 18-24 month average
 - Temporizing treatments
- Plateau, Fibrotic or Chronic phase
 - Typically Lifelong
 - Reconstructive surgery planning phase
- Recurrence is rare
 - <5%
 - Changes in thyroid status, other orbital disease
 - RAI

Rundle's Curve

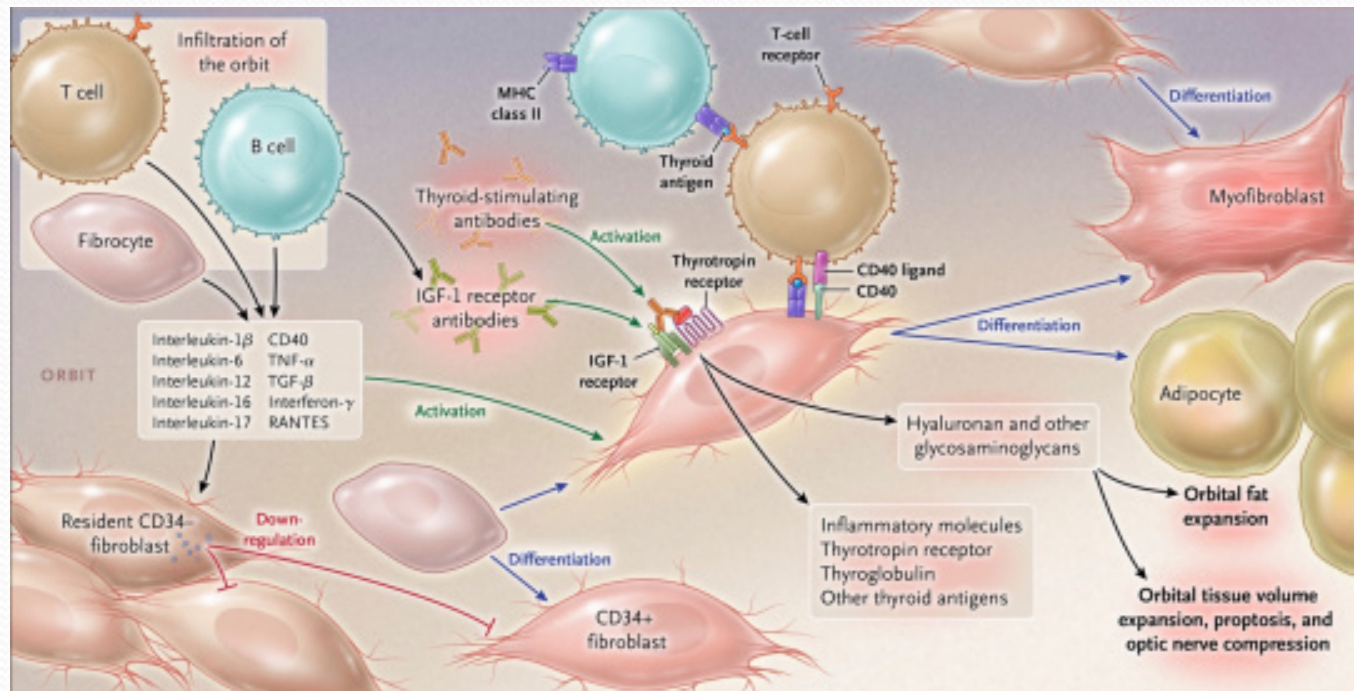


Diagnosing TED



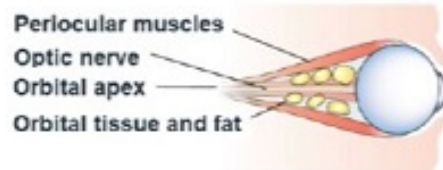
- Signs
 - *Eyelid retraction, Lid lag, chemosis, injection over muscle insertions, periorbital edema / fat pads, superior limbic keratoconjunctivitis, proptosis, restrictive myopathy, exposure keratitis, optic neuropathy
- Symptoms
 - Ocular irritation (no contact lenses), diplopia, pain, decreased vision, early morning swelling
- Patients often initially misdiagnosed
 - Dry Eye, conjunctivitis, NSOI

Pathophysiology of TED

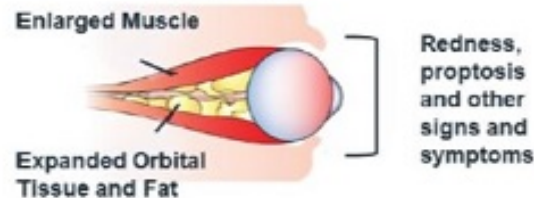


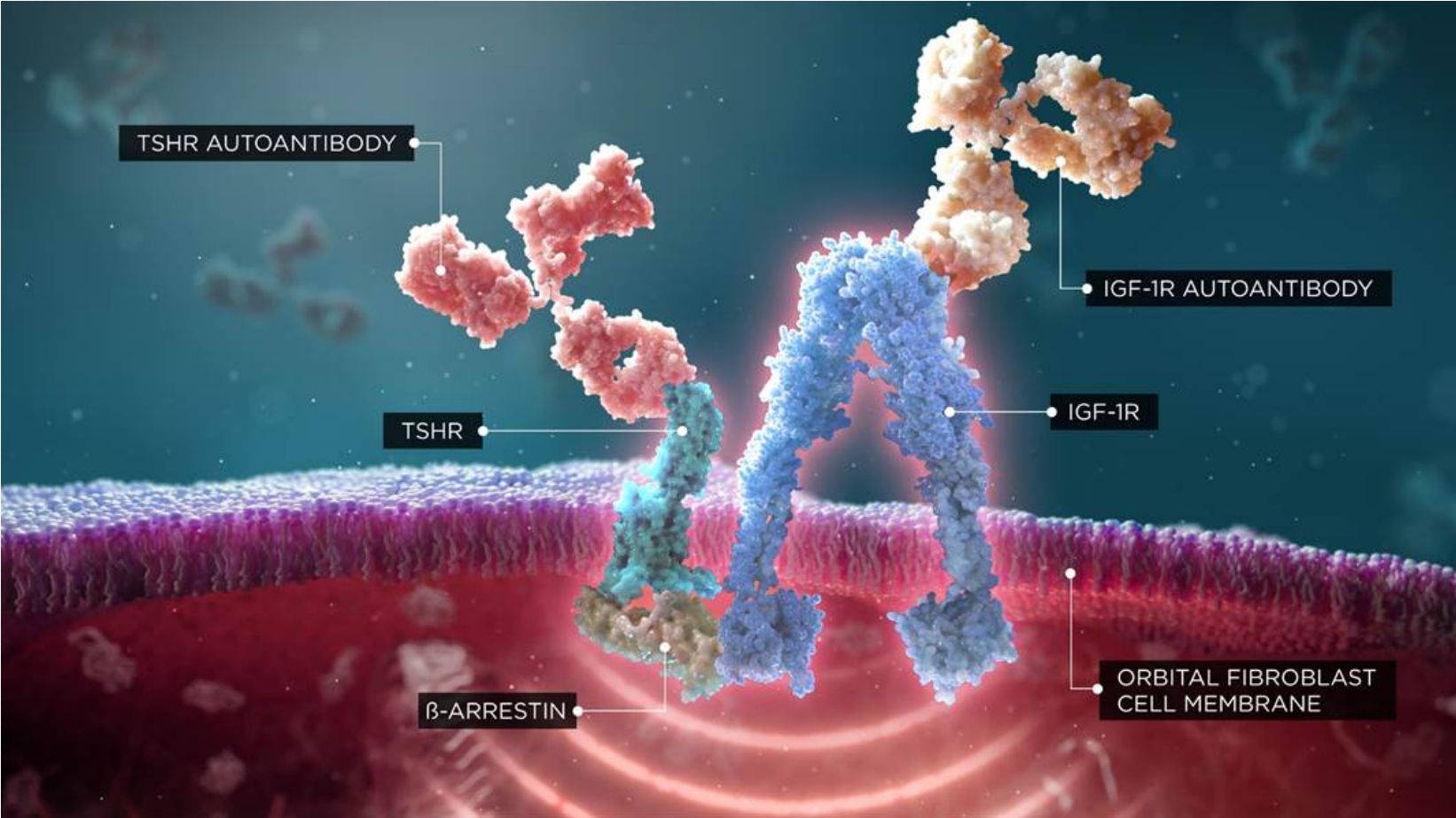
Pathology of Thyroid Eye Disease Occurs in Tissues Behind the Eye

Healthy Eye and Orbital Tissue



Thyroid Eye Disease





Work up

- Full eye exam
 - Acuity, pupils, pressures, exophthalmometry, eye movements / alignment
- Visual Fields
 - Looking for optic neuropathy
- Orbital ultrasound
 - Isolate MR and IR
- CT Scan (non contrast axial / coronal)
 - Looking at Apex / surgical planning
 - Confirm myopathy
- TSH / T4 – Possible Endocrinology consult

WILSON JANICE F
51Y9M,F,001831459
2-35
-482.5 mm
Acc# 5290158
Patient Pos: HFS

Lossy

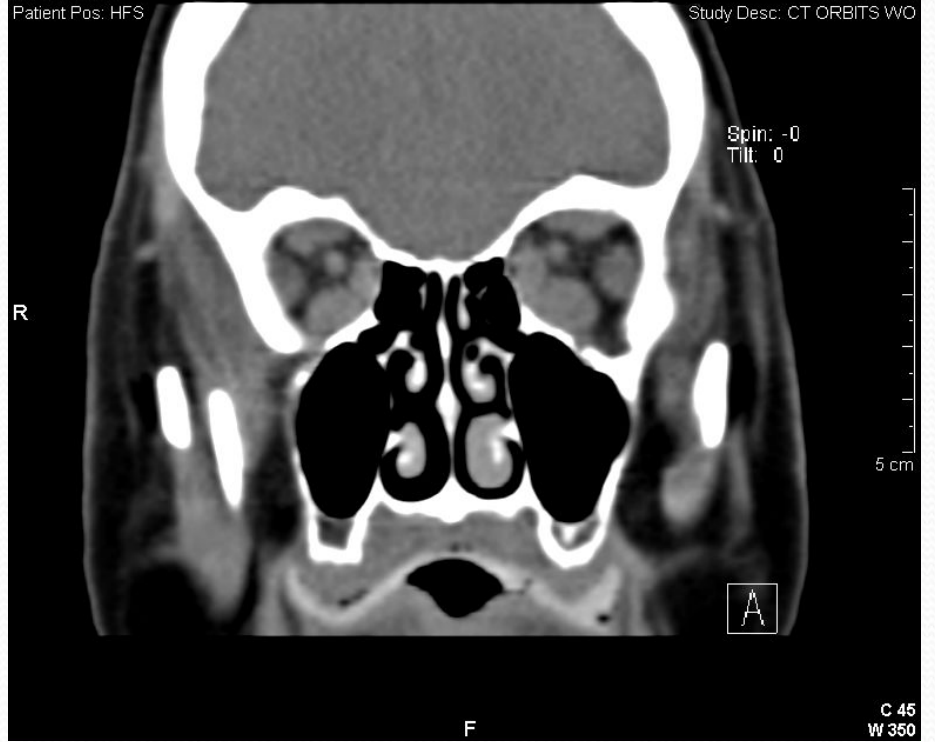
Allegheny General CT 4
SIEMENS Volume Zoom
Sep 21, 2007 3:32:31 PM
120kV, 150mAs
SW 3.0 mm
Study Desc: CT ORBITS WO



WILSON JANICE F
51Y9M,F,001831459
602-21
1 mm
Acc# 5290158
Patient Pos: HFS

Lossy

Allegheny General Hospital
Siemens Somaris/5 3D Postprocessing
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Study Desc: CT ORBITS WO



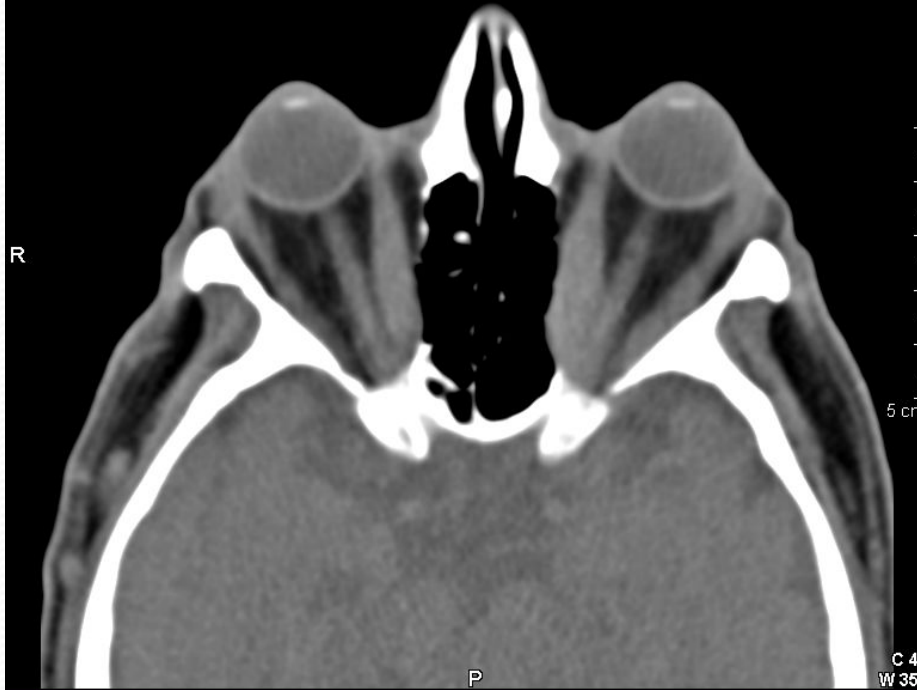
Myopathy

- “I’M SLOW” (IMSL)
 - IR, MR, SR
 - Less common LR/obliques
- Spares tendons
 - Distinguishes from myositis (NSOI)
- *Irreversible (in either phase)
- Restriction opposite to duction
 - Upgaze typically worst
 - Hypotropia most common

DETWILER ALLEN E
68Y3M,M,001708356
2-34
412.5 mm
Acc# 5328865
Patient Pos: HFS

Lossy

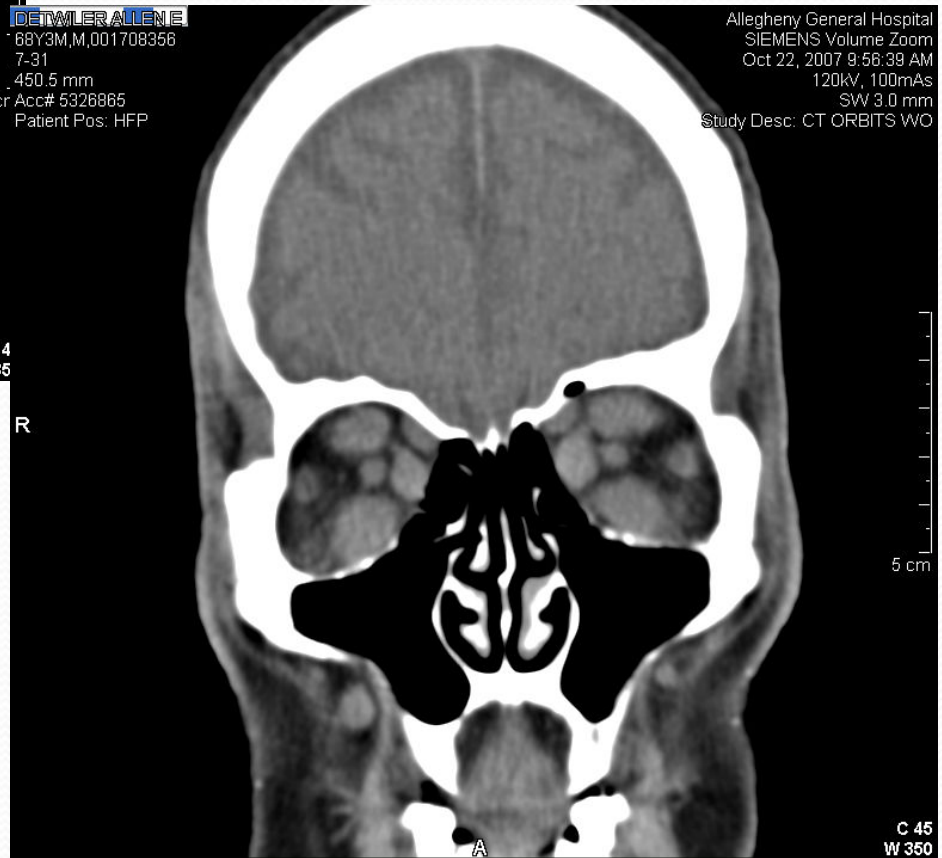
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Study Desc: CT ORBITS WO



C 4
W 35

DETWILER ALLEN E
68Y3M,M,001708356
7-31
450.5 mm
5 cr Acc# 5328865
Patient Pos: HFP

Allegheny General Hospital
SIEMENS Volume Zoom
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Study Desc: CT ORBITS WO

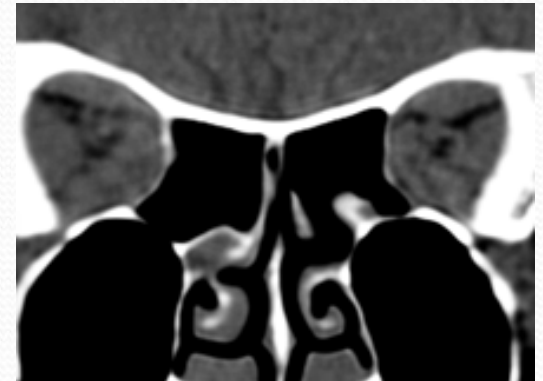


5 cm

C 45
W 350

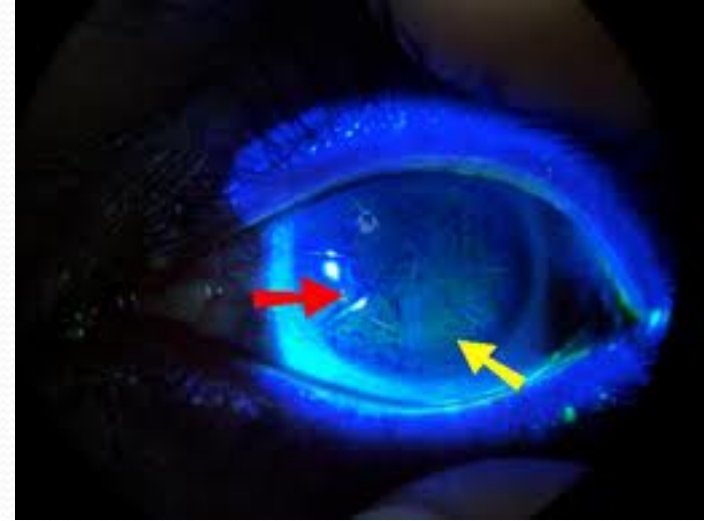
Optic Neuropathy

- Caused by compression at orbital apex
 - Less than 6% of all patients
- Can be insidious or acute
- Vision loss can be profound
- Typically reversible if relieved
 - Steroids, Radiation
- Urgent but not Emergent
 - Surgery last resort if still active



Exposure Keratopathy

- Combination of proptosis and lid retraction + dry eye
 - Lagophthalmos
- Can result in corneal abrasions, ulcers and scarring
- Must correct exophthalmos and lids before corneal surgery (transplant / PTK)
- May need tarsorrhaphy as temporizing measure



Older Management - Active Phase

- BUY TIME!
- Artificial Tears, gels, ointments
- HOB elevated
- Stop smoking!!!
- Steroids
 - Oral – slow taper
 - IV – Weekly infusions
 - Periorbital injections
- External Beam Radiation
 - Sub threshold dose (2000 Rads)

Oral Steroids

- Gold Standard for many years
- 60-100mg / day
- Taper over 6-8 weeks
- Good response
- High side effect profile
 - Weight gain – Cushings
 - Diabetes exacerbation
 - IOP / Cataract formation
 - GI stress

Orbital Steroids

- 40mg Retrobulbar Triamcinolone
- Very well tolerated
- Can be repeated
- Much lower side effect profile than PO
 - IOP / Cataract / Retrobulbar heme / Globe injury
- Effect typically lasts 2-3 months
- May be slightly less effective than orals or IV's

IV Steroids

- 250-1000mg IV Solumedrol / week
- 3-12 weeks
- Better tolerance than PO regimen
- Requires IV infusion
 - ER / Inpatient / Home healthcare / Infusion ctr.
- Urgent regimen for optic neuropathy
 - 1gram / day for 3 days

Older Management-Chronic Phase

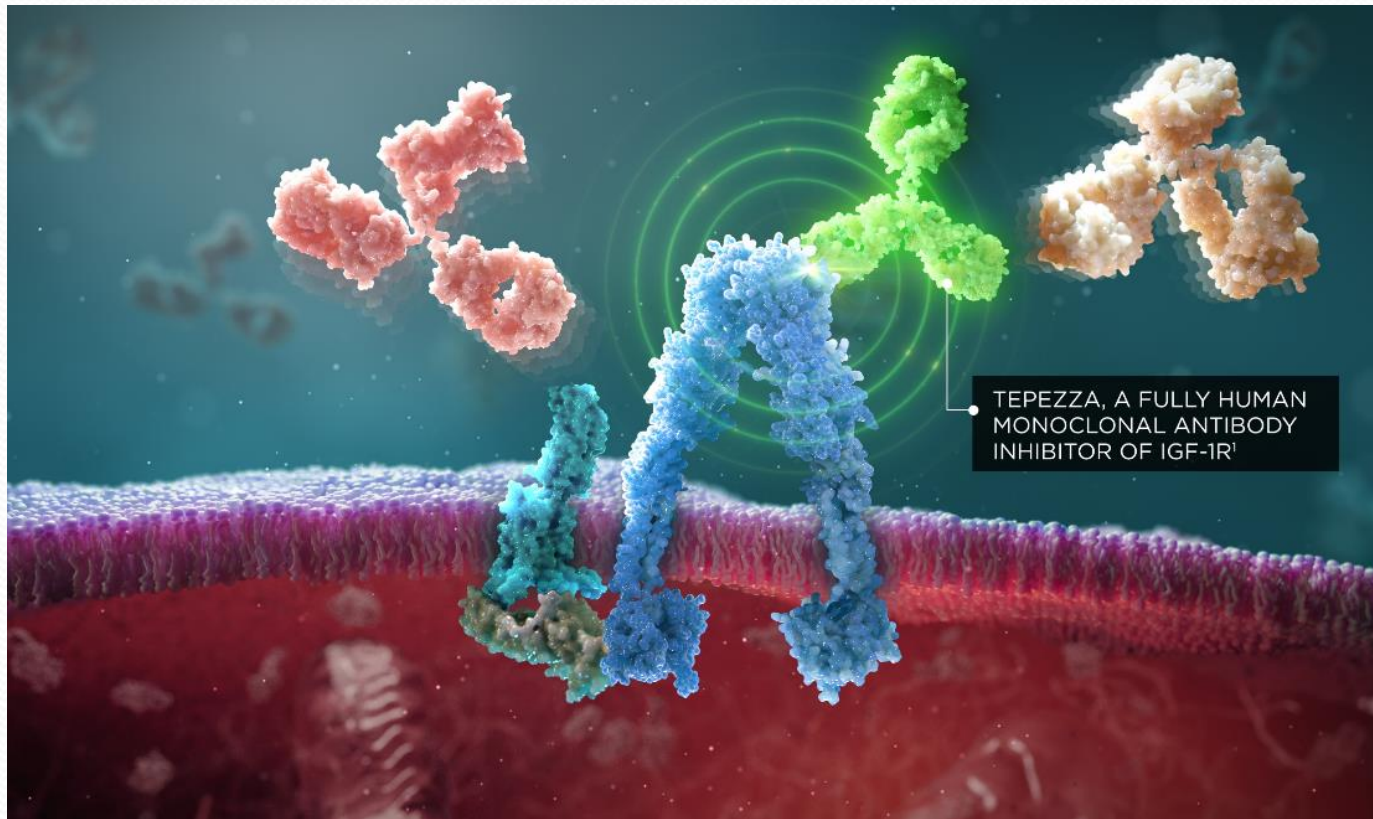
- “Stepping Stone” approach
- Orbital Decompression
 - Can be titrated (1,2,3 walls)
 - +/- Fat decompression
- Eye Muscle Surgery
 - Recessions only
- Eyelid position correction
 - Levator Recession, Spacer Grafts, Ptosis repair
- BONES, MUSCLES, LIDS

- This is where we were until Jan 21, 2020.....

New Treatment...any phase

- Teprotumumab
- Monoclonal antibody inhibitor – IGF-1R
- Targets IGR-1R / TSHR signal complex
- Blocks autoantibodies from attacking orbital cells

Teprotumumab MOA



FDA Trials (Phase II and III)

- Design
 - Teprotumumab (Tepezza) was evaluated in 2 randomized, double-masked, placebo-controlled studies in 171 patients with TED: Study 1 (phase II) and Study 2 (phase III)

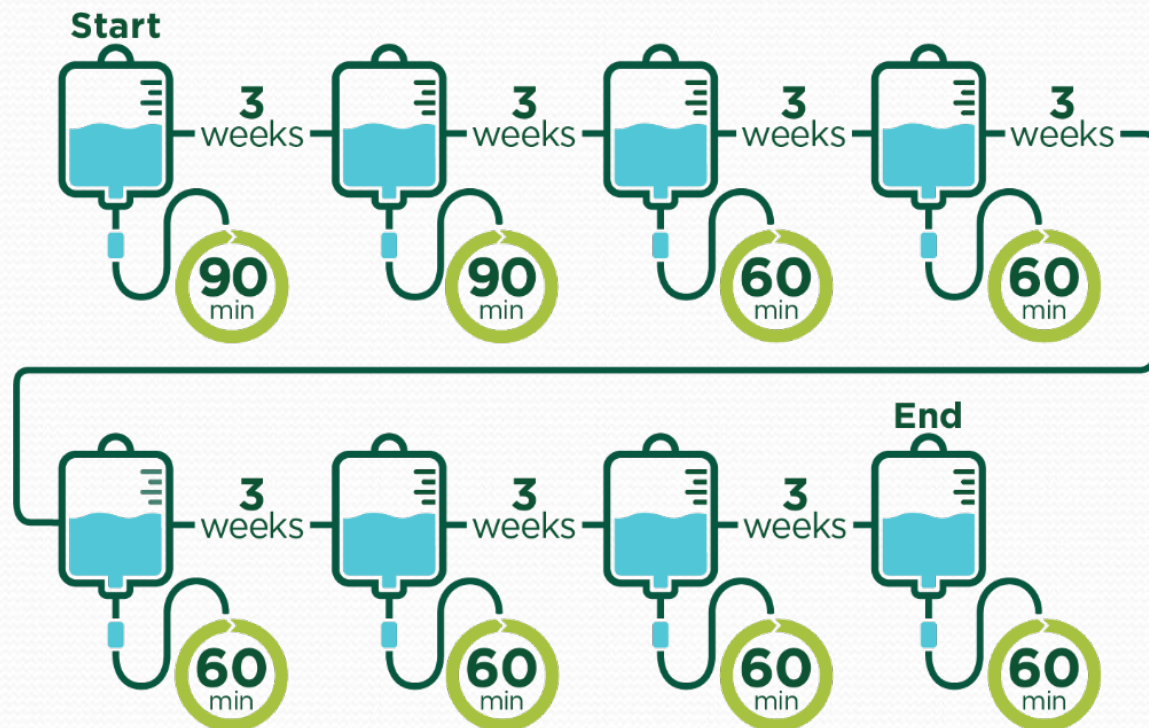


171 Patients With TED
TEPEZZA (n=84) **Placebo (n=87)**

Teprotumumab/placebo infusions

TEPEZZA Infusions: 10 mg/kg for initial dose followed by 20 mg/kg Q3W for 7 additional infusions (total of 8)

Placebo Infusions Q3W (total of 8)

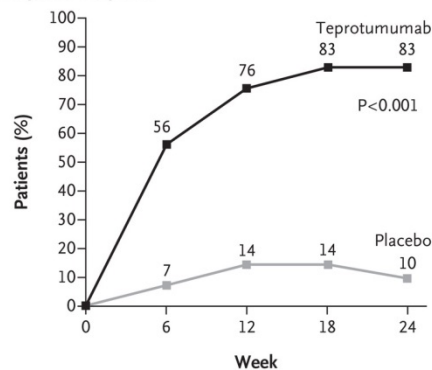


Endpoints

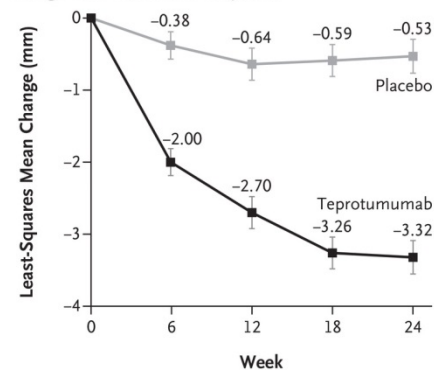
- Primary endpoint
 - Proptosis responder rate (percentage of patients with ≥ 2 -mm reduction in proptosis at Week 24)
- Secondary endpoints and observations
 - Mean change from baseline through Week 24 in proptosis measurement in study eye
 - Diplopia responder rate (combined across Study 1 and Study 2) at Week 24
 - Signs and symptoms of Thyroid Eye Disease, including pain, gaze evoked orbital pain, swelling, eyelid erythema, redness, chemosis, inflammation, clinical activity score
 - Assessments of functional vision and patient appearance

Results

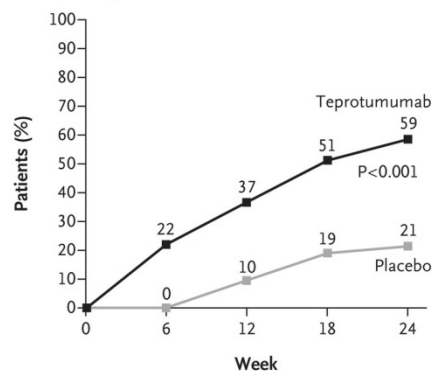
A Proptosis Response



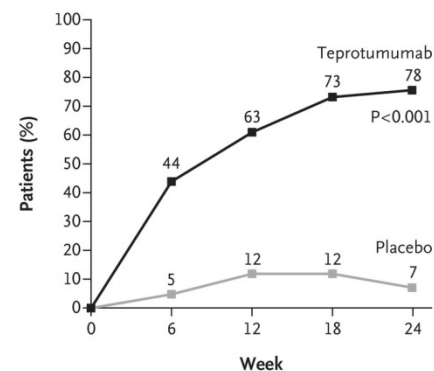
B Change from Baseline in Proptosis



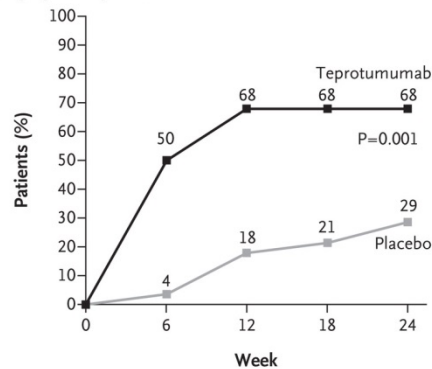
C Clinical Activity Score of 0 or 1



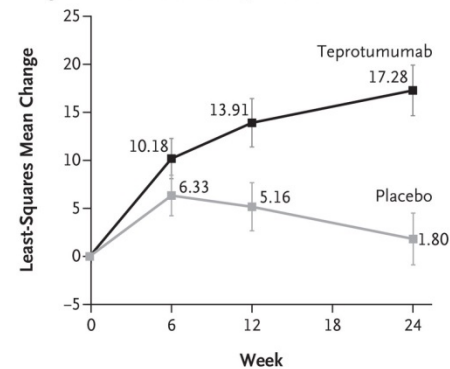
D Overall Response



E Diplopia Response



F Change from Baseline in GO-QOL Overall Score



FDA Approval

- Fast tracked (orphan drug / rare disease)
- Released 2 months ahead of schedule
- Label does not restrict to any phase of TED
- Trial inclusion / exclusion criteria no included on label

Safety profile

- Infusion reactions < 4%
- Most common side effect – leg cramps (25%)
 - Hydration, Epsom salt bath, magnesium
- Common side effects– nausea (17%), mild hair thinning/loss (13%), fatigue or diarrhea (12%), hyperglycemia (10%), hearing changes (10%), dysgeusia, headache or dry skin (8%)
- Low dropout rate

Warnings and Cautions

- Hyperglycemia
 - Monitor blood glucose or HgA1C
- Inflammatory Bowel Disease
 - May exacerbate UC or Chron's
- Contraindicated if pregnancy
 - Pregnancy test for all childbearing age women
 - Consider contraception during treatment

Clinical case

- Patient with Graves x 20 years
- TED for 6 years
- Steroids
- Orbital decompression

- Was scheduled for second decompression when Teprotumumab approved
- Started on Tepezza Feb 10, 2020 (19 days after FDA approval)

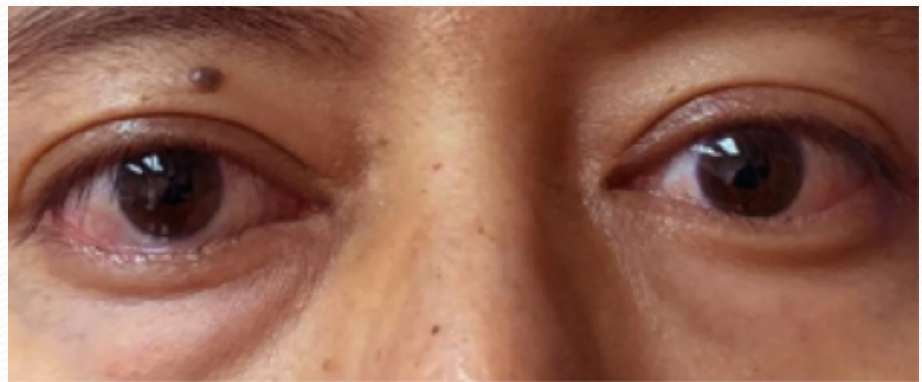
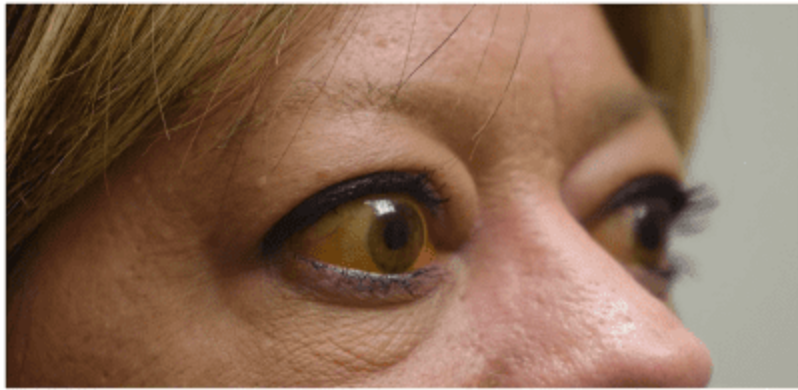
BEFORE TEPEZZA TREATMENT



AFTER 8 INFUSIONS

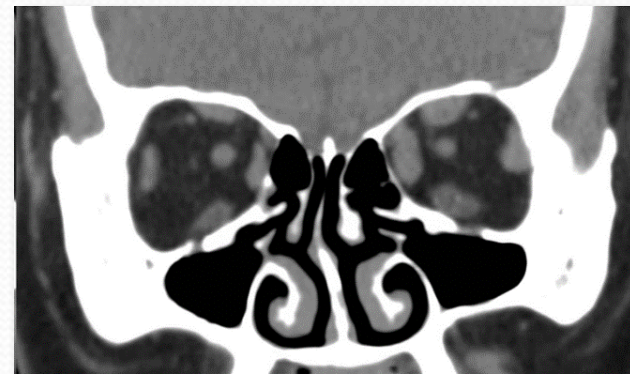
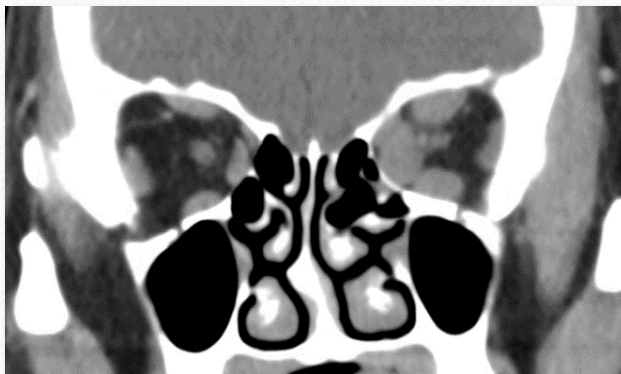
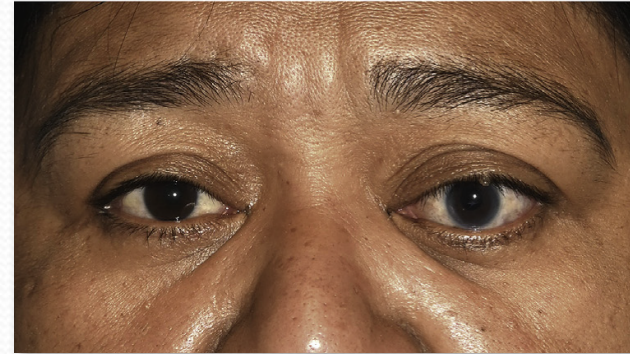
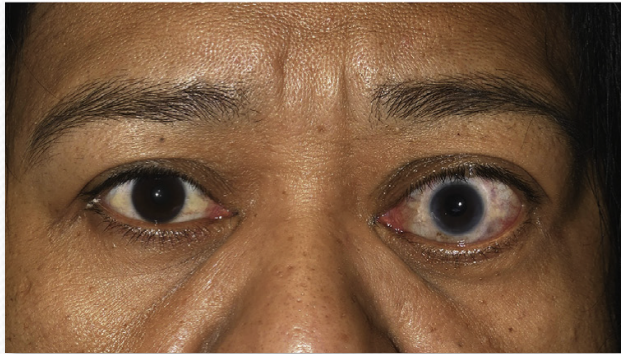


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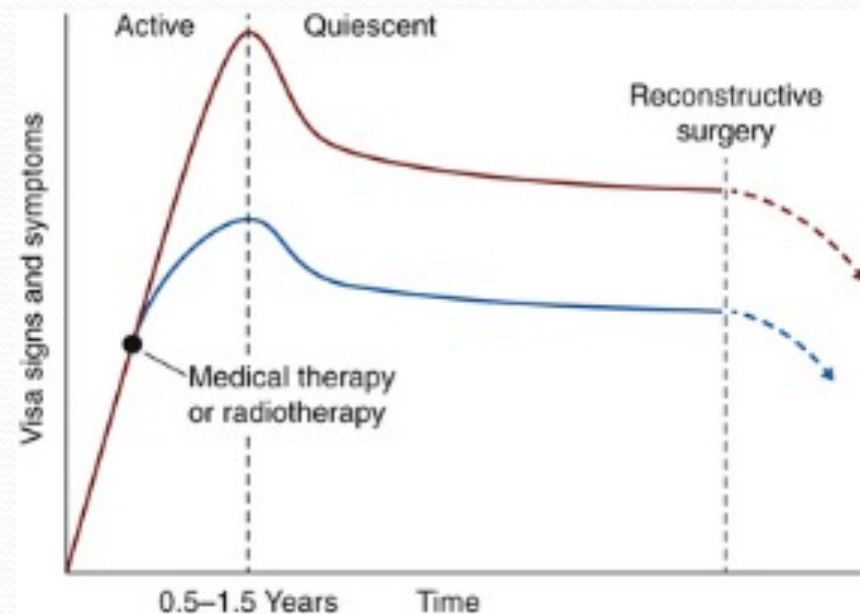
Pretreatment

After 3 infusions



What we are seeing

- Teprotumumab is effective in both active and chronic phases of TED
- Ideal to treat during active phase
 - (FDA study confined to narrow part of curve (3-9mos))
- During chronic phase still seeing orbital remodeling
- Ongoing studies to determine durability and possible stratification of dosing to severity of disease



TED then vs. now

- Thyroid eye disease remains a progressive disfiguring and debilitating orbital disease
- Prior treatments (steroids, radiation, surgery) were often unsatisfactory leaving patients functionally impaired
- Teprotumumab (Tepezza) is the first and only FDA approved drug to treat TED
- Clinical trials, follow on studies and clinical observations are showing teprotumumab as a potential paradigm shift in the management of TED

Questions?

- Erik M. Happ, MD
- dochapp@msn.com
- 412-359-6300 (o)
- 412-992-6288 (c)

- Thank you