Thyroid Eye Disease
An individualized approach

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- Vertical Pharmaceuticals – consultant
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What scares ophthalmologists?

• Optic Neuropathy
• Acute Proptosis
• Diplopia
Take a deep cleansing breath...
Preview

- TED Overview
- Management strategy
- Can lab testing including TSI be helpful?
- New therapeutic options
- What’s new in orbital decompression?
Who is out there today?

• 1. Ophthalmologist
• 2. Oculoplastic Surgeon
• 3. Pediatric Ophthalmologist
• 4. Ophthalmology Resident or Fellow
33 yo derm with proptosis OD
6 mos later
6 mos later

• Pregnant
• Wants to wait to have surgery until after baby is born
Pre and post decompression

What do you mean I have to wait?

Happy!
Patients May Experience Permanent Disfigurement With Thyroid Eye Disease (TED)

- Associated with significant emotional distress, especially when disfiguring signs are predominant
- Increased risk for suicide compared to the general population
- Patients experience POMS depression scores equivalent to cancer

Need for regular, active, psychological assessments and referral for psychological intervention\textsuperscript{11,25}
Thyroid Eye Disease (TED) Has a Significant Impact on Quality of Life

Multiple aspects contribute to impaired QOL, including:

- Vision impairment
- Inability to perform activities of daily living
  - Driving
  - Work
  - Social life
- Psychological consequences
- Anxiety/depression
  - Suicide
Terminology

• Graves’ Disease - Autoimmune thyrotoxicosis
  • diffuse goiter
  • systemic hypertension
  • heart palpitations
  • protrusion of the eyes
  • pretibial dermopathy
  • thyroid acropachy
Terminology

• Graves’ disease
• Endocrine exophthalmos
• Dysthyroid orbitopathy
• Thyroid related immune orbitopathy
• Thyroid Eye Disease (TED)
Relationship to thyroid status
Pathophysiology

- TED - T cells produce Auto Ab target orbital fat and EOM
- Orbital fibroblasts activated producing inflammatory cytokines and hyaluronic acid
- Leads to adipogenesis and swelling and fibrosis of the EOMS
Pathophysiology
Natural history
Demographics

- Most common cause of proptosis (U or B)
- 6-8:1 F:M
- Mean age 43 yrs
- Range 8-88 yrs
Clinical Findings
The most common manifestation of TED?

• 1- Proptosis
• 2- Optic Neuropathy
• 3- Eyelid Retraction
• 4- Strabismus
Eyelid retraction

- Sympathetic stimulation
- Inflammation and fibrosis of levator
- Proptosis
- 90% of TED patients
Eyelid retraction

• MRD 1 > 5mm
• Lid lag
• Lagophthalmos
• Lateral Flare
Ptosis

• Can occur in TED

• BEWARE OF MYASTHENIA!
  • 0.2% of TED pts will have co-existent MG
Eyelid edema

• Worse in the morning
• Can be permanent
Proptosis
60% of TED Patients
Proptosis

• Adults
  • Mean Hertel: 17 mm
  • Upper limit of normal: 22 mm
  • Asymmetry: < 2mm

• Children
  • Mean: 15 mm
  • Upper limit of normal: 19 mm
  • Asymmetry: < 1mm
Proptosis

• Type I TED
  • Predominantly fat hypertrophy
  • Minimal EOM
  • White eye

• Type II TED
  • EOM > fat
  • Red and hot eye
Conjunctiva

• Conjunctival or caruncular injection
• Chemosis
• Dilated veins over the EOM insertions
Cornea

- Exposure keratopathy
Strabismus

• 50% of TED patients
• Myopathy - tethering
  • Inferior
  • Medial
  • Superior
  • Lateral
• Orbital congestion
• Postoperative decompression (5-30%)
Imaging in TED

• CT ORBITS
  • Non-contrast
  • Axial and Coronal

• WHEN?
  1. Diagnosis in doubt
  2. Unilateral proptosis
  3. Compressive optic neuropathy
  4. Preoperative planning
55 y/o with h/o Graves’ disease with right proptosis

Hertel 27-22
55 y/o f w/ right proptosis
s/p drainage of mucocele
s/p bilat lat and r floor decomp
How do we decide what to do?
EUGOGO

• European group on Graves ophthalmopathy
• 9 centers in 6 countries
• Uses CAS, severity score, QOL to determine effects of various treatments on patients with TED
Clinical Activity Score (CAS)

- CAS ≥3/7 = active TED
  1. Spontaneous retrobulbar pain
  2. Pain with eye movement
  3. Redness of the eyelids
  4. Redness of the conjunctiva
  5. Swelling of the eyelids
  6. Inflammation of the caruncle and/or plica
  7. Chemosis

Bartelena 2008, BCSC
European Group on Graves’ Orbitopathy (EUGOGO) Severity Assessment

• **Mild GO**
  - Patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment
  - They usually have one or more of the following:
    - Minor lid retraction (<2 mm)
    - Mild soft-tissue involvement
    - Exophthalmos <3 mm above normal for race and gender
    - No or intermittent diplopia
    - Corneal exposure responsive to lubricants

• **Moderate-severe GO**
  - Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive)
  - They usually have two or more of the following:
    - Eyelid retraction ≥2 mm
    - Moderate or severe soft-tissue involvement
    - Exophthalmos ≥3 mm above normal for race and gender
    - Inconstant or constant diplopia

• **Sight-threatening GO (very severe GO)**
  - Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown
European Group on Graves’ Orbitopathy (EUGOGO) Severity Assessment

- Mild GO
- Moderate-severe GO
- Sight-threatening GO (very severe GO)
The Role of Autoantibodies in TED

• Types of TSH receptor (TSH-R) immunoglobulins
  • 1) Stimulating
    • Thyroid stimulating immunoglobulin (TSI)
  • 2) Blocking
    • Anti TSH-R (TRAb)
    • TSH binding inhibiting immunoglobulins (TBIi)
  • 3) Neutral activity
Do you test for antibodies in your TED patients?

• 1 - Yes
• 2 - No
Thyroid Stimulating Immunoglobulin - TSIg

- Proposed link between GD and TED: TSI
  - TSI stimulates TSH receptor
    - Thyroid gland $\rightarrow$ hyperthyroidism
    - Orbital fibroblast $\rightarrow$ TED

- TSI assessed by cell based bioassay
  - Measures effects on cAMP production

Case 1

- 67 yo WM referred for ‘eyelid evaluation’
- HPI:
  - Feels like eyelids are obstructing peripheral vision
  - Attributed to recent 40 lb weight loss
HPI continued

• Thyroid:
  • Recent diagnosis of hyperthyroidism not on medication
  • Non smoker

• Eyes:
  • Orbital discomfort at rest
  • No orbital pain with eye movements
  • 1 brief episode of double vision (upgaze)
  • No decreased vision
Exam

VA_{cc} \leftrightarrow 20/20
\leftrightarrow 20/20

P:
? Trace RAPD OS

CVF: full

IOP \leftrightarrow 18
\leftrightarrow 18

Motility: full

Color \leftrightarrow 10/10
\leftrightarrow 10/10

Red desaturation \leftrightarrow 100
\leftrightarrow 95
No eyelid edema or discoloration
Bilateral upper eyelid retraction
No lagophthalmos
Trace injection OU
Mild chemosis OU
Mild caruncle inflammation OU
Exophthalmometry 21,19
CAS = 4/7 (pain, injection, chemosis, caruncle inflammation)

TSI = 5.3 (normal <1.3)
Assessment

• Active moderate-severe TED
  • Proptosis
  • Eyelid retraction

• No definite optic neuropathy

• No significant exposure keratopathy
Case 2

- 43 yo WF self referred for second opinion on TED
- Thyroid:
  - Diagnosed with hyperthyroidism in 2010
  - Symptoms of feeling hyper/anxious
  - Treated with PTU for 2 years
- Eyes:
  - Left eye ‘bulging’ since 2012
  - No double vision
  - No orbital pain at rest or with eye movements
Exam

VA_{cc} \leftrightarrow 20/20
  20/20

P:
No RAPD

CVF: full

IOP \leftrightarrow 20
  25

Motility: full

Color \leftrightarrow 10/10
  10/10

Red desaturation \leftrightarrow 100

SLE: unremarkable

DFE: unremarkable
No eyelid edema or discoloration
Left lower eyelid retraction
No lagophthalmos
Trace injection laterally OU
No chemosis
No caruncle inflammation
Exophthalmometry 18,23
CAS = 1/7 (injection)

TSI = <1.0

Prior CT reviewed. No mass. Extraocular muscle enlargement consistent with TED
Assessment

• Inactive moderate-severe TED
  • Proptosis
  • Eyelid retraction

• No optic neuropathy

• No significant exposure keratopathy

• Increased intraocular pressure, left eye
How can we use TSI to complement our clinical assessment?
Research Questions

• How does TSI correlate with disease activity as measured by CAS?

• How do TSI and CAS differ in patients presenting with an optic neuropathy vs. those without an optic neuropathy?

• Do patients with elevated TSI follow a different clinical course with regard to duration of the active inflammatory phase (i.e. a longer Rundle’s curve)?
Research Question #1

• How does TSI correlate with disease activity as measured by CAS?
<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hertel OD</td>
<td>0.32</td>
</tr>
<tr>
<td>Hertel OS</td>
<td>0.53</td>
</tr>
<tr>
<td>Gorman diplopia score</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Brow expansion</strong></td>
<td><strong>0.015</strong></td>
</tr>
<tr>
<td>Esotropia</td>
<td>0.23</td>
</tr>
<tr>
<td>Hypertropia**</td>
<td>0.051</td>
</tr>
<tr>
<td>Upper eyelid retraction</td>
<td>0.078</td>
</tr>
<tr>
<td>Lower eyelid retraction</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>CAS total</strong></td>
<td><strong>0.026</strong></td>
</tr>
<tr>
<td>Eyelid swelling</td>
<td>0.24</td>
</tr>
<tr>
<td>Eyelid erythema</td>
<td>0.12</td>
</tr>
<tr>
<td>Conjunctival redness</td>
<td>0.21</td>
</tr>
<tr>
<td>Chemosis</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Caruncle inflammation</strong></td>
<td><strong>0.040</strong></td>
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<tr>
<td>Spontaneous orbital pain</td>
<td>0.20</td>
</tr>
<tr>
<td>Pain with eye movement</td>
<td>0.80</td>
</tr>
</tbody>
</table>

*Binary variables tested using logistic regression analysis; continuous variables tested using linear regression analysis

**Hypertropia negatively associated with TSI values
Correlation of TSI and Clinical Activity

• TSI correlates with clinical activity as previously reported

• Variability in the manifestation of disease activity as measured by CAS

• Total CAS is useful measure of disease activity

Research Question #2

• How do TSI and CAS differ in patients presenting with an optic neuropathy vs. those without an optic neuropathy?
### Demographic and Clinical Data of 6 Patients Presenting with Thyroid Eye Disease and an Optic Neuropathy

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>1 (16.7)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>5 (83.3)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>African-American</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td><strong>Age (in years, mean, range)</strong></td>
<td>68 (54-89)</td>
</tr>
<tr>
<td><strong>Smoking, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Former</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td>Never</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td><strong>Thyroid function, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td><strong>Treatment of hyperthyroidism, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>No current therapy</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Antithyroid medication</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Radioactive iodine ablation</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (20)</td>
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<tr>
<td><strong>Previous systemic steroids for TED, n (%)</strong></td>
<td>3 (50)</td>
</tr>
<tr>
<td><strong>CAS (mean, range)</strong></td>
<td>2.3 (0-6)</td>
</tr>
<tr>
<td><strong>TSI (mean, range)</strong></td>
<td>5.9 (3.9-7.6)</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Optic neuropathy at presentation</td>
<td>6</td>
</tr>
<tr>
<td>No optic neuropathy at presentation</td>
<td>52</td>
</tr>
</tbody>
</table>

p = 0.02  

p = 0.4
TSI and CAS in Optic Neuropathy

- Patients with an optic neuropathy:
  - May not have significantly active disease as previously reported
  - Tend to have a high TSI

- Absence of TSI/CAS correlation in this subgroup suggests a unique pathophysiology

- Carefully exclude optic neuropathy in a patient without very active disease and with high TSI

Neigel 1988, McKeog 2006
Research Question #3

- Do patients with elevated TSI follow a different clinical course with regard to duration of the active inflammatory phase (i.e. a longer Rundle’s curve)?
TSI and Time to Stability

Days until stable for surgery

Thyroid Stimulating Immunoglobulin (TSI) at initial visit

p = 0.007
TSI Affects Duration of Active Phase

Baseline TSI positively associated with time to stability ($p=0.01$)

Higher TSI
Normal TSI Indicates Disease is no Longer Active

Elevated TSI

Normal TSI

Clinical manifestations

active inflammatory phase

chronic fibrotic phase

Time
Conclusions

• TSI may be used as biomarker of disease activity to aid in decision making and patient counseling

• Optic neuropathy should be carefully excluded in patients with an elevated TSI but without very active disease

• TSI may be used to predict time to surgical clearance
Case 2

Inactive Moderate-severe TED

• Findings:
  • CAS = 1/7
  • TSI = <1.0
  • Exophthalmometry 18,23

• Interpretation of TSI:
  • TSI has high sensitivity for TED in active untreated disease
  • When diagnosis is definitive, normal TSI is suggestive of inactive disease

• Recommendations:
  • Left medial and lateral wall and fat orbital decompression
Management

During the active phase
Management

• Stop smoking
Selenium

• Italian study- Marocci, et al *NEJM* 2011
• 100 mcg bid for 6 months
• Improved QOL
• Improved eye symptoms
• Less progression of disease
• Minimal downside

• Main criticism is that study was performed in selenium deficient area
Anterior segment

• Lubrication
• Punctal plugs
• Taping lids shut at night or

Glad Press’n Seal for the Treatment of Chronic Exposure Keratopathy
Scolfield-Kaplan, Stacy; Dunbar, Kristen; Kazim, Michael
Eyelid edema

• Off label
  • HCTZ 12.5 mg – 25 mg qhs
• Raise the head of bed or sleep sitting up
Strabismus

- Patch
- Gift wrap tape
- Fresnel Prism
Moderate to Severe Disease

- Active inflammatory signs
- CAS > 4
- No optic neuropathy
How do you treat moderate-severe TED?

• 1. Oral Steroids
• 2. IV Steroids
• 3. Other Immunosuppression
• 4. Orbital Radiotherapy
Corticosteroids

IV methylprednisolone is superior to oral prednisone
- Efficacy
- Side effects

Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves’ orbitopathy.

J Clin Endocrinol Metab. 2005 Sep

Improvement: 77% of IV group vs. 51% of oral group

“In patients with active and severe GO, IV glucocorticoids were more effective and better tolerated than oral steroids.”
Corticosteroids

IV methyprednisolone dosing regimens

1. 500 mg qwk x 6 wks then 250 mg qwk x 6 wks (4.5 g total)  
   Kahaly

2. 500 mg qday x 3 days, 4 cycles every 4 weeks (6 g total)  
   van Geest

3. 15 mg/kg x 4 cycles, then 7.5 mg/kg x4 cycles (cycle = infusion on days 1 and 3, then repeat at day 15) (9 to 12 g total)  
   Marcocci
Corticosteroids

IV methyprednisolone dosing regimens

1. 500 mg qwk x 6 wks then 250 mg qwk x 6 wks (4.5 g total)

Kahaly
Immunotherapy in TED

Clinical manifestations

Time

Active inflammatory phase

Chronic fibrotic phase

Treatment most effective

Treatment less effective

Treatment minimally effective

Treatment not effective
Case 1

6 weeks (6 infusions)

‘Pressure is off’

Improved eyelid retraction

Proptosis reduction

Caruncle edema improved

+Chemosis

No RAPD

No red desat

Full HVF

CAS = 4/7  TSI = 5.3

CAS = 1/7  TSI = 3.8
Radioactive Iodine

- Mild to Moderate TED – pretreat with prednisone 0.5mg/kg/day starting 1 week before treatment and taper over 3 months
- Very Mild TED – 0.3mg/kg/day
- No TED – No Pred
Radiation for TED

- 1500-2000 cGy/ orbit
- Equally effective to prednisone (in the inflammatory stage)
- Effect takes 4-6 weeks
- Risk of radiation retinopathy
  - increased in diabetics
Controversy

• Ophthalmology, Sept 2001
  • Prospective, randomized, internally controlled, double blind trial at Mayo Clinic
  • 2000 cGy to one orbit, sham tx to other; switch at 6 mos.
  • Multiple measurements at 3 mos intervals

• No clinical or statistical difference 6 mos
• Decreased proptosis and muscle volume in first tx orbit at 12 mos
Controversy

• Did not include optic neuropathy
• Eye symptom to study enrollment was \(0.2-16\) years
• Less than 1.3 years in 19 patients (n=42)
• May have missed Rundle’s curve
Radiation for TED

- Active disease CAS >4
- Responds to steroids, but recurs on taper
- Compressive neuropathy s/p decompression with continued vision loss
- Unable to tolerate or refuses surgery
- >50 y/o (relative)

- Contraindications (relative)
  - Diabetic
  - Younger patients
New biologics

- Rituximab – monoclonal antibody against CD20 (B cells)
- Tocilizumab – IL-6 receptor antibody
- Teprotumumab – IGF-1 receptor antibody
Antigen specific therapy blocking Insulin-like Growth Factor-1 Receptor (IGF-1R)
Insulin-like Growth Factor-1 Receptor

- Overexpressed on Graves' Disease (GD) fibroblasts
- Signaling of fibroblasts and immune cells mimics pathologic findings
- Antibodies to these receptors in GD patients
IGF-1R overexpression is a hallmark of GD

IGF-1R⁺ T cells are more frequent in Graves disease but not all autoimmune diseases.
TSH-R and IGF-1R interact

J Immunology, 2008
Thyroid Eye Disease: Mechanism

- GD-IgG
- Cytokines (e.g. IL-16, RANTES)
- T-Cell / Monocyte Infiltration
- Inflammation
- GO Orbital Fibroblast
- Tissue Edema
- Proliferation
- Adipogenesis
- Hyaluronan
Thyroid Eye Disease (TED) Is Driven by Autoantibody Activation of IGF-1R

- IGF-1R is overexpressed in TED orbital fibroblasts\textsuperscript{12}
- Activation of IGF-1R stimulates release of inflammatory cytokines and production of hyaluronan\textsuperscript{13,14}
- IGF-1R and TSHR colocalize in orbital fibroblasts\textsuperscript{12}

CD, cluster of differentiation; IGF-1R, insulin-like growth factor-1 receptor; MHC, major histocompatibility complex; TSHR, thyroid-stimulating hormone receptor.
Teprotumumab

- Fully human monoclonal antibody inhibitor of IGF-1R
- Targeted binding to 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
Thyroid Eye Disease: Disease Time Course

Disease Activity

1.5 → 2 years
3 → 6 years

Untreated

Teprotumumab

Smith & Douglas (2011)

Efficacious therapy
“In conclusion, a 24-week course of teprotumumab therapy provided clinical benefit in patients with active, moderate-to-severe thyroid-associated ophthalmopathy by reducing proptosis and the Clinical Activity Score and by improving the patients’ quality of life.” (1)
Phase 3  24-week randomized, double-masked, placebo-controlled treatment trial of Teprotumumab

Active TED
- 18 to 80 years
- < 9 mo. since active TED onset with no prior treatment
- CAS ≥ 4
- FT4 and FT3 <50% above or below normal limits

Primary Endpoint:
≥2 mm improvement in proptosis at Week 24
Subject Disposition

83 underwent randomization
83 received study drug (ITT population)

42 randomized to received placebo
- 2 subjects discontinued early
  - Adverse event (1; “visual field defect”)
  - Withdrew consent (1)

41 randomized to receive teprotumumab
- 2 subjects discontinued early
  - Adverse event (1; “infusion reaction”)
  - Withdrew consent (1)

40 completed double-masked treatment period
39 completed double-masked treatment period
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≤0.001):
- 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 one 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
Pre treatment

Week 24 control
Teprotumumab

Pre treatment

Week 24
Teprotumumab

Week 0

Week 24
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

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

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<0.001)
Proptosis Reductions

Average Change From Baseline in Proptosis to Week 24, Study 2

Baseline score, tobacco use status (non-user, user), treatment group, visit, and visit-by-treatment and visit-by-baseline score interactions; least square mean ± standard error.
Overall Responders:
Reduction of ≥2 mm proptosis + ≥2 points CAS improvement in the study eye without deterioration in the fellow eye (i.e. increase in CAS or proptosis ≥2)

![Graph showing overall response]
Phase 2  Teprotumumab – effective regardless of baseline proptosis

Mean Reduction = 3.7
Mean Reduction = 2.6

Reduction from Baseline at Week 24 (mm)

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

Pre-treatment

- Inflammation/edema of the inferior rectus muscle (thin white arrow) and orbital fat (thick white arrow)
- Enlargement of inferior rectus muscle

Post-treatment

- Resolved inflammation/edema of the inferior rectus muscle and orbital fat
- Reduction of the inferior rectus muscle by 49% and medial rectus muscle by 41%
Diplopia Responders:
≥1 Grade Improvement in those with Baseline Diplopia

Diplopia Score

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

Diplopia Responder Rate, Study 1 and Study 2

<table>
<thead>
<tr>
<th></th>
<th>Week 24</th>
<th>Complete resolution of diplopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 grade improvement in diplopia</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Complete resolution of diplopia</td>
<td>70</td>
<td>53</td>
</tr>
</tbody>
</table>

Vertical (Value) Axis

P<0.001

P<0.01
GO-QOL Improvements - Overall

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\(^1\)

The effects of Teprotumumab appear to be durable 51 weeks post last infusion.

53% of proptosis responders (at Week 24) maintained a response 51 weeks after their last TEPEZZA infusion.

67% of diplopia responders (at Week 24) maintained a response 51 weeks after their last TEPEZZA infusion.
Before and After treatment in the clinical trials
### Safety Overview

89% of Teprotumumab and 93% of placebo patients completed all 8 infusions.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>TEPEZZA* (n=84), n (%)</th>
<th>Placebo (n=86), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle spasms</td>
<td>21 (25%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (17%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11 (13%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (12%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Fatigue†</td>
<td>10 (12%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Hyperglycemia‡</td>
<td>8 (10%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hearing impairment§</td>
<td>8 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>7 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (8%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>7 (8%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Optic neuropathy

• 5% of patients with TED
• Unilateral in 20% at presentation
• More common among smokers
• 50% normal, 25% swollen, 25% pale
• Acuity 20/40 or better in 50%
Scenario 1

- Compression of the optic nerve by enlarged...
Scenario 2

- Stretch of the optic nerve by proptosis
Clinical diagnosis

- Visual acuity
- Color vision
- Optic disc
- Visual field
- RAPD
How would you treat a patient with compressive neuropathy?

• 1. Oral Steroids
• 2. IV Steroids
• 3. Orbital Decompression
• 4. Orbital Radiation
Optic neuropathy

- Intravenous solumedrol 1 g/day or oral prednisone 1mg/kg / day
- Urgent orbital decompression
  - Medial wall
62 yo female w/ “red eye”
Management

During the fibrotic phase
Oculoplastic Rehabilitation in Thyroid Eye Disease

• Typically performed after the disease has entered the quiescent phase
• 6 months of stable measurements
• Lack of inflammatory activity
  • CAS < 4
Surgical Rehabilitation in Thyroid Eye Disease

- Orbital Decompression
- Strabismus Repair
- Eyelid Repositioning
- Blepharoplasty ("cosmetic clean up")
Staging of surgery

First decompression,
then bilateral LR recession
Orbital Decompression

• Urgent Indications
  • Compressive optic neuropathy
  • Corneal decompensation and ulceration secondary to massive proptosis

• Non-Urgent Indication
  • Disfiguring proptosis
  • Preop for strabismus
Orbital Decompression

• Risks
  • Blindness
  • Bleeding
  • Numbness
  • Diplopia
  • Pupillary abnormalities
  • Scarring
Orbital Decompression
Traditional Options

- Transconjunctival floor and medial wall
- Limited decompressive effect
- Limited view of the medial wall due to orbital soft tissue
- Leaving bony strut intact decreased postoperative strabismus
Orbital Decompression
Newer Techniques

- Transnasal endoscopic medial wall decompression
- Balanced decompression
- Deep lateral wall removal
- Fat decompression
Endoscopic medial wall decompression

- Similar to functional endoscopic sinus surgery (FESS)
- Typically performed by an ENT surgeon
- Allows excellent visualization to the optic canal/ sphenoid sinus
The Medial Wall
Nasal vs. Orbital Approach
Endoscopic Medial Wall Decompression
Balanced decompression

- By balancing medial and lateral bone removal the muscle cone shifts posteriorly rather than inferiorly with:
  - Less globe ptosis
  - Less diplopia
Deep Lateral Decompression

- Allows more decompressive effect through a single site
- Can also augment or advance the lateral rim to decrease apparent proptosis
- Less diplopia
- Risks = CSF leak
Orbital Fat Decompression

• Removal of fat through blepharoplasty incisions in the superior nasal and inferior temporal quadrants
• Less diplopia
• Excellent adjunct to other procedures
Which Walls to Remove?
What do I do?

• Hertel Exophthalmometry (Normal 15-20mm)

• ≤24 mm - Lateral decompression + fat or fat only decompression

• 24-26 mm – Balanced endoscopic medial and lateral decompression + fat removal

• ≥26 mm – Balanced endoscopic medial and lateral decompression + fat removal and transconjunctival posterior floor decompression
Technique

• Typically ENT performs the endoscopic medial wall decompression first
• The lateral wall decompression is performed through a lateral canthal or bleph incision
• The floor is decompressed through a transconj incision (if necessary)
• The periorbita is opened and fat removed
New technology

- Navigation
- Sonopet
Intraoperative Navigation

- Used in ENT and Neurosurg for many years
- New systems allow greater access and are much more accurate and easier to work with
Navigation
Intraoperative Navigation
What’s the problem with drills?

- Drills can be bulky and in the deep orbit can compromise visualization
- Drill can catch and tear soft tissue and lead to bleeding and bone dust which can obscure visualization
- Heat and vibration generated by high speed drills can lead to optic nerve damage
A better way?

• **Sonopet Omni**
  • Released in **1993**
  • Now distributed by Stryker

• Low ultrasound frequency vibration is transmitted to a cutting tip.

• Irrigation and aspiration occur at the handpiece tip (sound familiar?)
Drill vs Sonopet
Two-wall Decompression
Three-Wall Decompression

Lower Lid Retraction

• Inferior scleral show
• Worse with inferior rectus recession

Treatment
• Release retractors
• Place spacer
• Suspend tendon
Alloderm

• Freeze dried acellular dermal matrix (LifeCell Corp.)
• Use “THICK” Alloderm for eyelid spacer grafts
Lower Eyelid Retraction
Upper lid retraction

- Internal Procedure: Muellerectomy
- External Procedure: Levator Recession
- Full Thickness Blepharotomy
BUL bleph and levator recession and BLL bleph
Lid retraction
Lid retraction after strab
Discussion #1: “We have to wait”

- RHoT 70, ET 35.
- Proptosis R>L
- Marked restriction right eye, trace left
Motility?
What to do? When?

• @ 7 months into disease 8 Units botulinum toxin A to RMR and RIR

• @ 9 months: 10 Units to RMR and RIR

• No response?!
After 1 year of hand holding:

• Lateral orbital decompression
• Right inferior, medial and left superior recti recession on adjustable
• Bilateral upper eyelid and right lower eyelid retraction repair.
We can rebuild her, we have the technology!
Customized approach
Evaluation and Treatment Paradigm at the University of Minnesota Center for TED

- Multidisciplinary evaluation
  - Oculoplastic Surgery
  - Neuro-Ophthalmology
  - Adult Strabismus

- CAS

- TSI

- Oral steroids and urgent (within ~ 2 weeks) endoscopic medial wall decompression for DON

- IV steroid protocol for moderate-severe active disease (Kahaly et al.)

- Rehabilitative surgery offered once clinically stable and inactive for at least 6 months
  - 1) Orbital decompression
  - 2) Strabismus surgery
  - 3) Eyelid retraction repair
Summary

• CAS to determine ACTIVITY
• TSI can help determine course
• IV steroids vs XRT for moderate to severe disease
• Teprotumumab – new treatment option
• Order of surgical restoration – orbital decompression, strabismus surgery, eyelid surgery
• Need serologic and clinical evidence of TED or imaging is indicated
• Radioactive iodine may worsen clinically active TED
• STOP SMOKING
THANK YOU!
Questions?