What’s New in Thyroid Eye Disease?

James A. Garrity MD
Mayo Clinic
Rochester, MN
What’s New in Thyroid Eye Disease?

• **Diagnosis**
  - TRAb/TSI: diagnosis/prognosis
  - IgG4: diagnostic confusion

• **Therapy**
  - Surgery: nothing new
  - Radiation therapy: nothing new
  - Medical therapy: yes
• Thyroid:
  - 1992 (age 18): ?”might be hyper” but never confirmed and never treated
  - TrAb < 1 numerous occasions

• Eyes:
  - 1992: progressive proptosis X 3 yrs
    • Oral steroids with response
    • Steroids 3 times/year
  - 2011: Bilateral 2-wall decompression for proptosis
  - 12-11: recurrent proptosis
Case Report
38 M
12-11

• 20/20 OU

• Lids puffy but no edema or discoloration

• Mild injection, no chemosis, caruncle minimally swollen

• Lid fissures: 12, 10 (?subtle lag RUL)

• Hertel: 36, 32
38 M, IgG4-Related Disease, Pre-Decompression 2-11

Lateral rectus disproportionately enlarged, morphology wrong, big infraorbital nerves
38 M, IgG4 Related Disease
Pre-Muscle Biopsy
12-11

Frontal nerves

Infraorbital nerves
Pathogenesis of TED

- Activated T-cells/Ag (TSHR/IGF-1R)
  - Cytokines
  - Chemokines
- Recruits more cells
- Affect target cells (fibroblasts)
  - Glycoaminoglycans
- Swelling of tissues

Lancet Diabetes Endocrinol 5:134, 2017
Pathogenesis of TED

• **Antigen:**
  - TSH receptor (TSHR)
  - Insulin like growth factor-1 receptor (IGF-1R)
  - Cross talk between TSHR and IGF-1R

• **Target cell:**
  - fibroblast
Therapeutic Targets

• **Lymphocyte**
  - rituximab

• **Cytokines**
  - IL-6
    - tocilizumab
  - TNF-α
    - Etanercept
    - Infliximab
    - Adalimumumab

• **Antigen receptors**
  - IGF-1R
    - teprotumumab
Clinical Activity Score

- Lid edema
- Lid erythema
- Conjunctiva injection
- Conjunctiva chemosis
- Caruncle swelling
- Pain, eye movement
- Pain, at rest
Rituximab

• **Anti-CD20**
  - CD20 on immature/mature B-cells, absent on plasma cells

• **TED: T-cell and B-cell**

• **Mechanism?**
  - ? ↓ stimulatory antibodies?
    • Probably not
  - ? antigen presentation?
    • Probably
  - ? ↓ cytokine production?
    • Probably

• **Anecdotal success**
Rituximab for TED
2 Randomized Trials

**US Trial**
- N=13
- Placebo
- 1000 mg X 2
- <CAS by 2
  - 24 weeks
- No

**Italian Trial**
- N=15
- IVMP (7.5 gm)
- 1000 mg X 2
  - Or 500 mg X 1
- <CAS by 2
  - Or CAS =3
- Yes

*JCEM 100: 432, 2015*
*JCEM 100:422, 2015*
Rituximab for TED
2 Randomized Trials (24 Weeks)

**US Trial**
- Placebo (n = 12)
  - CAS: 5.3 to 3.8
  - Proptosis: no change
  - TRAb: 19.5 to 16.3
- RTX (n = 13)
  - CAS: 4.9 to 3.7
  - Proptosis: 17.3 to 17.3
  - TRAb: 20.0 to 14.7
- DON X 2

**Italian Trial**
- IVMP (n = 16)
  - CAS: 4.7 to 2.3*
  - Proptosis: no change
  - TRAb: 18.1 to 17.5*
  - 5 relapse
- RTX (n = 15)
  - CAS: 4.4 to 0.6*
  - Proptosis: no change
  - TRAb: 10.7 to 4.0*
  - 0 relapse

* Statistically significant
### Rituximab for TED
2 Randomized Trials: Why the Difference?

**Table 2** Population differences between the two RCTs.

<table>
<thead>
<tr>
<th></th>
<th>Italian study (n=15)</th>
<th>US study (n=13)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>51.9</td>
<td>57.6</td>
<td>Possibly different</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>93</td>
<td>69</td>
<td>Possibly different</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>66.7</td>
<td>15.4</td>
<td>Likely to be different</td>
</tr>
<tr>
<td>GO duration (months)</td>
<td>Mean: 4.5 ± 2.9</td>
<td>Mean: 30 ± 47.6</td>
<td>Likely to be different</td>
</tr>
<tr>
<td>CAS baseline</td>
<td>Mean: 4.4/10 ± 0.7</td>
<td>Mean: 4.9/7 ± 1.0</td>
<td>Likely to be same</td>
</tr>
<tr>
<td>CAS ≥4/CAS ≥6</td>
<td>14/15 and 2/15</td>
<td>13/13 and 3/13</td>
<td>Likely to be same</td>
</tr>
<tr>
<td>GO severity</td>
<td>Moderate-to-severe</td>
<td>Moderate-to-severe ± progressive</td>
<td>Likely to be same</td>
</tr>
<tr>
<td>Previous steroid therapy</td>
<td>3/15 (20%) (≥12 weeks prior)</td>
<td>4/13 (31%) (≥8 weeks prior)</td>
<td>Likely to be same</td>
</tr>
<tr>
<td>TRAb (IU/L)</td>
<td>Mean: 10.7 ± 9.1</td>
<td>Mean: 28.1 ± 23.4</td>
<td>Likely to be different</td>
</tr>
<tr>
<td>TRAB &gt;20</td>
<td>4/15</td>
<td>Median: 20 (9–60)</td>
<td>Likely to be same</td>
</tr>
</tbody>
</table>

**Eur J Endocrinol 176:R101-R109, 2017**
Rituximab for TED

Conclusions

• Jury still out
Cytokines for TED
TNF Inhibitors

• 3 drugs:
  - Adalimumab
  - Etanercept
  - Infliximab

• All retrospective case series

• No controls

• Measurements at 3 months
Anti-TNF for TED
Adalimumab

• N = 10
• Every other week
• Inflammatory signs, all 10
  - 6/10 better
  - 3 worse
  - 1 same
• Concomitant steroids 8/10 (IVMP)
• “No change, although 5 highest had significant improvement

Anti-TNF for TED

Infliximab

• Single case report
• 40 mg prednisone
• CAS = 7 (+ 3: ↑proptosis, ↓ EOM, ↓ vision) = 10
• DON
• IV infliximab
  - Dramatic, immediate improvement (72 hours)
    • CAS = 3, vision improved over 2 weeks

Orbit 24:117, 2005
Anti-TNF for TED
Etanercept Pilot Study

• N = 10 (7 F), 50 years (39-59 years)
• 25 mg twice weekly X 12 weeks, no control
• Duration of TED: 4 months (2-6 months)
• CAS: 4 (3-6)
  - At 12 weeks: CAS = 1.6 (0-4)
• Proptosis: 21.9 (15-30 mm)
  - At 12 weeks: 21.9 )15-28
• 2 early DON resolve
• 3 TED flare after trial

Eye 19:1286, 2005
Tocilizumab for TED
Anti-IL-6

• **IL-6:** pro-inflammatory cytokine
  - T-cell differentiation
  - secretion of acute phase reactants
  - B-cell activation

• **Anti-IL-6**
  - Given 8 mg/kg q 4 weeks X 4
  - Associated with ↓ TSI and ↓ proptosis
  - Minimal side effects

• 2 papers out
Anti-IL-6 for TED

• 2 patients
  - DON: IVMP (6 grams), decompression,
    • Marked improvement 1 dose
  - Corneal exposure: lid surgery, IVMP (4 grams), decompression
    • Marked improvement after 3 doses
Anti-IL-6 for TED
n = 18 (16F)

- Non-randomized, open-label, uncontrolled study, 8mg/kg/month X 5 (4-8)
- Inclusion: CAS ≥ 4, resistant to IVMP (500 mg X3), elevated TSI, 9 mo F/U
- Age: 47.9, 9 smokers
- Duration of TED: 16 months
- DON: 1 patient improved, 1st dose

Anti-IL-6 for TED
n = 18

- **Initial proptosis:** 22.3 (17-29)
  - **Reduction:**
    - N=13: -3.92 mm
    - N=4: no change
    - N=1: increased

- **CAS:** initial average 6.5
  - Final average: 0.61

- **TSI:** -76.2% within first dose

- **Minimal side effects**
  - “seems too good to be true” (Wiersinga)

- **RCT trial with placebo control done but not published yet**

Teprotumumab for TED “IGF-1R Inhibitor”

- Cross-talk between TSHR and IGF-1R
- Multicenter
- Duration of disease
  - < 9 months
- CAS ≥ 4
- No steroids X 6 weeks
- DON excluded

Lancet Diabetes Endocrinol 5:134, 2017
NEJM 376:1748, 2017
Teprotumumab for TED
“IGF-1R Inhibitor”

- \( N = \)
  - 45 placebo X 24 weeks \( \rightarrow \) 39 follow-up
  - 42 tepro X 24 weeks \( \rightarrow \) 36 follow-up

- **IV infusion:** q 3 weeks X 8

- **Primary endpoints**
  - \( \text{CAS} \leq 2 \)
  - \( \text{Proptosis} \leq 2 \text{ mm} \)

NEJM 376:1748, 2017
Teprotumumab for TED “IGF-1R Inhibitor”

Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Teprotumumab</th>
</tr>
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<tbody>
<tr>
<td><strong>CAS:</strong></td>
<td>5.2 → 3.35</td>
<td>5.1 → 1.67</td>
</tr>
<tr>
<td><strong>Proptosis:</strong></td>
<td>23.1 → 22.9</td>
<td>23.4 → 20.9</td>
</tr>
<tr>
<td><strong>Time to response</strong></td>
<td>18.7 weeks</td>
<td>11.2 weeks</td>
</tr>
</tbody>
</table>

NEJM 376:1748, 2017
Teprotumumab for TED
“IGF-1R Inhibitor”

• Adverse events
  - Hyperglycemia

• Notable features
  - Drug not yet commercially available
  - Drug company paid for study
  - No imaging done during study

NEJM 376:1748, 2017
What’s New in TED?

Summary

• More accurate diagnosis
  - Better TSH receptor Aby studies
    • More clinicians aware of TRAb for Dx
  - More critical review of imaging

• Prospective studies
  - Better reports of results

• Encouraging Rx results with receptor antibodies