ADVANCES IN THE TREATMENT OF THYROID EYE DISEASE

M. Reza Vagefi, M.D.
Associate Professor of Ophthalmology
Division of Oculofacial Plastic Surgery
University of California, San Francisco

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I have no financial interests or relationships to disclose.

The presentation covers off-label application of certain drugs.
Objectives

To understand:

- The epidemiology, pathogenesis and clinical course of thyroid eye disease
- Traditional therapeutic approaches used to treat moderate to severe active disease
- The cellular targets and newer biologic agents used to treat moderate to severe active disease

Thyroid Eye Disease (TED)

- Most common extrathyroidal manifestation of autoimmune hyperthyroidism
- Pathogenic mechanisms are still being elucidated with the orbital fibroblast playing a key role
- Disfiguring condition affecting ocular function & appearance
The Eye Disease

Pathogenesis of TED

- Initiation of Thyrotropin Receptor Autoimmunity
- Activation of Orbital Fibroblasts

Disease Course: Rundle’s Curve

- Curve is a descriptor of the natural history of TED
- Disease signs and symptoms are thought to worsen rapidly during a dynamic phase
- Signs and symptoms then abate to a static plateau

Clinical Course of TED

- Active Inflammatory Phase
- Chronic Fibrotic Phase
- Irreversible soft tissue changes

The Acute Phase

- What is the slope?

- Where is the peak?
The Acute Phase

- What is the slope?
- Where is the peak?
- Is it a linear escalation?

The Acute Phase

- What is the slope?
- Where is the peak?
- Is it a linear escalation?
- Does disease activity predict clinical severity?
Primary Goal of Treatment of TED

- **Active Inflammatory Phase**
- **Chronic Fibrotic Phase**

**Disease Activity** vs **Clinical Severity** over **Time**

Intervention

Irreversible soft tissue changes

Prevalence of TED in setting of Hyperthyroidism

- **No disease**: 74%
- **Mild disease**: 20%
- **Moderate to severe disease**: 6%

2.4% will develop moderate to severe disease at 18 months.

2.6% will develop moderate to severe disease at 18 months.

Assessing Activity

- Clinical Activity Score
- VISA Inflammatory Index
- NO SPECS Ophthalmopathy Index

### Table 2. NO SPECS Classification

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>Class</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caruncular ec</td>
<td>0</td>
<td>No signs or symptoms</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Only signs</td>
</tr>
<tr>
<td>Choriocapillaris</td>
<td>2</td>
<td>Soft tissue involvement, with symptoms and sign</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td></td>
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<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marked</td>
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<tr>
<td>Conjunctival ic</td>
<td>3</td>
<td>Proptosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;25mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22-24mm</td>
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<td></td>
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<td>20-21mm</td>
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<td>Lid redness</td>
<td>3</td>
<td>Extraocular muscle involvement</td>
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<tr>
<td></td>
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<td>Absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limitation of motion in extremes of gaze</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exertion restriction of movement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fixed eyeball</td>
</tr>
<tr>
<td>Lid edema</td>
<td>4</td>
<td>Corneal involvement</td>
</tr>
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</tr>
<tr>
<td></td>
<td></td>
<td>Stealing of cornea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coughing</td>
</tr>
<tr>
<td>Retrobulbar a</td>
<td>5</td>
<td>Sphincter involvement</td>
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<tr>
<td>At rest</td>
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<td>Absent</td>
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<tr>
<td>With Gaze</td>
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<td>Steeping of cornea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coughing</td>
</tr>
<tr>
<td>Diurnal varia</td>
<td>6</td>
<td>Sight loss</td>
</tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>20/20 - 20/16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20/16 - 20/20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;20/20</td>
</tr>
</tbody>
</table>

### Traditional Therapeutic Approaches to Active Disease

**Glucocorticoids**

**Immunosuppression**

**Intravenous Methylprednisolone Pulses:**

**Side Effects:**

- The eye disease routinely flares upon withdrawal of steroids.
- There is a 20 to 25% non-responder rate.

**Psychosis**

*Cumulative doses greater than 8 g should be avoided.*
Traditional Therapeutic Approaches to Active Disease

Immunosuppression

Orbital Radiotherapy

American Academy of Ophthalmology Technology Assessment 2008

1 Evidence based assessment of role of XRT to treat non-sight-threatening TED is limited by the heterogeneity and variable quality of published reports.

2 Based on the highest-quality RCT evidence, orbital radiation has a limited role in treating non–sight-threatening TED.

3 Several well-conducted RCTs indicate that the effect of orbital radiation may be limited to improving ocular dysmotility or halting its progression.

Indications for Urgent Decompression:

- Compressive optic neuropathy
- Severe corneal exposure from lid retraction/lagophthalmos
- Uncontrolled glaucoma from orbital congestion

Right Eye | Left Eye
---|---
VA 20/70 | 20/25
Pupils 3 mm | 2 mm
Color Plates 6/14 | 14/14
Fundus Disc Swelling | Normal
An Evolving Treatment Paradigm

- Moderate to Severe Active TED
  - Glucocorticoids (IV/Oral/Retrobulbar)
  - Inactive TED
  - Partial or No Response
    - Glucocorticoids +/- XRT
    - Alternative Immunomodulator
    - Biologics

Rehabilitative Surgery

Immunologic Soup

- Immunologic response is mediated through antigen, humoral and cellular immunity, cytokines, and the effector cell (fibroblast)
- There are therefore a number of potential targets to combat the inflammatory response.

What have we targeted with biologics?

- TNF-α
- IL-6
- B-Cell
- IGF-1R

M. Reza Vagefi, MD
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Tumor Necrosis Factor-α

- Cytokine involved in systemic inflammation and a part of the acute phase reaction.
- TNF-α expression has been demonstrated in orbital tissue specimens from patients with TED.
- Two classes of drugs have been used:
  - TNF-α monoclonal antibody
  - Soluble TNF receptor-Fc protein
Etanercept

- It is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1.

- Etanercept binds specifically to TNF and blocks its interaction with cell surface TNF receptors.

- It is FDA approved for RA, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and moderate-to-severe plaque psoriasis.

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**Study Design**

- Non-controlled interventional pilot study

**Cohort**

- 10 patients (7 females; 3 males)
- Recent-onset, active, mildly to moderately severe TED

**Intervention**

- Subcutaneous injections of 25 mg of etanercept twice weekly for 12 weeks

**Outcome Measure**

- Clinical Activity Score
- Ophthalmopathy Index
Results: Paridaens D et al. 2005

- Mean reduction in clinical scores with largest improvement at 6 weeks.
- The difference was particularly evident on soft tissue changes, including periocular chemosis and redness.
- The mean exophthalmometry values did not change.
- In all, 60% percent of patients reported moderate to marked improvement.
- In three patients, the disease flared up again after cessation of treatment.

Clinical Scores before and after Etanercept

Adalimumab

- It is the first fully human, high-affinity, recombinant immunoglobulin G1 (IgG1) anti-TNF monoclonal antibody.
- It is composed of human-derived heavy- and light-chain variable regions and human IgG1:κ constant regions engineered through phage display technology and produced in a Chinese hamster ovary mammalian cell line.
- It binds to TNF-α and blocks its interaction with cell surface TNF receptors.
Adalimumab as steroid-sparing treatment of inflammatory-stage thyroid eye disease.

Ayabe R1, Rootman DB, Hwang C, Ben-Artzi A, Goldberg R.

Study Design

• Non-controlled retrospective case review

Cohort

• 10 patients (5 females; 5 males)
• Diagnosis of TED within 9 months of initiating Rx
• Presence of at least 1 inflammatory finding
• Most of subjects were also receiving steroids

Intervention

• Treatment for at least 10 weeks at a standard dosing of one 80 mg injection followed by biweekly 40 mg injections

Outcome Measure

• Inflammatory index

Results: Ayabe R et al. 2014

- After 3 months, the inflammatory composite score was decreased for 6 patients, increased for 3 patients, and the same for 1 patient.
- The average reduction in inflammatory composite score did not achieve statistical significance.
- A subset of patients with a baseline inflammatory composite score >4 demonstrated a significant decrease in inflammatory composite score.
- One patient was admitted to the hospital for diarrhea and sepsis while on treatment and IV steroids.
Interleukin-6

- It plays an essential role in the final differentiation of B cells into immunoglobulin-secreting cells.
- It is secreted by T cells and macrophages to stimulate immune response leading to inflammation.
- Its levels are found to be elevated in patients with TED and it stimulates thyrotropin receptor expression in fibroblasts from TED patients.

Tocilizumab

- It is a recombinant, humanized monoclonal antibody.
- It binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors.
- It is FDA approved for RA, systemic juvenile idiopathic arthritis, GCA and cytokine release syndrome.
### Study Design
- Prospective interventional nonrandomized study

### Cohort
- 18 patients (16 females; 2 males)
- Active TED defined by Clinical Activity Score ≥4 patients resistant to previous intravenous steroids

### Intervention
- IV tocilizumab 8 mg/kg every 4 weeks for at least 4 cycles

### Outcome Measure
- Visual acuity, Hertel exophthalmometry, CAS, TSI levels, ocular motility, and side effects were registered at a 4-week intervals.

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### Results: Perez-Moreiras JV et al. 2014

- All patients had a significant progressive CAS improvement (mean CAS score reduction 5.89 ±1.41 points, p < 0.00027).
- Mean TSI levels were significantly lower at the end of the treatment (mean −76.18% ±17.80%, p = 0.00007).

- Thirteen patients (72.22%) reduced proptosis a mean of $-3.92 \pm 1.54$ mm ($p = 0.002$).
- Fifteen patients (83.33%) had an improvement in extraocular motility, and 7 patients of 13 resolved their diplopia (53.85%).
- No severe side effects or relapse of active TED were observed at the end of follow up.

B-Cells

- B cells appear to play multiple critical roles in the pathogenesis of TED.
- They provide support for the function of both T cells and fibroblasts.
- They also produce autoantibodies and can act as antigen presenting cells.
Rituximab

- A chimeric mouse-human monoclonal antibody directed against the CD20 antigen on B lymphocytes.
- Binding results in B-cell depletion for 4 to 6 months.
- It is FDA approved for CD20+ non-Hodgkins lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis.

Study Design
- Prospective, randomized, double-masked, placebo-controlled trial

Cohort
- 21 patients completed (17 females; 4 males)
- Active moderate to severe TED defined by Clinical Activity Score ≥4 patients resistant to previous intravenous steroids

Intervention
- Two rituximab infusions (1000 mg each) or two saline infusions were given 2 weeks apart

1° Outcome Measure
- Reduction in clinical activity score assessed as a continuum and separately as improvement by 2 points at 24 weeks
No differences were found in the proportions of patients showing CAS improvement at 24 weeks (25% placebo; 31% RTX, P=.75) or in CAS decrease from baseline to 24 or 52 weeks [mean 1.5 points (1.8 SD) placebo; 1.2 (2 SD) RTX at 24 weeks, P=.73].

There were no differences between groups in any of the secondary endpoints at either 24 or 52 weeks.
Conclusions: Stan MN et al. 2015

- Rituximab offered no additional benefit over placebo to patients with active and moderate to severe TED and carried with it non-negligible adverse effects.

- Main criticism:
  - Patients receiving rituximab had a mean duration of disease of 12.4 months.
  - Both groups had received prior glucocorticoids within 6 weeks of trial.
  - Small number of participants.

**Table 3. Adverse Effects**

<table>
<thead>
<tr>
<th>Side-effect type</th>
<th>Placebo (N)</th>
<th>Rituximab (N)</th>
<th>Overall (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias/arthritis</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Skin (rash, itching)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Infectious (bronchitis, conjunctivitis)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe lacrimation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal (tongue pain, abdominal pain, diarrhea)</td>
<td>1 + 1</td>
<td>2 + 1</td>
<td>3</td>
</tr>
<tr>
<td>Moderate/severe*</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total events</td>
<td>4</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Total patients</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

*Bold numbers indicate moderate/severe adverse effects.

**Study Design**

- Prospective, randomized, double-masked, placebo-controlled trial.

**Cohort**

- 32 patients completed (26 females; 6 males).
- Active moderate to severe TED defined by Clinical Activity Score ≥4.

**Intervention**

- Randomized to receive either IV methylprednisolone (7.5 g) or rituximab (2000 or 500 mg).

**1° Outcome Measure**

- Reduction of the clinical activity score of 2 points or to less than 3 at 24 weeks.
Results: Salvi M et al. 2015

- The clinical activity score decreased with both treatments but more after RTX at 16, 20, and 24 weeks (P<.04, P<.02, P<.006, respectively)
- The dose of RTX whether 1000 mg twice or 500 mg once was used was not significant (P=NS).
- At 24 weeks 100% of RTX patients improved compared with 69% after IV steroids (P < .001)

Results: Salvi M et al. 2015

- Disease reactivation was never observed in RTX patients but was observed in five after IV steroids.
- Patients treated with RTX scored better motility at 52 weeks in both eyes.
- Overall rehabilitative surgical procedures carried out during follow-up were less in the RTX group (P=.049)
Conclusions: Stan MN et al. 2015

- The results of this trial confirm preliminary reports on a better therapeutic outcome of Rituximab in active moderate to severe TED, when compared with IV steroids, even after a lower RTX dose.

- Main criticism:
  - Small number of participants
  - Differences in baseline parameters such as TRAbs, soft tissue involvement, and amount of diplopia in the two groups of patients

Insulin-like Growth Factor-1

- Similar in structure to insulin.
- Plays an important role in childhood/pubertal growth and may have anabolic effects in adults.
- IGF-1 receptors on almost every cell in the body.
- Critical for growth and proliferation and inhibits apoptosis.
Insulin-like Growth Factor-1R

- In vitro studies showed autoantibodies recognizing IGF-IR and activating IGF-IR signaling in orbital tissues of patients with autoimmune hyperthyroidism.
- IGF-IR overexpression in patients with autoimmune hyperthyroidism.
- Actions of thyrotropin and thyroid-stimulating immunoglobulins are in part dependent on IGF-IR activity.

Teprotumumab

- It is a human monoclonal antibody that binds to Insulin-like growth factor 1 receptor.
- It was first investigated for the treatment of solid and hematologic tumors, including breast cancer, Hodgkin's and non-Hodgkin's lymphoma, non-small cell lung cancer and sarcoma.
- FDA granted it orphan drug status for TED.
Prospective, randomized, double-masked, placebo-controlled trial

76 patients completed (26 females; 6 males)

Active moderate to severe TED defined by Clinical Activity Score ≥4

Randomized to receive either IV methylprednisolone (7.5 g) or rituximab (2000 or 500 mg)

Reduction of the clinical activity score of 2 points
Reduction of 2 mm of proptosis

Results: Smith TJ et al. 2017

- The time to the first response was markedly shorter in the teprotumumab group than in the placebo group.
- The proportion of patients who had a response was greater in the teprotumumab group than in the placebo group at weeks 6, 12, and 18 (P<0.001).
- The level of response was greater in the teprotumumab group than in the placebo group (P<0.001).
Results: Smith TJ et al. 2017

- All secondary efficacy end points were statistically significant for the teprotumumab group compared to placebo.
- The only drug-related adverse event was hyperglycemia in patients with diabetes.
- This event was controlled by adjusting medication for diabetes.

Conclusions: Smith TJ et al. 2017

- In patients with active TED, teprotumumab was more effective than placebo in reducing proptosis and the Clinical Activity Score.
- Main criticism:
  - Differences in drug and placebo group that favored the drug including:
    - drug was initiated sooner in course of thyroid disease
    - less smokers in drug group
    - more euthyroid patients in drug group
My Paradigm

Moderate to Severe Active TED

IV Glucocorticoids

Inactive TED

Partial or No Response

Rehabilitative Surgery

Glucocorticoids + Antimetabolite

Tocilizumab SQ

Pending Trials

Tocilizumab Treatment in Graves’ Ophthalmopathy (Graves’ Orbitopathy or Thyroid Eye Disease) (GRC)

Treatment of Graves’ Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis With Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (OPTIC)
Conclusion

- Thyroid eye disease is the most common extrathyroidal manifestation of autoimmune hyperthyroidism.
- Progression to moderate to severe active thyroid eye disease is fortunately not a common occurrence.
- For steroid resistant disease, a host of cellular targets can be exploited to quell disease activity.
- It is likely that in the near future, there will be a biologic agent with FDA approval for the treatment of thyroid eye disease.

Thank you