Rituximab for Thyroid Eye Disease

Rona Z. Silkiss, M.D., FACS
Adam Gess, M. D.
California Pacific Medical Center
San Francisco, California
www.eyework.com

Thyroid Eye Disease (TED) Pathophysiology

- TED is an orbital inflammatory disease involving T lymphocytes, B lymphocytes and fibroblasts.

- TED results from immunological cross-reactivity between thyroid and orbital tissue antigens (TSH receptor).

Financial Disclosure

- The authors have no conflicting financial disclosures.

Thyroid Eye Disease Pathophysiology

- TSH receptor hyperstimulation in the orbit leads to glycosaminoglycan secretion by pre-adipocyte fibroblasts and an increase in the volume of intraorbital tissues.

- Eye muscles, connective tissue and fat are infiltrated by lymphocytes and are the target of acute inflammation.
Thyroid Eye Disease Pathophysiology

- Given this pathophysiology, anti-inflammatory interventions are utilized.
- Of these, biologics will become the preferred and increasingly targeted therapy.

Therapeutic Choices

- Steroids - oral + IV (64%)
- Steroids + Radiation (70%)
- Radiation (6%)
- Rituximab (98%)

Steroids

- Steroids are the mainstay of TED therapy.
- Effective.
- Inexpensive.
- Widely available.
- Broad spectrum anti-inflammatory.
- Side effects are known and extensive.

Side Effects of Steroid Use

- Diabetes
- Weight gain
- Facial swelling
- Depression, psychosis
- Peptic ulcer
- Muscle atrophy
- Cataracts
- Glaucoma
- Infections
- Osteonecrosis
- Osteoporosis
- Avascular necrosis
- Hepatic steatosis
- Hypertension
- Striae
- Cushingoid features - buffalo neck, moon facies

Steroid Therapy for Graves’ Ophthalmopathy

*Nippon Rinsho. 2006 Dec;64(12):2279-85

- Fatal liver failure 0.8%
- Associated with 9-12 gram total dose
- Recommendation: Limit IV dose to 4.5-6 g

Ophthalmic Technology Assessment Orbital Radiation for Graves’ Ophthalmopathy


- 0/3 sham controlled randomized studies demonstrated efficacy for improvement of proptosis or soft tissue changes.
- 2/3 sham controlled studies demonstrated only improved vertical range of motion.
- 3/5 observational studies - widely variable favorable outcome (40-97%).
Conclusion

- Orbital radiation has a *limited role* in treating non-sight threatening TED.
- The effect may be limited to improving or halting progression of ocular dysmotility (vertical).
- Unclear as to whether improved motility translates into enhanced functioning and quality of life.

Radiation Risks

- Risk of *definite* radiation retinopathy within 10 years- 1-2%
- Risk of *possible* radiation retinopathy within 10 years- 21%
- Contraindicated- severe htn, diabetes
- Mutagenic and carcinogenic potential in those <35 years old
- Risk of radiation induced cataract

Orbital Radiation Recommendations - Limited

- Patients with active disease with diplopia or ocular restriction not responsive to steroid therapy alone.
Rituximab (RTX)

- Mouse - human chimeric monoclonal antibody targeting CD20 protein on pre-B and mature B lymphocytes.
- Blocks B-cell activation and differentiation.
- Does not affect B cell regeneration from stem cells nor immunoglobulin production from B cells.

Rituximab Rationale

- RTX blunts the active inflammatory phase, inducing a 4-6+ month B cell depletion with no change in serum immunoglobulins.
- RTX-induced depletion orbital B cells may interfere with antigen presentation and T cells.

Rituximab Effects

- Demonstrated efficacy for severe steroid resistant TED.
- RTX reduced TED activity and severity more than steroids.
- Relapse of active TED not observed, 10% in steroid group.
Rituximab Data to Date

- Total number of studies: 9
  - 3 controlled trials, 2 interventional non-controlled trials, 2 case series, 2 case reports
- Total number of patients: 59 (more have been treated)

Outcomes - different primary endpoints
- Favorable outcome - 7 studies, 1 case report
- Unfavorable outcome - 1 case report

Improvement of CAS - 3.3

Adverse effects - (20%) - mild, transient, usually limited to initial infusion - reduced with steroid or acetaminophen pretreatment

Phase I/II Clinical Trial
Silkiss and Lauer
OPRS, 26(5), 2010

- N=12
- Stabilized TFTs, no concurrent steroid tx
- Decline in CAS
- No association with TrAb
- No adverse effects
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Pts.</th>
<th>Dose</th>
<th>#</th>
<th>Freq</th>
<th>Findings</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvi 2006</td>
<td>Case Report</td>
<td>1</td>
<td>1000 mg</td>
<td>2</td>
<td>q 2 wk</td>
<td>Decr. inflammation; improved motility; improved CAS-3 points</td>
<td>Transient nasal occlusion</td>
</tr>
<tr>
<td>ElFassi 2006</td>
<td>Case Series</td>
<td>2</td>
<td>375mg /m²</td>
<td>4</td>
<td>weekly</td>
<td>Decr. proptosis-2nm; improved CAS-3.75 points</td>
<td>Pain; finger joints</td>
</tr>
<tr>
<td>ElFassi 2007</td>
<td>Controlled, non random</td>
<td>20</td>
<td>375mg /m²</td>
<td>4</td>
<td>weekly</td>
<td>Lower rate of relapse rate in RTX group vs control (393 d vs &gt;904 d)</td>
<td>Hypotension; nausea; fever, chills, tachycardia</td>
</tr>
<tr>
<td>Salvi 2007</td>
<td>Open Pilot</td>
<td>29</td>
<td>1000 mg</td>
<td>2</td>
<td>q 2 ks</td>
<td>CAS (2.9 pts); RTX Decr. prop. &amp; inflamm both No relapses RTX; Higher adv rate steroid (33%).</td>
<td>Nose, throat, itching, temp. elevation 1st infusion.</td>
</tr>
<tr>
<td>Heems tra, 2008</td>
<td>Prosp. Phase II Open</td>
<td>13</td>
<td>1000mg</td>
<td>2</td>
<td>q 2 wk</td>
<td>9/13 patients decr. FT4 vs baseline; Remained euthyroid, median 18 months</td>
<td>Temp joint</td>
</tr>
<tr>
<td>El Fassi, 2009</td>
<td>Cont trial: RTX + MMI vs MMI</td>
<td>20</td>
<td>375mg /m²</td>
<td>4</td>
<td>weekly</td>
<td>No difference in IgG levels, lower IgM levels in RTX group; RTX lowered proportion of stimulating TRAbs compared with non-stimulating TRAbs</td>
<td>100% recurr.</td>
</tr>
<tr>
<td>Salvi, 2009</td>
<td>Series: Ritux vs Steroids</td>
<td>4</td>
<td>1000mg</td>
<td>2</td>
<td>q 2 wk</td>
<td>Depletion of CD-20 lymphocytes from orbit of RTX-treated patient, no depletion in steroid-treated patients</td>
<td>None</td>
</tr>
<tr>
<td>Silkiss, 2010</td>
<td>Phase II Open Label Intervent Trial</td>
<td>12</td>
<td>1000mg</td>
<td>2</td>
<td>q 2 wk</td>
<td>Significant decrease in CAS (-2.3 to -4.7) and TAOS scores (-3.3 to -6.0) for all time points during the 52-week study period</td>
<td>None</td>
</tr>
</tbody>
</table>

### Rituximab Side Effects

- Well over 1 million doses administered.
- Rare - anaphylaxis, infection reactivation, cv events, tardive mucocutaneous reactions
- Progressive multifocal leukoencephalopathy (PML) - reactivation of J polyomavirus - rare
- Incidence in RA = 0.51/10,000 (est.)
- The cases of PML in RA are complex and rare.
Cost of Rituximab
- 2 doses (1000 mg IV), Day 1 and Day 14
- Cost of medication $5000/dose
- Cost of infusion $500/infusion
- Monitoring labs $1570
- Total $12,700 (Radiation $15,000)
- Currently considered experimental - not routinely covered by insurance - this will change….soon.

Biologics - Rituximab
- Highly selective, targeted biologic.
- Reduces overall inflammation (CAS) rather than just improve vertical diplopia.
- Potentially more effective than radiation.
- Lower potential complication rate than radiation.
- Fewer side effects than steroids.
- Cost comparable to radiation.

The Present
- No single intervention including biologics provides a cure.
- All current therapies remain “palliative” and currently target only a section of a complex immunologic cascade.

Biologics currently are the best technology available with the potential to deliver targeted therapy with the fewest side effects.
Thank you