Myositis Treatment Update

British Society for Rheumatology
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Chester V. Oddis, MD
Division of Rheumatology and Clinical Immunology
University of Pittsburgh
Disclosures

Genentech: Advisory Board; RIM Study support
Lecture Objectives

1. To review the therapies for adult inflammatory myopathy
2. To understand the rationale behind therapies for the treatment of myositis
3. To discuss the results of biologic therapeutic trials for adult dermatomyositis and polymyositis

Essentially none of the agents discussed today are “approved” for use in myositis
Pharmacologic Therapy of IIM

- Corticosteroids
- Immunosuppressive Agents
- Combination regimens
- IVIg
- Biologic agents
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Common side effects</th>
<th>Level of evidence for use in myositis</th>
<th>Special comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Starting at 1 mg/kg or 60–80 mg/d in 2 or 3 divided doses</td>
<td>Osteoporosis, steroid myopathy, glaucoma, cataract, risk of infection</td>
<td>Case series</td>
<td>Usual initial therapy with or without additional immunosuppression</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Starting at 10–15 mg/wk (orally or subcutaneously) with an increase to 25 mg/wk</td>
<td>Hepatic toxicity, bone marrow suppression, risk of infection</td>
<td>Uncontrolled cohort studies</td>
<td>First-line immunosuppression unless contraindicated</td>
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<tr>
<td>Azathioprine</td>
<td>Starting at 50 mg/d and increased by 50 mg every 2 wk up to 2–3 mg/kg/d</td>
<td>Gastrointestinal symptoms, bone marrow suppression, hepatic toxicity, pancreatitis, risk of infection</td>
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<td>Cyclosporine</td>
<td>Starting at 50 mg twice daily and increasing to final dose of 100–150 mg twice daily</td>
<td>Nephrotoxicity, neurotoxicity, abnormal glucose metabolism, hyperkalemia, headache, tremor, hypertension, risk of infection</td>
<td>Case series</td>
<td>Second-line immunosuppression; some evidence of efficacy in myositis-associated lung disease</td>
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<td>Tacrolimus</td>
<td>Starting at 1 mg twice daily and slowly increasing for trough level of 8–12</td>
<td>Similar to cyclosporine</td>
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<td>Immunoglobulins</td>
<td>Starting at 2 g/kg/mo given over 2–5 d</td>
<td>Hypertension, volume overload, renal toxicity, headaches</td>
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<td>Mycophenolate</td>
<td>Starting at 500 mg twice daily, slowly increasing to 2–3 g/d</td>
<td>Bone marrow suppression, gastrointestinal intolerance, risk of infection</td>
<td>Case series</td>
<td>For refractory cases; some efficacy in refractory skin disease and possibly in interstitial lung disease</td>
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<td>Cyclophosphamide</td>
<td>Oral: 2-mg/kg/d dose</td>
<td>Malignancy, bone marrow suppression, hepatotoxicity</td>
<td>Case reports</td>
<td>Limited to very refractory cases with interstitial lung disease</td>
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<td>Rituximab</td>
<td>2 doses of 1,000-mg intravenous infusion 2 wk apart</td>
<td>Risk of infection</td>
<td>Case series</td>
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Combination Therapy in Myositis

- Multiple reports of combination therapy in treatment of refractory PM and DM

- Literature support for combination of methotrexate and azathioprine in IIM [Villalba, Arthritis Rheum, 1998]
  - effective in treatment-resistant myositis
  - beneficial in those who had failed either mtx or aza alone
IS Agents Beyond Mtx and Aza...

- Mycophenolate mofetil
- Cyclosporine/tacrolimus
- Cyclophosphamide
**Mycophenolate Mofetil in Myositis**

- 6 of 10 patients with DM successfully tapered CS with MMF [Rowin, Neurology, 2006]
  - 3 developed opportunistic infections (other risk factors)

- Improvement in **cutaneous features** in 10/12 DM patients [Edge, Arch Derm, 2006]

- IVIg as add-on therapy to MMF effective in 7 severe and refractory pts (4PM/3DM) [Danielli, Autoimmunity Rev, 2009]
  - Safe and steroid-sparing

- Retrospective review of 50 JDM pts using MMF for 12 months [Rouster-Stevens, Arth Care Rsch, 2010]
  - Improved skin and muscle; steroid-sparing; well-tolerated
IS Agents Beyond Mtx and Aza…

- Mycophenolate mofetil
- Cyclosporine/tacrolimus
- Cyclophosphamide
## Tacrolimus in Myositis and ILD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
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</thead>
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<tr>
<td>FVC</td>
<td>&lt;0.0001</td>
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<tr>
<td>FEV-1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DLCO</td>
<td>0.0046</td>
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<tr>
<td>CK</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MMT</td>
<td>0.06</td>
</tr>
<tr>
<td>CS Dose</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Retrospective study of 13 synthetase (+) pts (12 with Jo-1)

Oddis, Lancet, 1999
Wilkes, Arth Rheum, 2005
Treatment of ILD in Myositis Patients

- Corticosteroids remain the initial treatment

- Cyclophosphamide and azathioprine used early or in CS resistant cases with variable results
  - Intermittent IV ctx pulse [Okada, Mod Rheumatol, 2007]

- MMF in CTD-associated ILD [Swigris, Chest, 2006; Campbell, ACR 2009, #590]

- Cyclosporine and tacrolimus used in both adult and pediatric patients with promising results
Is Anti-T cell Therapy Rational in Myositis-associated ILD?
T cells as Therapeutic Targets in Myositis-Associated ILD

- Pathology: abundant lymphocytes and plasma cells in the lung of PM/DM pts (form lymphoid follicles)

- Infiltrating lymphocytes in myositis NSIP pts revealed “activated” CD8+ T-cells [Yamadori, Rheumatol Int, 2001]

- CD8+ and “activated” T-cells increased in BAL fluid of PM/DM pts (n=22) [Kurasawa, Clin Exp Immunol, 2002]

- Decrease in regulatory T cells in IP of CTD-ILD [Katigiri, Mod Rheumatomol, 2008]

Implicates activated CD8+ T-cells in myositis-associated ILD
Anti-T cell Therapy in Myositis-associated ILD

- Accumulating data on efficacy of tacrolimus/CsA
  - Wilkes, Arth Rheum, 2005
  - Takada, Autoimmunity, 2005
  - Takada, Mod Rheumatol, 2007
  - Guglielmo, Eur Respir J, 2009
    - ARDS reversed with tacrolimus
  - Ando, Clin Rheumatol, 2010
    - ADM pt refractory to CsA responded to tacrolimus
## IVlg for Refractory ILD in IIM

### Table

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>ILD-PM</td>
<td>ILD-ADM</td>
<td>ILD-ADM</td>
<td>ILD-ADM</td>
<td>ILD-ADM</td>
</tr>
<tr>
<td>Initial treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>Pulse, PSL 50 mg</td>
<td>PSL 60 mg</td>
<td>Pulse, PSL 60 mg</td>
<td>Pulse, PSL 50 mg</td>
<td>Pulse, PSL 50 mg</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td>CyA, IVCYC</td>
<td>CyA</td>
<td>CyA, IVCYC</td>
<td>CyA</td>
<td>CyA</td>
</tr>
<tr>
<td>Interval from admission to start of CS</td>
<td>3 days</td>
<td>2 days</td>
<td>10 days</td>
<td>3 days</td>
<td>9 days</td>
</tr>
<tr>
<td>Interval from CS to addition of CyA</td>
<td>Concomitant</td>
<td>7 days</td>
<td>Concomitant</td>
<td>Concomitant</td>
<td>Concomitant</td>
</tr>
<tr>
<td>Interval from CS to IVIG</td>
<td>43 days</td>
<td>65 days</td>
<td>46 days</td>
<td>8 days</td>
<td>11 days</td>
</tr>
<tr>
<td>No. of IVIG cycles</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Maintenance after IVIG therapy</td>
<td>PSL, CyA</td>
<td>PSL, CyA</td>
<td>PSL, CyA, PMX-DHP</td>
<td>PSL, CyA, IVCYC</td>
<td>PSL, CyA, IVCYC</td>
</tr>
<tr>
<td>Outcome</td>
<td>Alive</td>
<td>Alive</td>
<td>Died 64 days after onset</td>
<td>Died 47 days after onset</td>
<td>Died 29 days after onset</td>
</tr>
</tbody>
</table>

- **Salvage therapy**
- **2/5 pts survived**

Suzuki, Lung, 2009
IVIg in Myositis

- Literature review of 308 adult patients
  - 14 articles
  - only 2 RCT
- Steroid-sparing
- Safe with tolerable adverse events
- Effective in esophageal involvement and rapidly progressive disease

Wang, Clin Rheumatol, 2012
Lecture Objectives

1. To review the therapies for adult inflammatory myopathy

2. To understand the rationale behind therapies for the treatment of myositis

3. To discuss the results of biologic therapeutic trials for adult dermatomyositis and polymyositis
## IMACS Core Set Measures: Assessing Outcome in Myositis

<table>
<thead>
<tr>
<th>Domain</th>
<th>Core Set Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Activity</td>
<td><strong>Physician</strong> global disease activity</td>
</tr>
<tr>
<td></td>
<td><strong>Patient</strong> global disease activity</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td><strong>MMT</strong> to include proximal, distal and axial muscles in adults and children</td>
</tr>
<tr>
<td>Physical Function</td>
<td>Validated patient/parent questionnaire of activities of daily living <em>(HAQ/CHAQ)</em></td>
</tr>
<tr>
<td>Laboratory Assessment</td>
<td><strong>Muscle enzymes</strong> <em>(CK, aldolase, LDH, ALT and AST)</em></td>
</tr>
<tr>
<td>Extramuscular disease</td>
<td>Assessment of constitutional, cutaneous, GI, articular, cardiac and pulmonary activity.</td>
</tr>
</tbody>
</table>
Preliminary Definition of Improvement (DOI) for IIM Clinical Trials

3 of any 6 CSM improved by $\geq 20\%$, with no more than 2 CSM worsening by $\geq 25\%$
(cannot include MMT)

Rider, Arth Rheum, 2004

DOI not just a consensus definition, but partially validated using adult trial data ($n=4$) and pediatric natural history data
Potential Targets in Myositis

- TNF – alpha
Role of TNF-α in Pathogenesis of Myositis

Super-normal TNF-α levels:
- ↑ own (TNF-α) production in myoblasts

Physiologic TNF-α levels in muscle:
- affect glucose metabolism
- ↓ membrane electric potentials
- ↑ protein break-down and ubiquinization

Directly toxic to existing myofibers

Prevents myofiber regeneration

TNF-α enhances other pro-inflammatory cytokines:
- ↑ IL-1α, IL-1β, MCP-1, RANTES, IL-6 and IL-8

In DM, TNF-α expressed in endothelium:
- ↑ surface adhesion molecules (ICAM, VCAM, E-selectin) & facilitates monocyte trafficking into target tissues

Efthimiou, Semin Arth Rheum, 2006
Open Pilot Study of Infliximab: Baseline Demographic Data of Refractory IIM Cohort

- **13 patients with refractory myositis (5 PM; 4 DM; 4 IBM)**
- **4 infliximab infusions (5 mg/kg) over 14 weeks (0/2/6/14)**
- **Outcome measures: IMACS; MRI; disease activity score**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Sex/Age</th>
<th>Disease duration (years)</th>
<th>Previous treatment</th>
<th>Concomitant treatment, daily doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PM</td>
<td>F/49</td>
<td>5</td>
<td>Pred, MTX, AZA, MMF, CsA, SSZ</td>
<td>Pred 15 mg, MTX 7.5 mg/week</td>
</tr>
<tr>
<td>2</td>
<td>PM*</td>
<td>F/52</td>
<td>7</td>
<td>Pred, MTX, AZA, CyX</td>
<td>AZA 100 mg</td>
</tr>
<tr>
<td>3</td>
<td>PM</td>
<td>M/53</td>
<td>4</td>
<td>Pred, MTX, AZA, IVIG, CyX</td>
<td>Pred 17.5 mg, AZA 200 mg</td>
</tr>
<tr>
<td>4</td>
<td>PM*</td>
<td>F/76</td>
<td>5</td>
<td>Pred, MTX, AZA</td>
<td>Pred 2.5 mg, MTX 15 mg/week</td>
</tr>
<tr>
<td>5</td>
<td>PM</td>
<td>F/56</td>
<td>4</td>
<td>Pred, MTX, AZA, CyA, CyX, IVIG</td>
<td>Pred 5 mg, MTX 15 mg/week</td>
</tr>
<tr>
<td>6</td>
<td>DM*</td>
<td>M/50</td>
<td>10</td>
<td>Pred, ARA, MTX, CsA</td>
<td>MTX 15 mg/week</td>
</tr>
<tr>
<td>7</td>
<td>DM</td>
<td>M/44</td>
<td>20</td>
<td>Pred, MTX, AZA, IVIG, CsA</td>
<td>Pred 5 mg, AZA 150 mg, IVIG</td>
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<td>8</td>
<td>DM</td>
<td>F/54</td>
<td>1</td>
<td>Pred, AZA</td>
<td>Pred 8 mg, MTX 20 mg/week, AZA 150 mg</td>
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<tr>
<td>9</td>
<td>DM</td>
<td>F/74</td>
<td>3</td>
<td>Pred, MTX, AZA, IVIG</td>
<td>Pred 10 mg, AZA 150 mg</td>
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<td>10</td>
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<td>12</td>
<td>IBM</td>
<td>F/50</td>
<td>6</td>
<td>Pred, MTX, AZA, IVIG</td>
<td>Pred 3.75 mg, MTX 7.5 mg/week</td>
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<tr>
<td>13</td>
<td>IBM</td>
<td>M/64</td>
<td>4</td>
<td>Pred, MTX, CsA</td>
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Dastmalchi, Ann Rheum Dis, 2008
Results of Infliximab Therapy

- 9 of 13 completed study
- 3 discontinued due to adverse events
- 3 of the completers improved by ≥ 20% in 3 or more variables, 4 were unchanged, 2 worsened ≥ 30%
- No patient improved their MMT

Dastmalchi, Ann Rheum Dis, 2008
Thigh MRI (PM Patient) Before and After Infliximab

2 patients had active MRI at baseline but 5 were active at follow-up

Dastmalchi, Ann Rheum Dis, 2008
Muscle Biopsy Data

• T lymphocytes/macrophages/ cytokine expression/MAC deposition – *all still evident after treatment*

• Type I IFN tissue (and serum) signature increased

Dastmalchi, Ann Rheum Dis, 2008
A Randomized, Pilot Study of Etanercept in Dermatomyositis

Anthony A. Amato, M.D.
Brigham and Women’s Hospital
Harvard Medical School
&
THE MUSCLE STUDY GROUP

Amato, Ann Neurol, 2011
New Pts (n=40)
Prednisone 60 mg/d for 2 months

3:1 Randomization
ETN 50 mg/wk or Placebo
52 wks

5mg Prednisone taper every 2 weeks

Week 24
All subjects off prednisone if taper tolerated
OR
Treatment failure

Forced Prednisone Taper

Amato, Ann Neurol, 2011
Principal Outcomes

1. Adverse events
2. Average prednisone dose after week 24
3. Time from randomization to treatment failure (inability to wean off prednisone on schedule)

Amato, Ann Neurol, 2011
A Pilot Study of Etanercept in DM

Treatment Failures

a. Worsening of MD Global ≥ 2cm on a VAS
b. Worsening of the MMT score by ≥ 20%
c. Increased dysphagia with risk of aspiration
d. Increased dyspnea with FVC or DLCO decline by 20%
e. No improvement after 12 wks

Study physician could slow or halt prednisone taper, increase dose, or add alternative agent at any point during the study per standard of care

Amato, Ann Neurol, 2011
**New**
Prednisone 60 mg/d for 2 months

**Flare**
Prednisone 60 mg/d for >2 months, stable mtx dose or IVIg

3:1 Randomization
ETN 50 mg/wk or Placebo-52 wks

5mg Prednisone taper every 2 weeks

**Week 24**
All subjects off prednisone if taper tolerated

*OR*
Treatment failure

Forced Prednisone Taper

Amato, Ann Neurol, 2011
Assessed for eligibility (n=153)

Excluded (n=137)
- Did not meet eligibility criteria (n=99)
- Declined to participate (n=25)
- Other reasons (n=13)

Randomized (n=16)

Aliocation

Allocated to Etanercept (n=11)
- Received allocated intervention (n=11)
- Did not receive allocated intervention (n=0)

Allocated to Placebo (n=5)
- Received allocated intervention (n=5)
- Did not receive allocated intervention (n=0)

Follow-Up

Completed (n=10)
Withdrew (n=1)
- Lost to follow-up (n=1)

Completed (n=4)
Withdrew (n=1)
- Lack of perceived benefit (n=1)

Analysis

Analyzed (n=11)
- Excluded from analysis (n=0)

Analyzed (n=5)
- Excluded from analysis (n=0)

5 new/11 refractory DM
Outcome Measures

- MD and Patient Global Assessment
- MMT and quantitative myometry
- Quality of Life (SF-36)
- Functional testing
- IMACS DOI

Amato, Ann Neurol, 2011
Principal Outcomes

1. Adverse events
2. Average prednisone dose after week 24
3. Time from randomization to treatment failure

Amato, Ann Neurol, 2011
Results: Adverse Events

• No significant differences in adverse event rates between the treatment groups (although 5 ETN-treated and 1 placebo-treated subject developed worsening rash)

Amato, Ann Neurol, 2011
Principal Outcomes

1. Adverse events
2. Average prednisone dose after week 24
3. Time from randomization to treatment failure

Amato, Ann Neurol, 2011
Other Results

• Median prednisone dose after week 24:
  – Placebo arm: 29.2mg/day
  – Etanercept arm: 1.2mg/day \( (p=0.02) \)

• Week 52:
  – 6 ETN subjects met IMACS DOI
  – 4/6 remained off prednisone and on no additional treatment

Amato, Ann Neurol, 2011
Principal Outcomes

1. Adverse events
2. Average prednisone dose after week 24
3. Time from randomization to treatment failure

Amato, Ann Neurol, 2011
Results: Time to Treatment Failure

- All 5 subjects receiving placebo were treatment failures (median time to treatment failure = 148 days)
- 5 of 11 subjects in ETN arm were successfully weaned off prednisone (median time to treatment failure = 358 days (p=0.0002))
Conclusions

• No significant AEs in subjects receiving ETN/prednisone/other IS meds compared to placebo

• Design of a forced prednisone taper may be useful to assess steroid-sparing effect of study drug

• Steroid-sparing effect suggests further investigation of ETN in DM is warranted

Amato, Ann Neurol, 2011
Biologic Targets

• TNF – alpha
• Interleukin – 1
IL-1 Blockade (Anakinra) in Myositis

6 PM, 4 DM and 5 IBM refractory patients
- 12 month open-label trial
- 100 mg anakinra/day subcutaneously

Muscle Biopsy
Functional Index (FI)
Disease Activity (DA)

Dorph, ACR abstract, 2009
## Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Month(s) of IMACS Improvement</th>
<th>Month(s) of FI improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>3, 6, 12</td>
<td>3, 6, 12</td>
</tr>
<tr>
<td>PM</td>
<td>3</td>
<td>3</td>
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<tr>
<td>DM</td>
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<td>PM</td>
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</tbody>
</table>

7 of 15 subjects met IMACS definition of improvement

Dorph, ACR abstract, 2009
Muscle Biopsies After Anakinra

• No significant change in the expression of T cells, macrophages, IL-1α, IL-1β, IL-1Ra, or MHC class I expression on fibers

"The clinical effect of anakinra could not be explained by reduced inflammation in muscle tissue, thus the role of IL-1 in myositis is still uncertain"

Dorph, ACR abstract, 2009
Biologic Targets

- TNF – alpha
- Interleukin – 1
- B cell
Rituximab in Myositis

• Open label study uncontrolled pilot trial in 7 adult refractory DM pts
  – Levine, Arth Rheum, 2005

• Effective in antisynthetase syndrome
  – Brulhart, Ann Rheum Dis, 2006
  – Sem, Rheumatol, 2009

• Effective in refractory myositis and DM rash (some longstanding remission)
  – Mok, J Rheumatol, 2007

• Ineffective for DM rash
  – Chung, Arch Dermatol, 2007
## AutoImmunity and Rituximab (AIR) Registry

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease</th>
<th>Age, years</th>
<th>Sex</th>
<th>Disease duration, years</th>
<th>Previous treatment</th>
<th>No. of infusions x dose, mg</th>
<th>Concomitant IS</th>
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<td>MMF + IVIG</td>
</tr>
</tbody>
</table>

Source: Couderc, Rheumatol, 2011
AIR Registry Results

- Rtx effective in 16/30 patients
  - CK, steroid-sparing, physician global
- MMT only done in 5 patients
- No IMACS measures used

Couderc, Rheumatol, 2011
Rituximab in Myositis

Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis

Chester V. Oddis, MD
Ann M. Reed, MD
and the RIM Study Group
Participating Centers

**Adult Sites**
- Alabama (Fessler)
- Boston (Narayanaswami)
- Czechoslovakia (Vencovsky)
- Dallas (Olsen)
- Kansas City (Barohn/Latinis)
- Kentucky (Crofford)
- London (Isenberg)
- Mayo Clinic (Ytterberg)
- Miami (Sharma)
- Michigan (Seibold/Schiopu)
- Michigan State (Martin/Eggebeen)
- Milwaukee (Cronin)
- New York: North Shore (Marder)
- New York: HSS (DiMartino)
- NIH (Miller)
- Philadelphia (Kolasinski)
- Phoenix (Levine)
- Pittsburgh (Oddis/Ascherman)
- Stanford (Chung/Fiorentino)
- Sweden (Lundberg)
- UCLA (Weisman/Venuturupalli)

**Pediatric Sites**
- Boston (Kim)
- Cincinnati (Lovell)
- Duke (Rabinovich)
- Mayo Clinic (Reed)
- Miami (Rivas-Chacon)
- Michigan State (Martin/Eggebeen)
- NIH (Rider)
- Nova Scotia (Huber)
- Philadelphia (Sherry)
- Pittsburgh (Kietz)
- Stanford (Sandborg)
- Toronto (Feldman)
RIM Study: Aim

To examine the efficacy of rituximab in refractory adult and juvenile myositis patients in a multicenter 44-week clinical trial enrolling 76 adult PM, 76 adult DM and 50 JDM patients
Randomized Placebo Phase Design (RPPD)

- Subjects randomly assigned, double-blind, to ‘Rtx Early’ or ‘Rtx Late’
- ½ subjects receive drug early and ½ subjects receive drug 8 wks later
- Week 8: last week of ‘randomized placebo-controlled trial’
- No corticosteroids at time of the 4 infusions
- 14 visits (specimens/CSM) over 44 weeks
Primary Endpoint and Hypothesis

• **Primary Endpoint**: Compare the time to DOI between the ‘Rtx Early’ and ‘Rtx Late’ groups

• **Hypothesis**: The time to DOI will be statistically less (shorter) in early vs. late treatment groups
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early Rituximab (n=96)</th>
<th>Late Rituximab (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian race (%)</td>
<td>62 (65)</td>
<td>81 (78)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>43 (18.2)</td>
<td>40 (18.4)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>68 (71)</td>
<td>78 (75)</td>
</tr>
<tr>
<td>IIM subset (PM/DM/JDM)</td>
<td>37/36/23 (n=96)</td>
<td>39/40/25 (n=104)</td>
</tr>
<tr>
<td>Mean disease duration (SD)</td>
<td>5.2 yrs (6.5)</td>
<td>5.4 years (6.0)</td>
</tr>
<tr>
<td>Mean prednisone dose (SD)</td>
<td>19.7 (12.1)</td>
<td>21.4 (14.4)</td>
</tr>
<tr>
<td>Non-corticosteroid immunosuppressive use (%)</td>
<td>84 (88)</td>
<td>89 (86)</td>
</tr>
<tr>
<td>Myositis autoantibody positivity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anti-synthetase</td>
<td>16 (17.8)</td>
<td>16 (15.8)</td>
</tr>
<tr>
<td>• Anti-SRP</td>
<td>13 (14.4)</td>
<td>12 (11.9)</td>
</tr>
<tr>
<td>• DM-associated</td>
<td>33 (36.7)</td>
<td>38 (37.6)</td>
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<tr>
<td>• Other autoantibody</td>
<td>8 (8.9)</td>
<td>16 (15.8)</td>
</tr>
<tr>
<td>None of the above</td>
<td>20 (22.2)</td>
<td>19 (18.8)</td>
</tr>
<tr>
<td>Undefined autoantibody</td>
<td>6</td>
<td>3</td>
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</tbody>
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B cell Numbers Before and After Rituximab

B cells / uL

Week

Early Rtx
Late Rtx
Primary Endpoint

Compare the time to DOI between the ‘Rtx Early’ and ‘Rtx Late’ groups
Primary Outcome: Entire Cohort

Median time to DOI:
Early Rtx = 20.0 weeks
Late Rtx = 20.2 weeks
p = 0.74 (log rank)
Primary Outcome: JDM

Median time to DOI:
- Early Rtx = 11.7 weeks
- Late Rtx = 19.6 weeks
p = 0.32 (log rank)
Overall, 83% (161/195) of subjects met the DOI during the course of the 44-week clinical trial.
Corticosteroid Sparing Effect

There was a significant difference in the mean corticosteroid dose at baseline compared to the final visit.
Retreatment With Rituximab

- 10 subjects (9 evaluable) met criteria for re-treatment with Rtx
- 4 were in ‘Early’ and 5 in ‘Late’ Rtx groups
- 8/9 again met the DOI

<table>
<thead>
<tr>
<th>Weeks to Initial DOI (mean, n=9)</th>
<th>Weeks from DOI to DOW (mean, n=9)</th>
<th>Weeks to Re-treatment DOI (mean, n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.4</td>
<td>16.5</td>
<td>19.9</td>
</tr>
</tbody>
</table>
RIM Study Summary

- The primary and secondary endpoints were not achieved in the RIM Study.
- 83% of refractory adult and juvenile myositis patients met the DOI in this trial.
- There was a significant corticosteroid sparing effect noted in this trial between the baseline dose and the dose at study conclusion.
- Rituximab was generally well tolerated.
RIM Study Conclusions

• Overestimate of the rituximab effect
  – SC postulated >50% would meet DOI by 8 weeks
    ▪ One-half responded by 20 weeks

• Underestimate of placebo effect

• Short placebo phase

• Heterogeneity of myositis
  – Increased variance around time to DOI in both arms

• Subjective Core Set Measures
Biologic Targets

- TNF – alpha
- Interleukin – 1
- B cell
- Other
  - Interleukin – 6
  - Type 1 IFN
IL-6 Blockade in Murine Model of PM

• IL-6 critically involved in development of myositis and muscles expressed IL-6

• Treatment with tocilizumab was effective in amelioration of myositis

• IL-6 blockade is potential new approach to treatment of myositis

• Anti-IL-6 effective/approved for RA

Okiyama, Arth Rheum, 2009
Cluster of genes known to be induced by IFN-α/β
- DM: genes were highly over-expressed compared to controls

Gene expression: Red: high; black: intermed; green: low

Greenberg, Ann Neurol, 2005
Type I IFN Gene Expression in DM

- Results essentially duplicated with blood IFN signature correlating with disease activity.
- Also, multiplex ELISAs demonstrate increased levels of IFN-regulated chemokines that also correlated with disease activity.
  - IP-10, MCP-1, MCP-2

IFN signature, IFN-related cytokines both correlated with disease activity

Cytokine/Chemokine: Modeling

• Combined peripheral blood IFN gene expression profiling, ELISA-based protein measurements in adult DM and JDM study (n=56)
  – IFN-inducible gene score correlated with various parameters of DM disease activity
  – IFN-inducible chemokine profile correlated with gene signature, disease activity scales and CK
  – IL-6 clustered with IFN-inducible chemokine profiles but not with other cytokines related to disease activity

Bilgic, Arth Rheum, 2009
Summary

• Exciting time for therapeutic intervention in myositis

• Suggestion that anti-TNFs might work in spite of generally negative trials
  – Design issues
  – Dosing questions (infliximab)

• B cell depleting therapies also reveal mixed results
  – RIM Study: trial design considerations

• Re-think the outcome measures/response criteria

• Temper our enthusiasm with a respect for all of these novel agents and their short and long-term side effects