Disclosures

Questcor: Advisory Board
Overview

• How does your doctor decide how to treat you
• Simple decisions
• More complex decisions
• How does a newer drug make it on the myositis treatment scene?
Simple Decisions

- Most physicians choose glucocorticoids as their initial treatment
- Methotrexate is often given next or even concomitantly with steroids
- Azathioprine may be given using same rationale
Rationale Behind the Simple Decisions

- Published studies
- Experience of the treating physician
  - Art > Science
- Rheumatology vs. Neurology
  - Methotrexate: rheumatologist
  - Azathioprine: neurologist
Beyond Steroids …Mtx…Imuran

- Many physicians still struggle with this in treating myositis patients
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Including me and the “experts” that you’ll meet over the next 2 days
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- Look at published studies
<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>
</tr>
<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>
<td>Uncontrolled cohort studies</td>
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</tr>
<tr>
<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>
</tr>
<tr>
<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>
<td>Case series</td>
<td>Second-line immunosuppression; some evidence of efficacy in myositis-associated lung disease</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Starting at 2 g/kg/mo given over 2–5 d</td>
<td>Hypertension, volume overload, renal toxicity, headaches</td>
<td>One double-blind, placebo-controlled trial</td>
<td>Second-line immunosuppression for refractory myositis patients; some evidence of efficacy in dysphagia and refractory skin disease; can be used in patients with infection</td>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
<td>For refractory cases; possible use in interstitial lung disease</td>
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- Look at published studies
  - Case series with very few ‘controlled’ trials
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- Experience with agents used for other diseases
General Concepts: Myositis Therapies

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- Borrowed from transplant surgeons
  - Cyclosporine, tacrolimus, MMF (CellCept)
Rituximab in Myositis
RIM Trial

Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis (DM) and Adult Polymyositis (PM)
Summary: Published Trials in IIM (2003)

• 26 prospective myositis trials reviewed
  ➢ 14 adult PM-DM; 5 adult IBM; 5 JDM; 2 adult PM/DM/IBM
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• Problems with trials
  - different myositis classification criteria
  - no uniformity with inclusion/exclusion criteria
  - variability in therapies combined with drug being studied
  - different intervals of assessment
  - no uniformity in outcome measures
‘Perfect Storm’ for RIM Trial

- IMACS
IMACS
International Myositis Assessment and Clinical Studies Group

• Coalition of health care providers with experience and interest in the myositis syndromes

• **Goal**: Improve the lives of children and adults with myositis
  - Discovering better therapies by understanding the causes of myositis
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  - Adult/pediatric/multidisciplinary/international
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• Disease activity and damage measures [Sultan/Isenberg]
Why Use Rituximab in Polymyositis and Dermatomyositis?
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Used over the past couple of years in many different “autoimmune” diseases in both adults and children with encouraging results.
Rituximab in the Treatment of Dermatomyositis

- Open-label uncontrolled pilot trial in 7 adult refractory DM patients
- 4 IV infusions of rituximab at weekly intervals

Levine, Arth Rheum, 2005
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RIM Trial

Facilitated by: IMACS

Supported by: NIAMS, NIAID, Genentech

- 200 myositis patients: 76 adult PM, 76 adult DM and 48 JDM patients
- Patients were followed for 44 weeks
- Myositis Core Set Measures (CSM) were assessed monthly
- Patients met a pre-defined ‘Definition of Improvement’
Participating Centers
Foreign Centers
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)
There are other ways to study or recommend drugs for myositis.
CARRA Approach: JDM
(Childhood Arthritis and Rheumatology Alliance)

• Randomized controlled trials are difficult and expensive
• So…sent survey to pediatric rheumatologists describing clinical JDM cases

Questions:
1. What other tests would your order?
2. What medicines would you start?

• 84% of pediatric rheumatologists responded

• Guidelines on treatment and diagnosis published
  – Steroid, methotrexate guidelines
  – Concern about biologics
  – MRI use (less EMG/muscle biopsy)

Stringer; J Rheumatol; 2010
TMA Approach

- Inadequate classification criteria limits clinical studies

- TMA funded study to redefine criteria for myositis
  - *International Myositis Classification Criteria Project* (Dr. Ingrid Lundberg)

- Lot of data generated from many adult and pediatric rheumatologists around the world
  - Clinical features (muscle, skin, lung etc.)
  - Laboratory tests (enzymes, autoantibodies, etc.)

- **Objective:** develop and validate newer classification criteria for adult/juvenile myositis
Taking Advantage of the IMCCP

• Go back to the doctors that contributed patient data to the project

• Combine collected data with additional treatment data

• Identify patients with a ‘complete response’
  – 6 months of no disease activity while on treatment

• Identify patients with ‘remission’
  – Complete response without treatment for 6 months

• **Goal:** Determine the therapies that lead to ‘complete responses’ or ‘remission’
Collaboration with Basic Scientists: The Value of Specimen Repositories

- Investigator determines a plausible mechanism for immune dysfunction in myositis
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- Type I Interferon (cytokine)
  - genes induced by IFN-I are ‘turned on’
  - proteins are produced from these genes and measured and correlate with clinical disease activity
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• Go from ‘bench to bedside’
  – Treat the patients and study their blood
  – Markers of activity dropped
These studies led to a trial targeting Type I IFN
Summary and Future Directions

• There are many similar examples of cytokines being studied and targeted (IL-6)

• Animal models can provide valuable plausible targets of therapies

• Clinician has an idea and treats several patients and publishes the data

• Stimulating research
  – Databases with longitudinal clinical data tied to a specimen repository
  – Well thought out specimen collection tied to a clinical trial