Discovery, Understanding, and Progress in Myositis

Steven Ytterberg, M.D.

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Disclosures

Financial:

• Dynavax Corp.
• Pfizer
• Mallinckrodt
• American Board of Internal Medicine

Off label use:

• Everything other than steroids and ACTH
What has changed in the last 40 years and what can we look forward to seeing as a result of current research?
Changes Over 40 years

• Diagnosis, defining disease, criteria

• Evaluation

• Understanding pathogenesis

• Treatment
Changes Over 40 years

- Diagnosis, defining disease, criteria
- Evaluation
- Understanding pathogenesis
- Treatment
Idiopathic Inflammatory Myopathies

- Polymyositis (PM)
- Dermatomyositis (DM)

- Isolated, adult
  - Juvenile
  - Malignancy
  - Overlap

Bohan et al., Medicine 56: 255, 1977
PM/DM Classification Criteria

- Proximal muscle weakness
- Elevated serum levels of skeletal muscle enzymes
- Myopathic changes on EMG
- Muscle biopsy evidence of inflammation
- Skin rash

*Definite PM or DM: 4 criteria*

*Probable PM or DM: 3 criteria*

*Possible PM or DM: 2 criteria*

Bohan et al., Medicine 56: 255, 1977
Problems with the Bohan & Peter criteria

- Inclusion body myositis (IBM) can be classified as PM
- Newer autoimmune muscle disorders, e.g., immune-mediated necrotizing myopathy, can be classified as PM
- Doesn’t account for amyopathic DM
Others

• Tanimoto
  *Tanimoto et al., J Rheumatol 1995; 22: 668-74*

• Targoff
  *Targoff et al., Curr Opin Rheumatol 1997; 9: 527-35*

• Dalakas & Hohlfeld
  *Dalakas & Hohlfeld, Lancet 2003; 362: 971-82*

• European Neuromuscular Centre
  *Hoogendijk et al., Neuromuscul Disorder 2004; 14: 337-45*

• International Myositis Classification Criteria Project
  *Lundberg et al., J Intern Med 2016; 280: 39-51*
Amyopathic Dermatomyositis
(Dermatomyositis siné myositis)

**Clinically Amyopathic Dermatomyositis (CADM)**

**Amyopathic DM (ADM)**
Biopsy-confirmed, typical cutaneous DM for ≥ 6 mos with no features of muscle involvement

**Hypomyopathic DM (HDM)**
Cutaneous DM for ≥ 6 mos without weakness but with at least one feature of muscle involvement

Premyopathic DM (PRMDM)

CADM evolving into DM

*Gerami et al., J Am Acad Dermatol 54:597-613, 2006*
Inclusion Body Myositis

• First description
  • *Chou, Science 1967; 158: 1453-5*

• Term “inclusion body myositis”
  • *Yunis & Samaha, Lab Invest 1971; 25: 240-8*

• Comprehensive review and proposed criteria
  • *Griggs et al., Ann Neurol 1995; 38: 705-13*

Inclusion Body Myositis and Myopathies

Robert C. Griggs, MD,* Valerie Askanas, MD, PhD,† Salvatore DiMauro, MD,‡ Andrew Engel, MD,§ George Karpatic, MD,† Jerry R. Mendell, MD,** and Lewis P. Rowland, MD††
Anti-synthetase Syndrome

- Anti-aminocacyl-tRNA synthetase antibodies
- PM/DM
- Interstitial lung disease
- Inflammatory arthritis
- Raynaud’s phenomenon
- Mechanic’s hands
- Fever
# Antisynthetase Antibodies

<table>
<thead>
<tr>
<th>Antigen</th>
<th>tRNA synthetase</th>
<th>JDM*</th>
<th>ADM*</th>
<th>Non-white</th>
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<tbody>
<tr>
<td>Any</td>
<td></td>
<td>1-5</td>
<td>30</td>
<td>AA 29</td>
</tr>
<tr>
<td>Jo1</td>
<td>Histidyl-</td>
<td>2-5</td>
<td>25-30</td>
<td>AA13</td>
</tr>
<tr>
<td>PL12</td>
<td>Alanyl-</td>
<td>1-3</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>PL7</td>
<td>Threonyl-</td>
<td>&lt;1</td>
<td>&lt;5</td>
<td>Japanese 17</td>
</tr>
<tr>
<td>EJ</td>
<td>Glycyl-</td>
<td>&lt;1</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>OJ</td>
<td>Isoleucyl-</td>
<td>&lt;1</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>KS</td>
<td>Asparagynyl-</td>
<td>NA</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>HA</td>
<td>Tyrosyl-</td>
<td>NA</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>ZA</td>
<td>Phenylalanyl-</td>
<td>NA</td>
<td>&lt;1</td>
<td></td>
</tr>
</tbody>
</table>

*Caucasian

Robinson & Reed, Nat Rev Rheumatol 2011; 7: 664-75
Immune-mediated Necrotizing Myopathy

- Characterized by muscle biopsy with necrotic muscle fibers without inflammation
- Specific autoantibodies
  - Anti-SRP
  - Anti-HMGCR
    - Often associated with statin use

Muscle histopathology

a) Normal muscle
b) PM – endomysial inflammation
c) DM – perifascicular atrophy
d) Necrotizing myopathy

Mammen, Nat Rev Neurol 2011; 7:343-54
Changes Over 40 years

- Diagnosis, defining disease, criteria
- Evaluation
- Understanding pathogenesis
- Treatment
Evaluation of Myositis – 1976

• Muscle weakness
• Elevation of muscle enzymes
• Electromyogram (EMG) changes
• Muscle biopsy
Evaluation of Myositis – 2016

• Muscle weakness – validation of testing
• Elevation of muscle enzymes – isotypes
• Electromyogram (EMG) changes
• Muscle biopsy – recognition of IBM and necrotizing myopathy
• MRI of muscle
• MR spectroscopy of muscle
• Muscle elastography?
Evaluation of Myositis – 2016

• Recognition that these are systemic disorders and not just muscle problems
  • Interstitial lung disease
  • Association with other autoimmune disorders
Autoimmune Connective Tissue Diseases

Other terms:
- Overlap CTD
- Undifferentiated CTD
- Mixed CTD
Core Set Measures to Assess IIM

International Myositis Outcome Assessment Collaborative Study Group (IMACS)

- Manual muscle strength testing
- Functional assessment - HAQ or CHAQ
- Global assessment
  - Physician
  - Patient/parent
- Assessment of extra-muscular activity - MDAAT/MITAX or CMAS
- Muscle enzymes - CK, aldolase, AST, ALT, LDH

Rider et al., Arthritis Rheum, 2004; 50: 2281-90
IMACS Preliminary Definitions of Improvement

• 3 of any 6 core set measures improved by ≥ 20%

• With no more than 2 worse by ≥ 25% (which cannot include MMT)

Rider et al., Arthritis Rheum, 2004; 50: 2281-90
Changes Over 40 years

• Diagnosis, defining disease, criteria

• Evaluation

• Understanding pathogenesis

• Treatment
Cytotoxic T-cells Damage Muscle PM/IBM

Arahata & Engel, Ann Neurol 16:193, 1984
Humoral Immune Mechanisms in DM/JDM

• Vasculopathy
• Deposition of complement components in vessels
• Th17 helper cells
Type I Interferon in DM Pathogenesis

• Type I interferon (IFN) activated in patients with DM, as is seen in systemic lupus erythematosus (SLE)

• Type I IFN is a signal generated when the body senses viral infection, among other things

• Type I IFN protects uninfected cells from becoming infected
DM is not PM with a rash
Genetics Factors in DM/JDM

Strongest association with MHC
Non-MHC SNPs:
- PLCL1
- BLK
- CCL21

Miller et al., Arthritis Rheum 2013; 65: 3239-47
Autoantibodies are frequent in IIM
Antibodies

- Immunoglobulin
- Produced by plasma cells in the immune system
- Identify and neutralize viruses and bacteria
- Each recognizes a unique protein (antigen)
Autoantibodies

- Antibodies directed toward an individual’s normal proteins
- Autoantibodies may:
  - Cause disease
  - Simply be markers of disease

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Target</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies (ANA)</td>
<td>Contents of cell nuclei</td>
<td>Lupus and related conditions</td>
</tr>
<tr>
<td>Rheumatoid factor (RF)</td>
<td>IgG</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Anti-Jo-1</td>
<td>Histidyl tRNA synthetase</td>
<td>Polymyositis with ILD</td>
</tr>
<tr>
<td>Anti-PR-3 (c-ANCA)</td>
<td>Neutrophil proteinase-3</td>
<td>Granulomatosis with polyangiitis</td>
</tr>
<tr>
<td>Anti-thyroid antibodies</td>
<td>TPO Thyroglobulin</td>
<td>Hashimoto’s thyroiditis</td>
</tr>
<tr>
<td>Anti-AChR</td>
<td>Acetylcholine receptor on muscle</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Anti-TTG</td>
<td>Tissue transglutaminase</td>
<td>Celiac disease</td>
</tr>
</tbody>
</table>
Description of a Serological Reaction Characteristic of Polymyositis

**Morris Reichlin and Martha Mattioli**

*Departments of Medicine and Biochemistry, SUNY at Buffalo School of Medicine, Veterans Administration Hospital, Buffalo, New York 14215*

Received May 1, 1975

*Reichlin & Mattioli, Clin Immunol Immunopathol 1976; 5: 12-20*
HETEROGENEITY OF PRECIPITATING ANTIBODIES IN POLYMYOSITIS AND DERMATOMYOSITIS

Characterization of the Jo-1 Antibody System

MASAHIKO NISHIKAI and MORRIS REICHLIN

Table 5. Incidence of Jo-1 antibody

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of patients</th>
<th>No. positive</th>
<th>% positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyositis</td>
<td>26</td>
<td>8</td>
<td>30.8</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>22</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Overlap syndromes*</td>
<td></td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>PM-PSS</td>
<td>11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PM-SLE</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PM-RA</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PM-Sjögren's</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Progressive systemic sclerosis</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Progressive muscular dystrophy</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* PM = polymyositis; PSS = progressive systemic sclerosis; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis. Total patients with overlap syndromes was 22.
Non-specific Autoantibodies in Myositis

Percent of Patients with Various Autoantibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>All (n=212)</th>
<th>PM (n=58)</th>
<th>DM (n=79)</th>
<th>CTM (n=36)</th>
<th>CAM (n=13)</th>
<th>IBM (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>52</td>
<td>40</td>
<td>62</td>
<td>77</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>ds-DNA</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>11</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>SSA/Ro</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>17</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>SSB/La</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>19</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Sm</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>U1RNP</td>
<td>11</td>
<td>7</td>
<td>13</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PM/Scl</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RF</td>
<td>6</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Love et al, Medicine 1991; 70: 360-74
## Serologic Subgroups of IIM: Myositis-Specific Antibodies (MSA)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Synthetase</th>
<th>SRP</th>
<th>Mi-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Arthritis, ILD fever, Raynaud’s</td>
<td>Cardiac myalgias; black women</td>
<td>Classic DM</td>
</tr>
<tr>
<td>Rate</td>
<td>Acute</td>
<td>Very acute</td>
<td>Acute</td>
</tr>
<tr>
<td>Severity</td>
<td>Severe</td>
<td>Very severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Season</td>
<td>Spring</td>
<td>Fall</td>
<td>Unknown</td>
</tr>
<tr>
<td>Response</td>
<td>Moderate</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor (70%)</td>
<td>Terrible (25%)</td>
<td>Good (~100%)</td>
</tr>
<tr>
<td>Frequency</td>
<td>20-25%</td>
<td>&lt;5%</td>
<td>5-10%</td>
</tr>
</tbody>
</table>
Myositis Specific Autoantibodies

Betteridge & McHugh, J Intern Med 2015; Epub
Why do MSA matter?

• Understand the cause of disease and/or mechanisms leading to specific clinical features

• Prognosis – may predict:
  • Need for more or less treatment
  • Need for more or less evaluation

• If they cause disease they might be a target for treatment
Changes Over 40 years

• Diagnosis, defining disease, criteria

• Evaluation

• Understanding pathogenesis

• Treatment
Treatment

1976
- Prednisone
- Prednisone
- Prednisone
- ? immunosuppressives

2016
- Prednisone
- Immunosuppressives
- IVIg
- Biologic agents
EFFECTS OF PITUITARY ADRENOCORticTROPIC HORMONE (ACTH) THERAPY

J. R. ELKINGTON, M.D.
A. D. HUNT Jr., M.D.
L. GODFREY, M.D.
W. W. McCORRY, M.D.
A. G. ROGERS, M.D.
and
J. STOKES Jr., M.D.
Philadelphia

The discovery by Hench and co-workers\(^1\) of the dramatic improvement in rheumatoid arthritis induced by the administration of certain steroids of the adrenal cortex and adrenocorticotropic hormone (ACTH) of the pituitary, has provided a clue to the pathogenesis of a wide variety of related diseases. These workers clearly established that 17-hydroxy-11-dehydrocorticoesterone (Kendall's compound E, or cortisone), 17 hydroxycorticosterone (compound P) and pituitary adrenocorticotropic hormone produced immediate remissions in the disease, remissions which lasted as long as these substances were administered. Improvement was also obtained in patients with acute rheumatic fever.\(^2\) Since this report appeared other investigators have confirmed these observations and widened the scope of disease states in which adrenocortical hormones are efficacious. Thorn and co-workers\(^3\) have reported the successful use of pituitary adrenocorticotropic hormone in 9 patients with rheumatoid arthritis, 3 with rheumatic fever, 3 patients with disseminated lupus erythematosus and 1 with gout. Rheumatoid arthritis has also been reported to have responded with good results to cortisone by Boland and Headley\(^4\) and to pituitary adrenocorticotropic hormone by Markson.\(^5\)

These spectacular though transitory therapeutic successes have captivated medical and lay minds alike. Unfortunately, the wide publicity given to the subject has left the impression, at least with the laymen, that the suffering arthritic patient has but to await the volume production of these substances for a complete resolution of his problems. That such is not the case was indicated by the evidence presented at the recent conference of investigators of the problem, sponsored by Armour and Company in Chicago.\(^6\) Two facts were apparent: (1) that the fundamental process by which adrenal cortical steroids affect these diseases is unknown and unmeasured in terms of the known metabolic functions of the adrenal cortex, and (2) that, although the use of pituitary adrenocorticotropic hormone and cortisone in human patients may result in dramatic remissions of these diseases, such use may also be attended with serious complications. The clinical and metabolic studies reported in this paper are a part of this evidence.

**CLINICAL MATERIAL AND METHODS OF STUDY**

Pituitary adrenocorticotropic hormone\(^7\) was administered to 8 patients with the following diseases: juvenile rheumatoid arthritis (2), disseminated lupus erythematosus (2), dermatomyositis (1), acute rheumatic fever (2) and status asthmaticus (1). The duration of therapy and dosage of the compound varied considerably according to the supply of the adrenocortical hormone and to the clinical response of the patient. Treatment was discontinued in 4 patients because of failure to respond or because the supply of the drug was temporarily exhausted. The other 4 patients were treated for prolonged periods as long as one hundred and forty-nine days.

Metabolic studies were conducted for shorter periods at the beginning of administration and later in the course

---

Elkington et al., JAMA, 1949; 141: 1273-9
The discovery by Hench and co-workers of dramatic improvement in rheumatoid arthritis, by the administration of certain steroids of the cortex and adrenocorticotropic hormone from the pituitary, has provided a clue to the possibility of a wide variety of related diseases. These workers have established that 17-hydroxy-11-dehydrocorticosterone (Kendall's compound E, or cortisol) and corticosterone (compound F) and pituitary adrenocorticotropic hormone produced immediate remission in the disease, remissions which lasted as long as substances were administered. Improved results were obtained in patients with acute rheumatic fever and this report appeared other investigators have confirmed these observations and widened the scope of states in which adrenocortical hormones are efficacious. Thorn and co-workers have reported the successful use of pituitary adrenocorticotropic hormone in 9 patients with rheumatoid arthritis, 3 with rheumatic fever, 3 patients with disseminated lupus erythematosus and 1 with gout. Rheumatoid arthritis has also been reported to have responded with good results to cortisone by Boland and Headley and to pituitary adrenocorticotropic hormone by Markson.

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3. Four patients were treated for prolonged periods. One patient with lupus and one with dermatomyositis, both apparently moribund before therapy, have maintained remission of symptoms after cessation of treatment with the drug. One patient with disseminated lupus or generalized collagen disease became refractory to the drug and died. One patient with acute rheumatoid arthritis tended to lose lessening degrees of relief from increasing doses of the adrenocortical preparation, which had to be withdrawn because of the appearance of signs of Cushing's syndrome.
CORTICOTROPHIN AND CORTISONE THERAPY IN DERMATOMYOSITIS

BY

MORGAN McELLIGOTT, M.D., M.R.C.P.I.
Consultant Physician, Portiuncula Hospital, Ballinasloe, Co. Galway

The first report of the treatment of acute dermatomyositis by corticotrophin was published in 1949 by Elkinton and his colleagues; it described the case of a moribund 5-year-old boy suffering from the disease which remitted after a four-weeks course of corticotrophin, following on two shorter unsuccessful trials. Thorn et al. (1950), in their paper on corticotrophin and cortisone, mentioned three cases, in two of which improvement occurred. This was not sustained according to Wedgewood et al. (1953), who described 10 cases and concluded that a cure by these hormones may be expected in the acute case only.

The following three instances demonstrate success and failure from the use of corticotrophin in this condition.

Summary

Three cases of dermatomyositis treated by corticotrophin and cortisone are reported. The literature on this form of therapy is reviewed.

It may be deduced from this review that cortisone or corticotrophin can be a life-saving drug in the acute fulminating attack of dermatomyositis, and in such a case the effect when it occurs is very dramatic. The drug usually fails to improve the more chronic form of the disease, but in view of the occasional success claimed in this category it should never be withheld. Likewise, in dermatomyositis associated with neoplasm a curative effect of the former process by the hormones has been described.

Patterns of Polymyositis and Their Responses to Treatment

CARL M. PEARSON, M.D., F.A.C.P., Los Angeles, California

TREATMENT PROGRAM

Therapeutic trials in polymyositis have, over the years, been many and varied (13). Prior to the discovery of adrenocorticotrophic hormone and the corticosteroids, none of the previous treatments had any noticeable or consistently beneficial effect upon the course of the disease. Now, with sufficient experience has been obtained with the use of the various corticosteroids in these conditions, it seems definite that the natural course of the disease can be satisfactorily altered in many cases. Also, suppression of the disease process is possible in most so that the previous prediction of the over-all mortality rate of 50 per cent (3) can be sharply reduced.

Four points are worthy of emphasis concerning corticosteroid therapy in polymyositis: [1] the earlier the treatment is begun after the appearance of clinical symptoms, the more favorable the outcome; [2] the various types of polymyositis, as classified herein, may respond differently to corticosteroid therapy, both in regard to the rate of improvement and to its eventual completeness; [3] careful and prolonged follow-up care is necessary in all cases; and [4] in the presence of malignancy, corticosteroid therapy is likely to only partially benefit the myopathy and to lose its effectiveness altogether as the malignancy advances.

TREATMENT

Over the years many agents were tried in the treatment of polymyositis, without significant benefit. With the advent of ACTH and the various corticosteroids, the natural course of the disease has been altered and satisfactory suppression is possible in most cases. We believe that every patient with acute polymyositis should receive corticosteroids. The initial dosage in adults should be 50 to 60 mg prednisone in three or four divided daily doses. In some children and in adults with coexistent malignancy or Sjögren’s syndrome, the response will be poor or only temporarily good. In almost all other patients it will be gratifying. Within the past several years a
IMMUNOSUPPRESSIVE THERAPY

There are a number of cases of any type of polymyositis or dermatomyositis that may not respond to corticosteroids, even in full doses over a long period of time. Because of this, and because some cases of polymyositis may represent examples of altered immune response or an autoimmune response, Malaviya and associates successfully used intermittent high-dose intravenous methotrexate in four patients with dermatomyositis, three of whom had recently proved to be refractory to corticosteroids. 54
TREATMENT OF DERMATOMYOSITIS WITH METHOTREXATE

Anand N. Malaviya
M.D. Lucknow

Amira Many
M.D. Jerusalem

Robert S. Schwartz
M.D. New York

From the Clinical Immunology Service, New England Medical Center Hospitals, and the Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

Summary

Four patients with dermatomyositis were treated with intravenous methotrexate. Three of them were refractory to corticosteroids, and one had received no other treatment. Each patient was bedridden by severe muscular weakness before treatment, and one was in the terminal phases of the disease. All patients responded to methotrexate with improvement of muscular strength to normal or near-normal and disappearance of the rash. Concomitantly, laboratory abnormalities indicative of muscle disease disappeared.
What needs to be treated?

• Be clear about the goals of therapy
  • Weakness
  • Rash
  • Shortness of breath
  • Swallowing trouble
  • Inflammatory arthritis
  • Raynaud’s
  • Pain
  • Fatigue
Core Set Measures for Myositis

- Muscle strength
- Physical function
- Patient global assessment
- Physician global assessment
- Muscle enzymes
- Extra-muscle activity

Approach to Management of Myositis

- **Disease**
  - Treat underlying process
  - Immuno-suppressives

- **Inflammation**
  - Corticosteroids

- **Symptoms**
  - Directed therapies
Approach to Management of Myositis

Disease → Inflammation → Symptoms

- Damage
- Treat underlying process
  - Immuno-suppressives
- Corticosteroids
- Directed therapies
My Approach to Prednisone

- Begin 1 mg/kg/d (usually max 80 mg/d)
- Continue 1 month
- 2 weeks each:
  - 40 mg/d
  - 30 mg/d
  - 25 mg/d
  - 20 mg/d
  - 17.5 mg/d
  - 15 mg/d
  - 12.5 mg/d
- 10 mg/d and then decide what next
My Approach to Immunosuppressives

First-line agents
• Methotrexate
• Azathioprine (Imuran)
• Mycophenolate mofetil (CellCept)
• Hydroxychloroquine (Plaquenil) – DM

Second-line agents
• IVIg
• Rituximab (Rituxan)
• Tacrolimus (Prograf)
• Cyclosporine A (Neoral, Sandimmune)
• Leflunomide (Arava)

Severe disease
• Cyclophosphamide (Cytoxan)

Never used
• ACTHAR gel

Studies
• Tocilizumab (Actemra)
• Belimumab (Benlysta)
• Abatacept (Orencia)
Other Things to Remember

- Osteoporosis
- Pneumocystis prevention
- Immunizations
**IVIg Recommendations from Various Expert Groups**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>AAN recommendation</th>
<th>EFNS recommendation</th>
<th>UK NHS recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatomyositis</td>
<td>May be considered for non-responsive patients Level C</td>
<td>Second-line treatment Level B</td>
<td>Appropriate for resistant or aggressive disease Level B</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>Insufficient evidence Level U</td>
<td>Not recommended Level A</td>
<td>Appropriate for resistant or aggressive disease Level B</td>
</tr>
</tbody>
</table>

- **AAN** – American Academy of Neurology
- **EFNS** – European Federation of Neurological Societies
- **UK NHS** – United Kingdom National Health Service
- **Recommendations based on level of evidence**
  - A: Established
  - B: Probable
  - C: Possible
  - U: Insufficient

*Hughes & Lunn, Nat Rev Neurol 2012; 8: 303-5*
Endurance Exercise in PM and DM

- Randomized, controlled trial, n = 21
- 12-week endurance exercise
  - 1 hr, 3 x/week – cycling 30’, 20’ knee extensors
  - 2x/week supervised, 1x/week at home
- Control – no change in exercise program
- Improved:
  - Physical function and vitality on SF-36
  - ADL score, strength
  - $V_0_2$ max
  - Disease activity (7/11 vs. 0/10)

Resistive Home Exercise in PM and DM

- Randomized, controlled trial, n = 19, early active
- Exercise group – with phone support
  - 12 weeks, 5x/week, resistive home exercise and brisk walking
  - 12 weeks, 2x/week home or gym exercise
- Control group – 15’ range of motion and usual walks
- Findings:
  - Improved muscle performance & aerobic capacity, both groups
  - Safe – no increase CK or inflammation on biopsy

Alexanderson et al, J Rheumatol 2014; 41: 1124-32
Exercise for Myositis

- 8 patients (5 DM, 3 PM)
- 7 week resistance exercise program
- Muscle biopsies pre- and post-
- Strength improved
- $\text{VO}_{2\text{max}}$ improved

*Nader et al, Mol Med 2010; 16: 455-64*
Exercise for Myositis

Gene transcript changes in muscle

• Inflammation
  • Downregulation of proinflammatory genes
  • Upregulation of antiinflammatory genes

• Fibrosis
  • Downregulation of profibrotic genes
  • Upregulation of antifibrotic genes

• Other
  • Upregulation of oxidative metabolism genes
  • Downregulation of lipid biosynthesis genes

Nader et al, Mol Med 2010; 16: 455-64
The Future

- Better definitions of the disorders and ability to separate them
- Better ways to evaluate how patients are doing
- Better understanding of pathogenesis
  - What genes are important?
  - What triggers the diseases?
  - What are the mechanisms?
- Better treatment or prevention
Questions?