Therapies for Myositis: How and Why?

2013 TMA Annual Patient Conference
Louisville, Kentucky

Chester V. Oddis, MD
University of Pittsburgh
Director, Myositis Center

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

Beyond Steroids …Mtx…Imuran

- Many physicians still struggle with this in treating myositis patients
- Including me and the “experts” that you’ll meet over the next 2 days

Beyond Steroids …Mtx…Imuran

- Many physicians still struggle with this in treating myositis patients
- Including me and the “experts” that you’ll meet over the next 2 days
- Look at published studies

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

Aggarwal/Oddis, Curr Rheum Rep, 2012

Beyond Steroids …Mtx…Imuran

- Many physicians still struggle with this in treating myositis patients
- Including me and the “experts”
- Look at published studies
  - Case series with very few ‘controlled’ trials

Beyond Steroids …Mtx…Imuran

- Many physicians still struggle with this in treating myositis patients
- Including me and the “experts”
- Look at published studies
  - Case series with very few ‘controlled’ trials
- Experience with agents used for other diseases

General Concepts: Myositis Therapies

- Myositis is inflammatory and autoimmune

General Concepts: Myositis Therapies

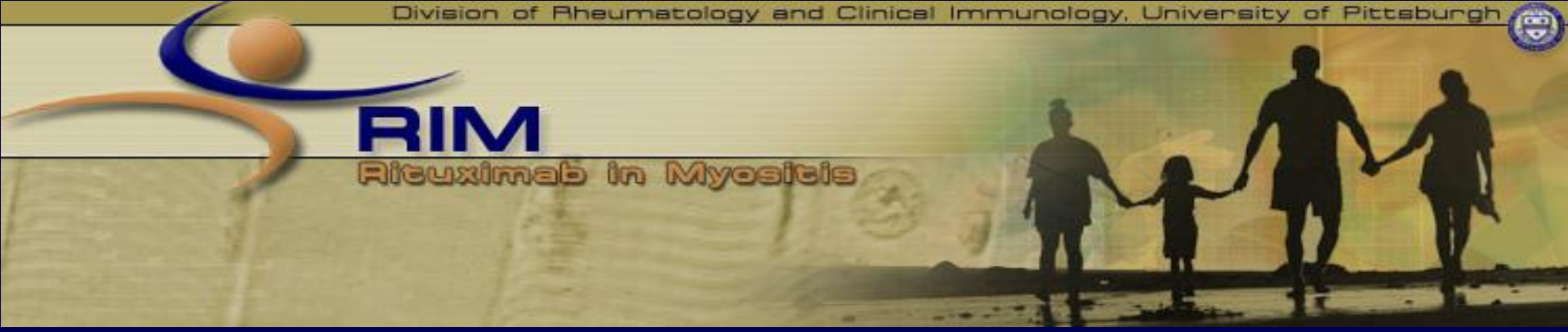
- Myositis is inflammatory and autoimmune
- Drugs will:
  - Decrease inflammation (e.g. steroids)
  - Suppress the immune system

General Concepts: Myositis Therapies

- Myositis is inflammatory and autoimmune
- Drugs will:
  - Decrease inflammation (e.g. steroids)
  - Suppress the immune system
- Borrowed from oncologists
  - Methotrexate, imuran, cytoxan and rituximab

General Concepts: Myositis Therapies

- Myositis is inflammatory and autoimmune
- Drugs will:
  - Decrease inflammation (e.g. steroids)
  - Suppress the immune system
- Borrowed from oncologists
  - Methotrexate, imuran, cytoxan and rituximab
- 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

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
- 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

‘Perfect Storm’ for RIM Trial

- IMACS
  - Adult/pediatric/multidisciplinary/international

‘Perfect Storm’ for RIM Trial

- IMACS
  - Adult/pediatric/multidisciplinary/international
- Agreed upon outcome measures [Miller]

‘Perfect Storm’ for RIM Trial

- IMACS
  - Adult/pediatric/multidisciplinary/international
- Agreed upon outcome measures [Miller]
- Definition(s) of improvement for myositis trials [Rider]

‘Perfect Storm’ for RIM Trial

- IMACS
  - Adult/pediatric/multidisciplinary/international
- Agreed upon outcome measures [Miller]
- Definition(s) of improvement for myositis trials [Rider]
- Consensus on conducting myositis clinical trials [Oddis/Rider]

‘Perfect Storm’ for RIM Trial

- IMACS
  - Adult/pediatric/multidisciplinary/international
- Agreed upon outcome measures [Miller]
- Definition(s) of improvement for myositis trials [Rider]
- Consensus on conducting myositis clinical trials [Oddis/Rider]
- Disease activity and damage measures [Sultan/Isenberg]

Why Use Rituximab in Polymyositis and Dermatomyositis?

Why Use Rituximab in Polymyositis and Dermatomyositis?

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

‘Perfect Storm’ for RIM Trial

- IMACS
  - Adult/pediatric/multidisciplinary/international
- Agreed upon outcome measures [Miller]
- Definition(s) of improvement for myositis trials [Rider]
- Consensus on conducting myositis clinical trials [Oddis/Rider]
- Disease activity and damage measures [Sultan/Isenberg]

RIM Trial

Facilitated by:

IMACS

Supported by:

NIAMS

NIAID

Genentech
IN BUSINESS FOR LIFE

RIM Trial

Facilitated by:

IMACS

Supported by:

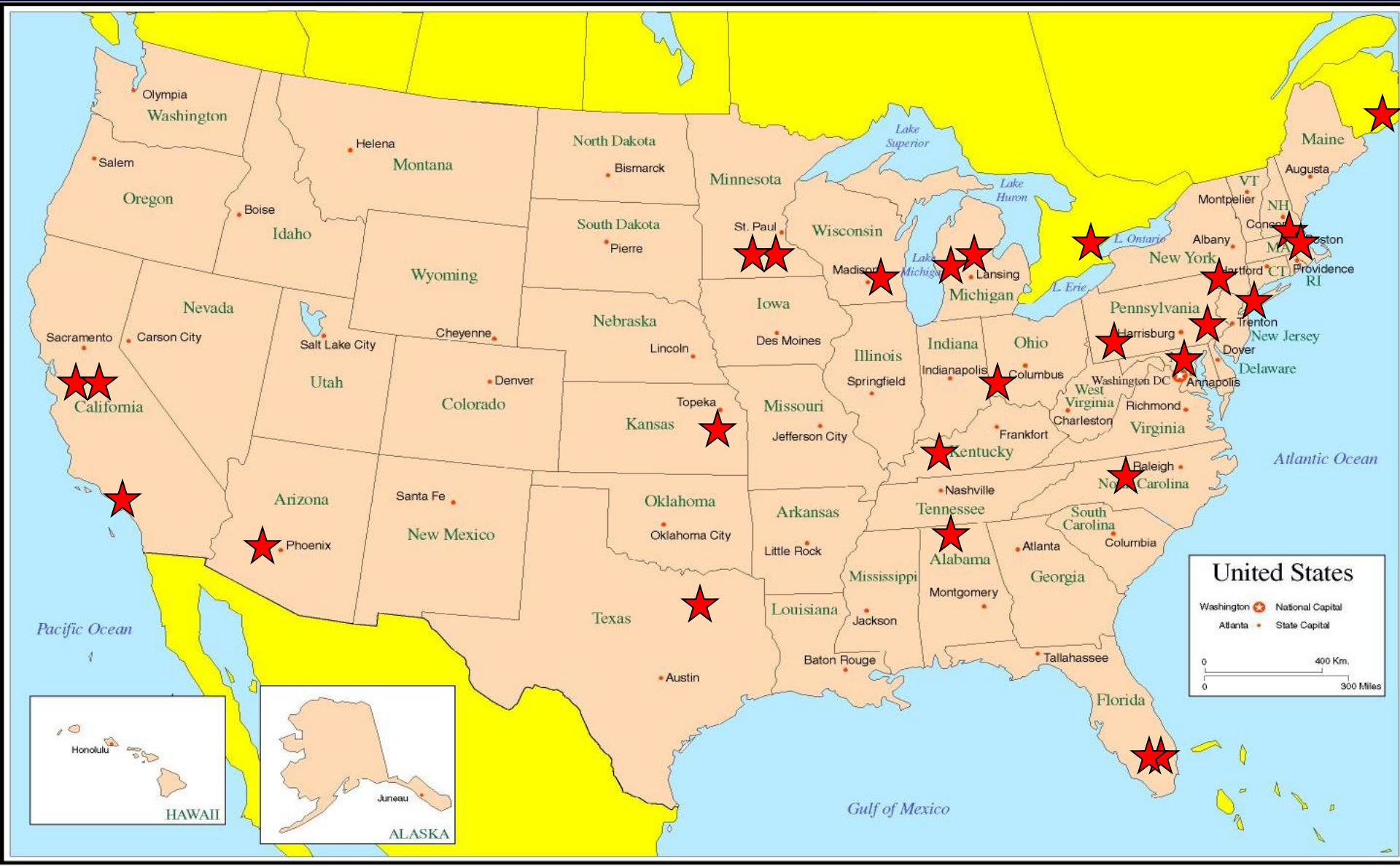
NIAMS

NIAID

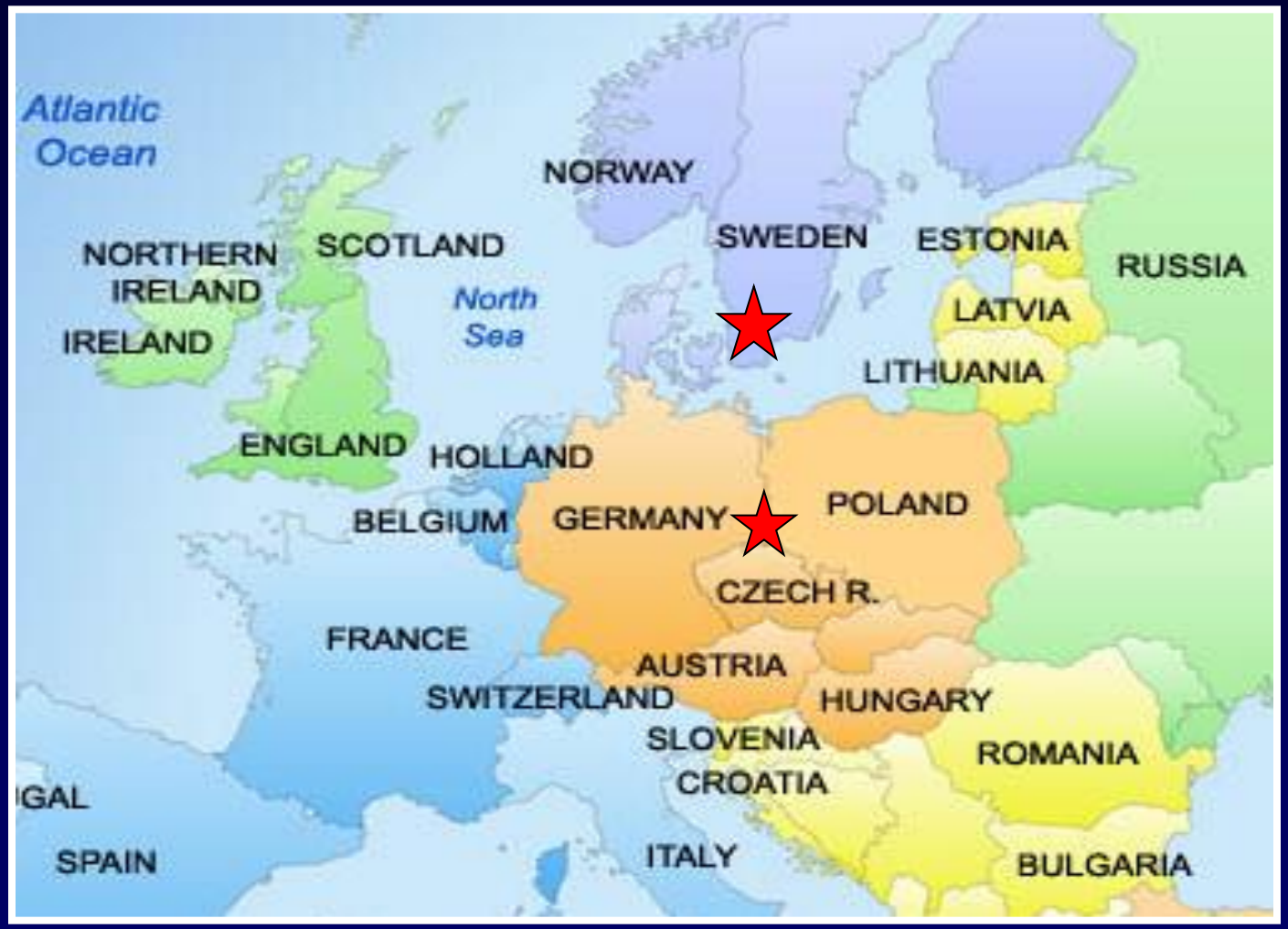
Genentech
IN BUSINESS FOR LIFE

- **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

Collaboration with Basic Scientists: The Value of Specimen Repositories

- Investigator determines a plausible mechanism for immune dysfunction in myositis

- 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

Collaboration with Basic Scientists: The Value of Specimen Repositories

- Investigator determines a plausible mechanism for immune dysfunction in myositis

- 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

- 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