Promising Research in PM and DM

The Myositis Association Meeting

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Relevant Disclosures

Clinical trial investigator and/or medical advisory board member:

- Novartis
- Idera
- Questcor

- Lisa Christopher-Stine, MD, MPH

A Primer: Clinical Trials Phases

- **Phase I:** Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

- **Phase II:** The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.

- **Phase III:** The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

- **Phase IV:** Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.

Glossary of Terms

- **Blinding/Masking**: The treatment assignment is not known to someone
- **Double blind**: Neither the investigator nor the patient know the assignment
- **Placebo**: an inactive substance or procedure ("sham") used as a control
- **Equipoise**: "equal balance of weight"
- **Informed consent**: consent to undergo research procedure after receiving materials outlining known risks, benefits, and alternatives

- **Institutional Review Boards** are authorized to approve, request modification in, or disapprove research activities and to conduct continuing reviews of the research activities at intervals appropriate to the degree of risk, but not less than once a year

Protection of Human Subjects

- Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the **Nuremberg code** was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.

- The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often were, however inadequate to cover complex situations; at times they came into conflict, and they were frequently difficult to interpret or apply. Broader ethical principles were needed to provide a basis on which specific rules may be formulated, criticized and interpreted.

http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

The Belmont Report: 1976

- Develop guidelines to be followed by those conducting research to assure that such research is conducted in accordance with these principles.
- **(i)** The boundaries between biomedical and behavioral research and the accepted and routine practice of medicine **(ii)** The role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subject
- **(iii)** Appropriate guidelines for the selection of human subjects for participation in such research
- **(iv)** The nature and definition of informed consent in various research settings.

Why you *may* be excluded from a clinical trial:

- Disease severity is too mild
- Disease severity is too severe
- Overlapping diseases (lupus, Sjogren's syndrome)
- Concomitant or previous malignancy
- Pregnant or nursing
- Other medical conditions specified by the trial's inclusion criteria
- Concurrent previous use of some medications (monoclonal antibodies such a rituximab)

CURRENT CLINICAL TRIALS IN PM AND DM

Clinical trials.gov

Title: Effects of Exercise Training in Primary Sjogren s Syndrome and Myositis

Purpose: Exercise may improve physical capacity and health parameters in Primary Syndrome s Sjogren and Myositis. Therefore, this study aims to investigate the role of an exercise training program in patients with Primary Syndrome s Sjogren and Myositis.

Study Type: Interventional

Study Design: Randomized

Masking: Open Label

Primary Purpose: Treatment

Status: recruiting

Sponsor: University of Sao Paulo

Estimated Primary Completion Date: December 2014

Title: An Open Trial with TNF Blockade with Infliximab (Remicade®), in Patients with Chronic Inflammatory Myopathies

Purpose: This is a 4 month open trial with TNF-blockade using infliximab (an antibody that blocks TNF) in adult patients with chronic myositis (PM, DM, IBM)) who have persisting muscle weakness and inflammatory active disease despite adequate treatment with immunosuppressives either currently or previously.

Infliximab is given as infusions, 5 mg/kg body weight, these infusions are repeated after 2, 6 and 14 weeks. The study involves 15 adult patients.

Primary outcome measure is muscle function assessed by muscle function index score.

Other outcome measures are Myositis Disease Activity core set: Patient's global assessment and physicians global assessment on visual analogue scales (VAS). Manual muscle test, Health assessment questionnaire (HAQ), serum levels of CPK, LD and extra muscular disease activity score. Muscle biopsy, Magnetic resonance imaging (MRI) of thigh muscles and Health related Quality of life, measured by SF-36.

Status: completed

Sponsor: Karolinska Institutet

Title: High Dose Cyclophosphamide & ATG With Hematopoietic Stem Cell Transplantation in Patients With Refractory Idiopathic Inflammatory Myopathy Diseases: A Phase I Trial

Purpose: This study is designed to examine whether treating patients with high dose cyclophosphamide and ATG, followed by return of previously collected blood stem cells will stop the progression of myositis.

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment
Status: recruiting
Sponsor: Northwestern University
Estimated Primary Completion Date: December 2015

Title: A Phase 2 Open-label Study to Evaluate the Long-term Safety of Sifalimumab in Adult Subjects with Systemic Lupus Erythematosus or Myositis

Purpose: To assess the safety and tolerability of sifalimumab in adult subjects with active systemic Lupus Erythematosus (SLE) or active dermatomyositis (DM) or polymyositis (PM) who participated in the following clinical studies: MI-CP151, MI-CP152, or MICP179.

Study Type: Interventional

Study Design: Endpoint Classification: Safety Study

Intervention Model: Single Group Assignment

Masking: Open Label

Primary Purpose: Treatment

Status: This study is ongoing, but not recruiting participants

Sponsor: MedImmune LLC

Estimated Primary Completion Date: March 2015

Title: A Phase 2 Open-label Study to Evaluate the Long-term Safety of Sifalimumab in Adult Subjects with Systemic Lupus Erythematosus or Myositis

Purpose: To assess the safety and tolerability of sifalimumab in adult subjects with active systemic Lupus Erythematosus (SLE) or active dermatomyositis (DM) or polymyositis (PM) who participated in the following clinical studies: MI-CP151, MI-CP152, or MICP179.

Study Type: Interventional

Study Design: Endpoint Classification: Safety Study

Intervention Model: Single Group Assignment

Masking: Open Label

Primary Purpose: Treatment

Status: This study is ongoing, but not recruiting participants

Sponsor: MedImmune LLC

Estimated Primary Completion Date: March 2015

Title: A Randomized, Double Blind Controlled Trial Comparing Rituximab against Intravenous Cyclophosphamide in Connective Tissue Disease Associated Interstitial Lung Disease

Purpose: This study has been initiated to evaluate the efficacy of rituximab (compared with standard therapy) in patients with progressive CTD related ILD.

Study Type: Interventional

Study Design: Allocation: Randomized

Endpoint Classification: Efficacy Study

Intervention Model: Parallel Assignment

Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)

Primary Purpose: Treatment

Sponsor: Royal Brompton & Harefield NHS Foundation Trust

Status: This study is not yet open for participant recruitment.

Estimated Primary Completion Date: June 2016

Title: An Open Label Study Evaluating the Safety and Efficacy of Apremilast in the Treatment of Cutaneous Disease in Patients with Dermatomyositis

Purpose: This study is designed to evaluate the safety and efficacy of an oral medicine (called apremilast) for treating skin involvement in patients with the disease dermatomyositis.

Study Type: Interventional

Study Design: Allocation: Non-Randomized

Endpoint Classification: Safety/Efficacy Study

Intervention Model: Single Group Assignment

Masking: Open Label

Primary Purpose: Treatment

Sponsor: Stanford University

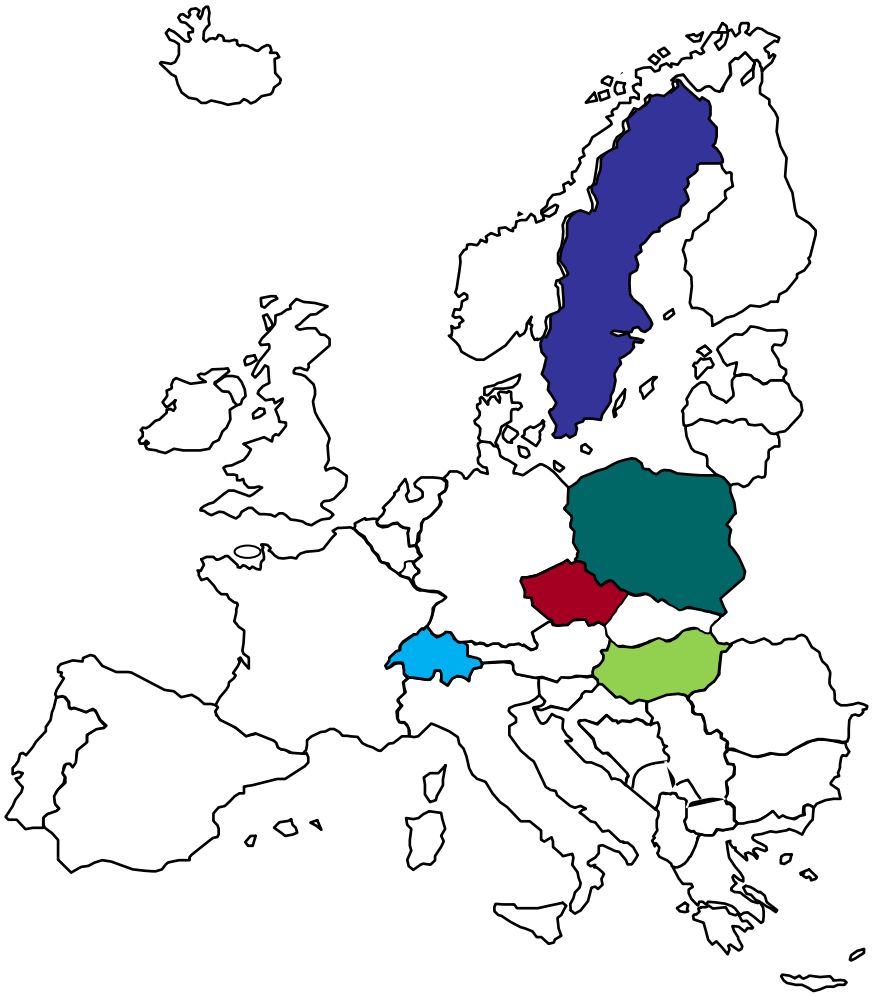
Status: Unknown

Estimated Primary Completion Date: ?

A prospective, randomized, open-label, assessor-blind, multicenter study of efficacy and safety of combined treatment of MTX+GC vs. GC alone in patients with PM and DM

(PROMETHEUS trial)

Multi-Center study in Europe



- Question
  - How beneficial is to use combined therapy from early stages of the disease
- Hypothesis
  - GC sparing effect in MTX arm
- Primary endpoint
  - total dose of glucocorticoids (in mg/kg weight) administered between baseline and week 48

- Secondary endpoints
  - Muscle strength by manual muscle testing
  - Assessment of disease activity and damage
  - Muscle enzyme levels
  - Muscle endurance
  - Final glucocorticoid dose
  - Glucocorticoid related side-effects
  - Disability index
  - Quality of life
  - Number of patients with treatment failures

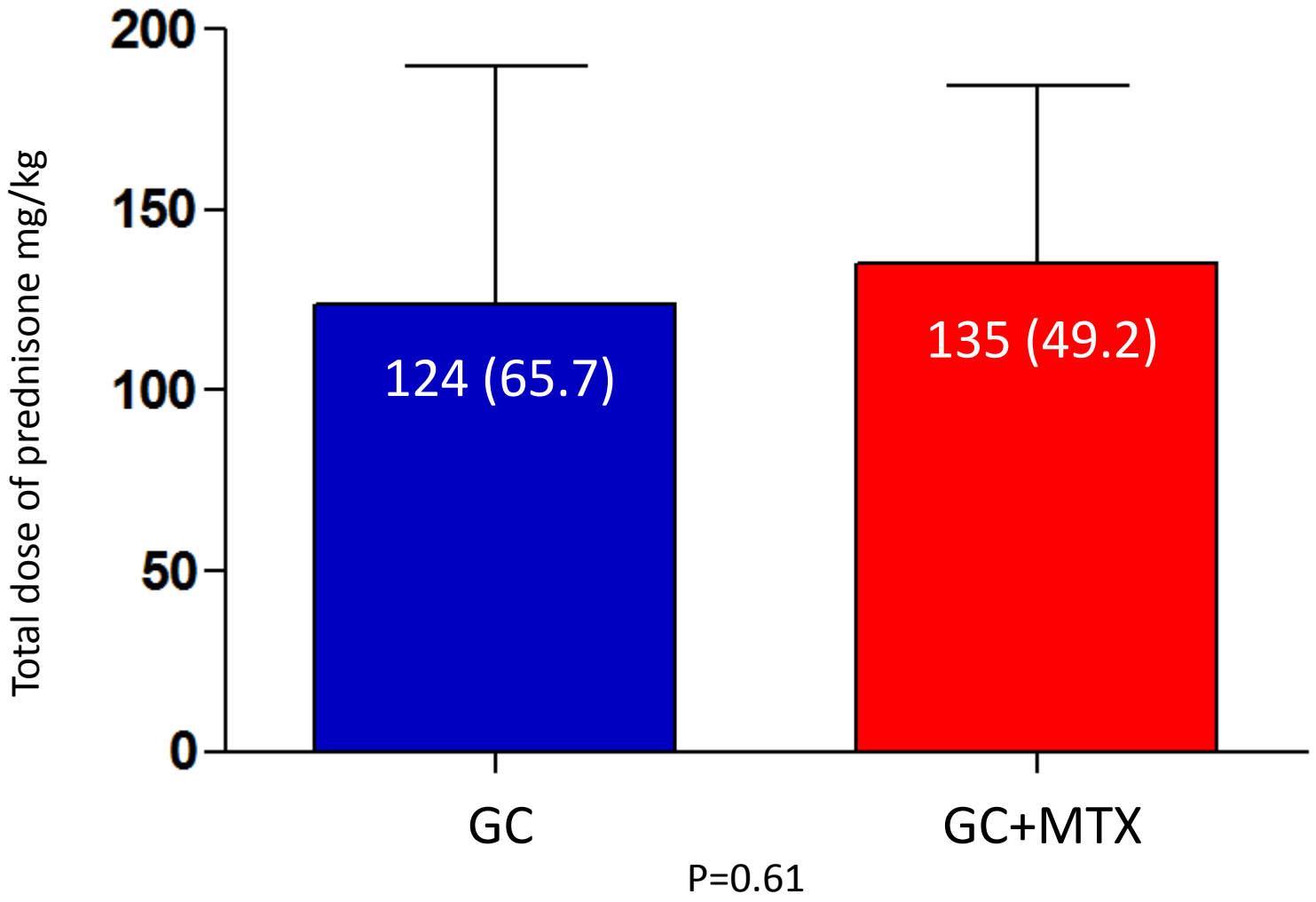
Methods

- Open label, assessor-blind
- Main inclusion criteria
  - PM and DM
  - Physician's own judgement of the disease activity that requires high dose immunosuppressive treatment (weakness, muscle enzymes, MRI…)
  - Previously untreated patients with the exception of GC treatment up to 8 weeks

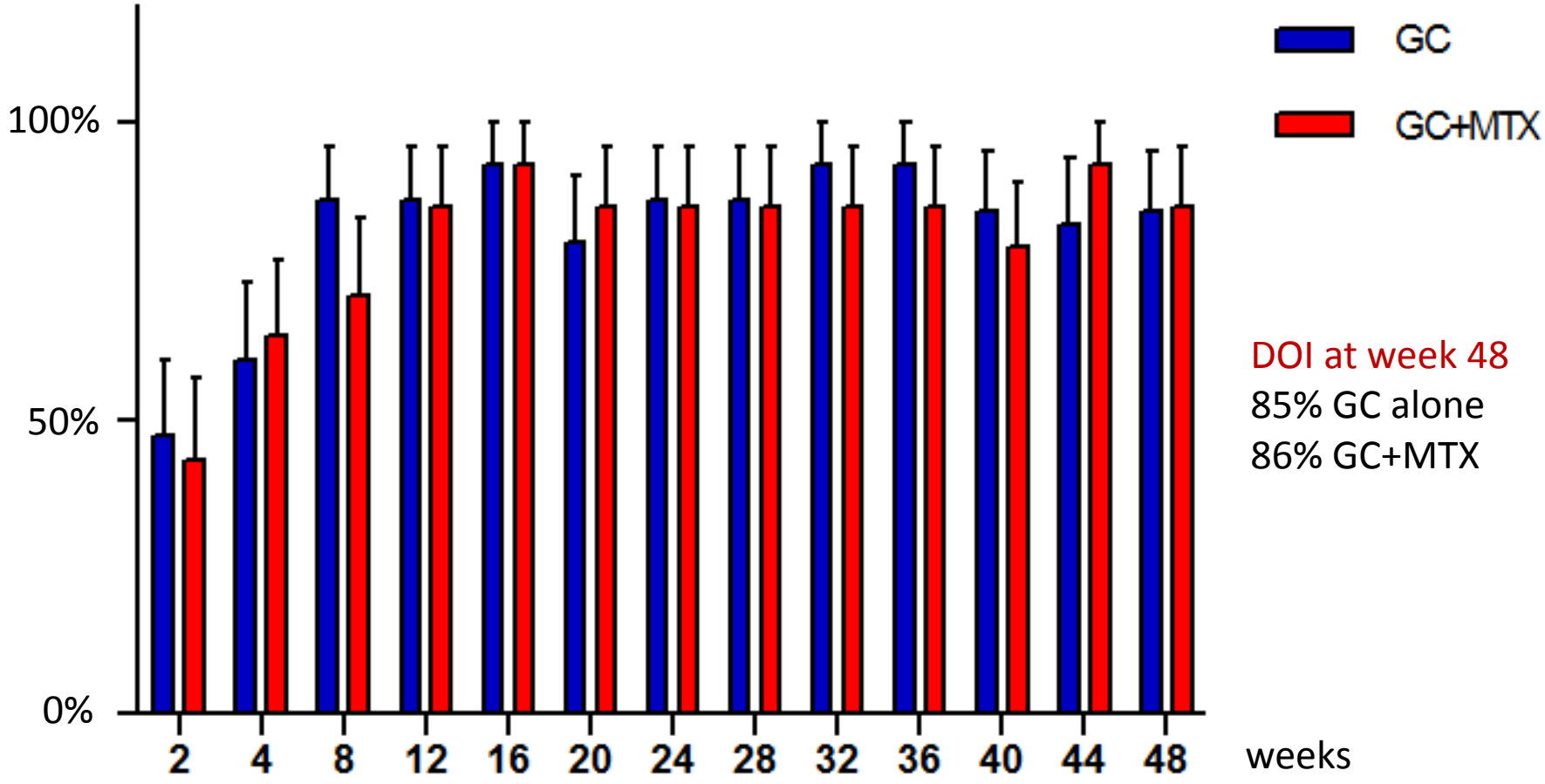
Definition of Improvement (DOI)

≥ 20% improvement in 3 of any 6 core set measures
(MMT, MD global, patient global, HAQ, muscle enzymes, extramuscular)
with no more than 2 CSM worsening by ≥ 25% (excluding MMT)

Total dose of prednisone in mg/kg



Patients meeting Definition of Improvement (DOI) during trial



Conclusions

- No difference in primary and secondary endpoints
- Good effect in both arms – DOI achieved in a majority of patients from week 12
- No difference between PM and DM
- No difference in adverse events

Title: Abatacept Treatment in Polymyositis and Dermatomyositis

Purpose: The purpose of this study is to investigate the clinical efficacy of abatacept on disease activity in polymyositis, and dermatomyositis patients.

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Single Group Assignment
Masking: Single Blind (Outcomes Assessor)
Primary Purpose: Treatment
Sponsor: Karolinska Institutet

J Rheumatol. 2014 Jun;41(6):1124-32. doi: 10.3899/jrheum.131145. Epub 2014 May 1.

Resistive home exercise in patients with recent-onset polymyositis and dermatomyositis -- a randomized controlled single-blinded study with a 2-year follow-up

Alexanderson H1, Munters LA2, Dastmalchi M2, Loell I2, Heimbürger M2, Opava CH2, Lundberg IE2.

Abstract

OBJECTIVE: To evaluate the outcome of resistive home exercise and its possible longterm influence on health, disability, and disease activity in patients with active polymyositis (PM) or dermatomyositis (DM).

METHODS: Nineteen patients with recent-onset PM/DM were included after introduction of high-dose prednisolone. They were assessed by independent assessors as to perceived health, muscle performance, aerobic capacity, and serum creatine phosphokinase (CPK) at baseline and after 24 weeks, including repeated muscle biopsies at 24 weeks (single-blinded randomized controlled study), and in an open-label followup at 52, 78, and 104 weeks. Patients were randomized to 12 weeks, 5 days/week resistive home exercise with telephone support and encouragement for another 12 weeks of twice-a-week home or gym exercise (EG, n = 10) or to 24 weeks, 5 days/week range of motion exercise (CG, n = 9). Patients in the CG group without inflammatory infiltrates in muscle biopsies at 24 weeks were invited to the 12-week resistive home exercises.

RESULTS: At baseline, the EG had poorer perceived health, but otherwise the groups were comparable. At 24 weeks, both groups improved in muscle performance and aerobic capacity ($p < 0.001$ to < 0.05) with no signs of increased inflammation assessed by CPK levels or muscle biopsies. Both groups improved in muscle performance and aerobic capacity up to 52 weeks ($p < 0.05$) lasting to 104 weeks in the EG ($p < 0.05$) and presented minor improvements in perceived health.

CONCLUSION: Our study supports the safety of resistive exercise in patients with active PM/DM but did not reveal any between-group differences in exercise effects. An individually adapted physical therapist-supervised home exercise program might be recommended in early active PM/DM, with regular evaluation of muscle performance and health.

CURRENT U.S. TRIALS

Title: Novel Drug Delivery of Sodium Thiosulfate for Calcinosis Associated With Adult and Juvenile Dermatomyositis

Purpose: The investigators have designed a pilot study to evaluate the use of topical sodium thiosulfate solution in treating superficial calcinosis in individuals with juvenile and adult dermatomyositis. The investigators will use laser to assist in the delivery of this medication to areas of calcinosis.

Study Type: Interventional

Study Design: Endpoint Classification: Safety/Efficacy Study

Intervention Model: Single Group Assignment

Masking: Single Blind (Outcomes Assessor)

Primary Purpose: Treatment

Sponsor: George Washington University

Status: recruiting

Estimated Primary Completion Date: August 2014

Title: Tocilizumab in the Treatment of Refractory Polymyositis and Dermatomyositis

Purpose: The purpose of this multi-center pilot study is to determine if the drug tocilizumab (Actemra) is effective in the treatment of patients with refractory adult polymyositis (PM) and dermatomyositis (DM).

Study Type: Interventional

Study Design: Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Intervention Model: Parallel Assignment

Masking: Double Blind (Subject, Caregiver, Investigator)

Primary Purpose: Treatment

Sponsor: University of Pittsburgh

Status: This study is not yet open for participant recruitment.

Estimated Primary Completion Date: August 2016

Title: Open Label Proof of Concept Study to Evaluate Efficacy and Safety of Adrenocorticotropic Hormone Gel in Refractory Dermatomyositis or Polymyositis

Purpose: To evaluate the effectiveness of the ACTH Gel in people diagnosed with DM/PM. The study doctors want to evaluate whether ACTH Gel will improve the symptoms of this disease. This drug is approved by the Food and Drug Administration (FDA) for dermatomyositis (DM) and polymyositis (PM). ACTH gel has been an FDA-approved treatment for myositis since 1952, and in 2010 the FDA retained PM and DM as diseases approved for ACTH gel use.

Sponsor: University of Pittsburgh

Status: recruiting

Estimated Primary Completion Date: November 2015

Title: A Double Blind, Randomized, Placebo-controlled Study to Evaluate, Safety, Tolerability, Efficacy and Preliminary Dose-response of BAF312 in Patients With Active Dermatomyositis.

Purpose: This study investigates the dose response relationship for the efficacy and safety of BAF312 compared to placebo in active DM patients over a treatment period of 6+6 months and to determine the minimum dose required for a maximal clinical effect. The study is composed of 2 periods: a double-blind period I with BAF312 administered at different daily doses (0.5, 2, 10 mg and placebo) and a fixed-dose Period II in which BAF312 will be administered at the dose of 2 mg daily.

*BAF312 (Fingolimod) is a sphingosine-1-phosphate receptor modulator for oral use. It agonizes the S1P receptor, preventing autoimmune lymphocytes from moving from the lymphoid organs to points of damage (muscle)

Study Type: Interventional

Study Design: Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Masking: Double Blind (Subject, Investigator, Outcomes Assessor)

Sponsor: Novartis Pharmaceuticals

Status: recruiting

Estimated Primary Completion Date: January 2016

Title: A Multi-Center Double-blind, Placebo Controlled, Proof of Concept Study to Evaluate the Efficacy and Tolerability of BAF312 in Patients with Polymyositis

Purpose: This study will assess the efficacy, safety and tolerability of BAF312 administered orally in patients with clinically active polymyositis who have shown inadequate response to corticosteroids and or DMARDs.

Study Type: Interventional

Study Design: Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: Double Blind (Subject, Investigator)

Primary Purpose: Treatment

Sponsor: Novartis Pharmaceuticals

Status: recruiting

Estimated Primary Completion Date: January 2016

Protocol 8400-211: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial of IMO-8400 in PM, NM, and DM

PROTOCOL REVIEW 29 AUGUST 2014

Protocol 8400-211 - What are we trying to achieve?

Is IMO-8400 safe and effective in patients with myositis?

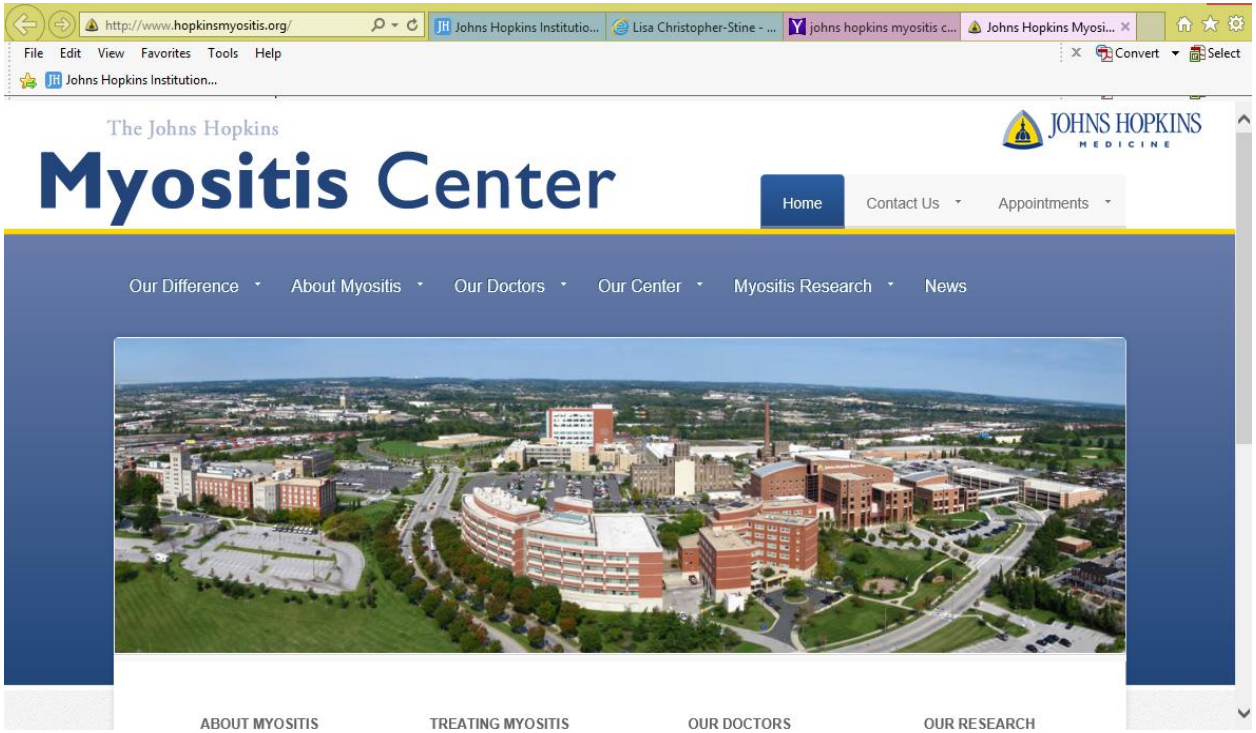
- IMO-8400 is a second-generation, oligonucleotide antagonist of toll-like receptors (TLR) 7, 8 and 9. The natural ligands for these intracellular TLRs are exogenous RNA / DNA characteristic of foreign pathogens (PAMPs). TLR activation and cytokine induction can also result from endogenous nucleic acids released from injured cells (DAMPs).

- Although the initial cause of myositis is unknown, once inflammation is present, the injured muscle cells release DAMPs, including nucleic acids. Functional TLRs are expressed on the regenerating muscle cells that develop to replace the injured ones. These TLRs react to the DAMPs released from damaged muscle cells and amplify the inflammatory response. Therefore TLRs directly contribute to ongoing muscle inflammation (myositis) resulting in further muscle damage.

- **By blocking activation of TLRs 7,8 and 9, IMO-8400 may provide a novel treatment approach for myositis by interrupting the cycle of pro-inflammatory activation that causes ongoing muscle inflammation.**

THANK YOU!

http://www.hopkinsmyositis.org/



*If you are interested in our upcoming clinical trials, please call my research assistant Will Kelly at **410-550-9005** to express your interest to be placed on our waiting list.