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Myositis papers published in the last two years

- Inclusion body myositis – 103 papers
- Polymyositis – 247 papers
- Skeletal muscle regeneration – 253 papers
- Alzheimer's disease - 6812

Research Topics Covered

- 2 relevant drug trials
- Exercise and dietary supplements in PM
- Statin use and myositis – a connection?
- Study underscoring difficulty in PM diagnosis
- Advances in muscle regeneration with possible relevance to myositis
- Autophagy in IBM

Etanercept for IBM

- Pilot trial of etanercept in the treatment of inclusion-body myositis
- Barohn et al, *Neurology*, 2006
- TNF α inhibitor
- 9 patients treated for average of 17 mo.
- Handgrip and elbow flexion compared to untreated patients
 - No difference at 6 months
 - Handgrip improved at 12 months
- Conclusions
 - Larger, placebo-controlled trial needed
 - Trial may need to be longer than 6 months.

Rituximab for Polymyositis

- Rituximab for Refractory Polymyositis: An Open-label Prospective Study
- To et al., *Journal of Rheumatology*, 2007
- Antibody binds to CD20 on B-cells
- Most recent in a series of open-label studies
- Four patients studied – had not responded to steroids plus two other medications
- 2 patients had clinically meaningful improvements in strength
- Conclusion – More reason to be hopeful about ongoing clinical trial of Rituximab (Dr. Oddis)

Benefits of Intensive Resistance Training in Patients With Chronic Polymyositis or Dermatomyositis

- Alexanderson et al., *Arth & Rheum*, 2007
- 5 DM and 3 PM patients on prednisone and other meds.
- Exercised 3 days/week
 - 10 min treadmill warm-up at 50% max heart rate
 - 45 minute exercise program
 - First week
 - 50% of 10 voluntary repetition maximum (VRM)
 - Five muscle groups
 - 3 sets separated by 90 second rests
 - 5 minutes of stretching
 - Following two weeks
 - Resistance gradually increased to 100% of individual VRM in 10 reps per set
 - After 3 and 5 weeks, new 10 VRM tests and new exercise loads

Benefits of Intensive Resistance Training in Patients With Chronic Polymyositis or Dermatomyositis

Number of Responders after 7 weeks of exercise (% increase in 10 VRM)

Also: No patient had signs of increased muscle inflammation (biopsied before and after exercise program)

Conclusions: Patients with chronic, stable PM and DM can safely perform this intensive exercise program with beneficial effects

Creatine Supplements in Patients With Idiopathic Inflammatory Myopathies Who Are Clinically Weak After Conventional Pharmacologic Treatment: Six-Month, Double-Blind, Randomized, Placebo-Controlled Trial

- Chung et al., *Arth & Rheum*, 2007
- 37 DM and PM patients (!), all on home exercise program
- Creatine 20 grams/day for 8 days, then 3 grams/day
- Improved “aggregate functional performance time” with creatine at 6 months
 - 50-foot timed walk
 - Stair ascent and descent tests
 - “get up and go test”
- Shoulder abduction and hip flexion strength improved with creatine at 3 and 6 months
- Conclusions: Works in DM and PM. Need an IBM trial.

Statins and myositis...

- Statin and statin-fibrate use was significantly associated with increased myositis risk in a managed care population
- McClure et al., *J Clin Epidemiol*, 2007
- Kaiser Permanente Colorado MCO
- Age 40-89
- 1999-2003
- 187,765 members studied

Statins and myositis...

- Myositis cases identified by CK > 10 times normal AND indications of myopathy in medical claims
- 98% of statins were lovastatin or simvastatin
- Statin use: 2.8-fold increased risk of “myositis”
- Statin-fibrate use: 9-fold increase in “myositis”

Conclusions from statin paper

- 1 of 1000 patients developed “myositis” as a result of statin use
- 1 of 40 patients treated with statins had a heart attack prevented
- However, I suspect this paper underestimates the number of patients who develop myositis (many patients with DM do not have > 10-fold increase in CK levels)
- Remaining question: Is it risky for patients with myositis to take statins??

Polymyositis Misdiagnosis

- Phenotypic Study in 40 Patients With Dysferlin Gene Mutations
- Nguyen et al., *Arch Neurol*, 2007
- 40 patients with mutations in the dysferlin gene (causes limb girdle muscular dystrophy)
- 10 of these were originally misdiagnosed as polymyositis because of inflammatory muscle infiltrates, rapid progression, and/or pain

New drugs to promote muscle regeneration? The losartan story...

- Angiotensin II type 1 receptor blockade attenuates TGF- β -induced failure of muscle regeneration in multiple myopathic states
- Cohn et al., *Nature Medicine*, 2007
- Patients with Marfan syndrome (MFS) are unable to increase muscle mass despite physical exercise
- Excessive signaling by TGF- β causes other manifestations of MFS (e.g., aortic dissection)
- Losartan is widely used to treat hypertension and also inhibits TGF- β pathway
- This study showed:
 - Losartan normalizes muscle in mouse model of MFS
 - Losartan normalizes muscle in mouse model of Duchenne muscular dystrophy

Losartan normalizes muscle in mouse model of Duchenne muscular dystrophy

Losartan for myositis?

- Clinical trials for losartan in Duchenne muscular dystrophy are being planned
- Unclear whether this will work in humans...
- Unclear whether this will work in other muscle diseases...
- Should patients with myositis take losartan? Could help, do nothing, or cause harm...
- What I tell my patients... "If you're taking a blood pressure medicine anyway, it's reasonable to consider losartan."

Augmenting muscle regeneration: more on the TGF- β pathway

- Quadrupling Muscle Mass in Mice by Targeting TGF- β Signaling Pathways
- Se-Jin Lee, *PLoS ONE*, 2007
- Already known that
 - Myostatin is a TGF- β family member that limits skeletal muscle growth
 - Mice, sheep, dogs, and humans with no myostatin have significantly increased muscle mass (2-fold). This is basis for MYO-029 trial.
 - Follistatin can bind myostatin and overexpressing follistatin leads to increased muscle mass

Se-Jin Lee, *PLoS ONE*, 2007

- This study: Follistatin was over-expressed in mice lacking myostatin
- These mice had 4-fold increased muscle mass (compared to 2-fold increase in myostatin mutants)
- What it means: Follistatin probably binds to – and blocks - other TGF- β -like substances in the blood that inhibit muscle growth

How are TGF- β , myostatin, and follistatin studies relevant to muscle disease?

- Losartan
- Other possible therapies
 - Develop a follistatin-like drug to reduce myostatin levels
 - Identify the other TGF- β -like substances and find ways to block them
- Useful for myositis? Perhaps...
 - TGF- β expression is up-regulated in DM muscle (Confalonieri et al., *J Neuropath Exp Neurol*, 1997)
 - “Myostatin is increased and complexes with amyloid- β within sporadic inclusion-body myositis muscle fibers.” (Wojcik et al, *Acta Neuropathol*, 2005.)

β -amyloid is a substrate of autophagy in sIBM

- Lunemann, et al, Neurology, 2007
- Cells have two major ways to degrade proteins
 - Ubiquitin-proteasome system
 - Lysosomal degradation - intracellular proteins carried to lysosomes by autophagosomes
- This paper showed that APP/ β amyloid is present in autophagosomes in IBM
- “harnessing the autophagic pathway could have therapeutic merit.”