How do I approach the patient with myalgias while on statins

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Disclosures

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Consultant  Merck, CSL
Research  Merck, CSL
Terminology

As defined by NLA Statin Safety Task Force:

**Myalgia** – muscle complaints without CK elevations

**Myopathy** – muscle complaints with CK elevation

**Rhabdomyolysis** – CK levels >10,000 or CK >10x ULN with elevated creatinine level

McKenney, *Am J Cardiol.* 2006
Incidence

RCTs:
- muscle complaints range from 1.5-3.0%
- myopathy occurs in 5 pts/100,000 person yrs
- rhabdo occurs in 1.6 pts/100,000 person yrs

Incidence

Issues with using RTC data

• Trial participants
  – Are generally younger and healthier than patients in the clinical setting
  – Trial participants are followed more closely
  – High Risk patients are excluded

• Most trials have had a run in period – excludes sensitive persons

• In PROVE-IT (no run in) rate was 3-5%

Symptoms of Myopathy

• Muscle weakness, or bilateral proximal muscle pain with no obvious cause are more specific symptoms, and such patients should have their creatine kinase measured.

• Myopathy is present if creatine kinase is more than ten times the upper limit of normal.

• Typically, ALT and AST are also elevated
Clinical Risk Factors for Myalgia

- **Patient-Related Risk Factors:**
  - Female, advanced age, low BMI
  - Hypothyroidism
  - Inherited muscle disorders
  - Heavy Alcohol Consumption
  - Heavy exercise
  - Chronic kidney or liver dz

Genetic risk for myopathy SNP in SLCO1B1 Chromosome 12

Organic anion transport protein OATB1P1 regulates hepatic statin uptake

60% of myopathy episodes in SEARCH

Prevalence of the allele was 15%
• OR for myopathy 4.5 per copy of C allele
• 16.9 for CC as compared to TT genotype

Figure 3. Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype.

SEARCH collaborative gp, NEJM 2008
The most common uncommon causes of statin intolerance

Account for 5% or less of cases of myalgia

- Genetic variants affecting pain perception
- Glycogen storage disorders
- Phosphorylase deficiency (McArdle disease)
- Alpha-glucosidase deficiency (Pompe’s disease)
- Carnitine palmitoyl-2 (CPT-2) deficiency
  - most common inherited disorder of lipid metabolism
  - usually manifesting in adulthood
- Myoadenylate deaminase (MADA) deficiency
- Mitochondrial myopathies
- Malignant hyperthermia susceptibility (MHS)

A. Ghatak et al. Atherosclerosis 2010
Approach to Muscle Pain

Routine measurement of creatine kinase is not helpful for detecting the rare cases of myopathy at statin standard doses.

Patients should be asked to report new or unexplained muscle pain or weakness, and creatine kinase should be measured in such patients.

Armitage Lancet 2007
Statins and muscle pain
PRIMO

• Estimated to occur in 7-10% of clinic populations

• Best large study evaluating MRE - PRIMO study
  – Population
    • 7924 outpatients receiving usual care in France
    • All were exposed to high dose statin within last 3 mo
    • First 3 patients from 2500+ practices that met inclusion/exclusion

Brucket et al CV drugs and therapy 2006
Statins and muscle pain
PRIMO Study

- Symptoms
  - Pain 10.5% of total population
    - Median onset 1 mo
    - Most common lower limbs
    - 25% complaints were of tendon pain
    - Sx more common in more active individuals
      10.8% vs 14.7%

- Reduction of activity 38% of the 832 with pain

- Bedridden 4% (31) of 832 with pain

Brucket et al CV drugs and therapy 2006
Statins and muscle pain

- Predictors in PRIMO
  - Hx of muscle pain on another statin OR 10
  - Hx of unexplained cramps OR 4
  - Hx of CK elevation OR 2
  - Hx no sx in 3 mo OR 0.28
  - Hx of anti-depressant OR 0.51

Brucket et al CV drugs and therapy 2006
**Statins and muscle pain**

**Predictors – PRIMO**

- **Statins**
  - Prava set at 1.0
  - Ratio of statin use
    - Fluva 3
    - Atrova 2
    - Prava 2
    - Simva 1

<table>
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<th>Rate %</th>
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<td>10.9</td>
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<tr>
<td>Atrova</td>
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<td>1.28</td>
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<tr>
<td>Simva</td>
<td>18.2</td>
<td>1.78</td>
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Brucket et al CV drugs and therapy 2006
Management of myalgia

Begin therapy

Muscle Symptoms

YES
Check CK

Tolerable symptoms; No or mild CK elevation
Continue therapy; Monitor symptoms

NO

Symptoms w/ severe increase in CK Or rhabdo
Discontinue therapy; Treat rhabdo; Weigh risk/benefit of restarting

Intolerable symptoms; No or mild CK elev; No other cause
D/c therapy; restart at same or reduced dose
If recurrence, adjust therapy

Management of muscle pain

Stop the statin
- Stopping for up to 6 weeks is considered very safe
- Longer (until symptom resolution) for myopathy

Rechallenge – 3 approaches
- Same dose - Atypical pain/symptoms and lower risks
- Lower dose - More typical pain/moderate risk
- New statin (usually at low dose)
  - Typical symptoms rated mod or severe
  - Higher risk/myopathy
Adjusting Therapy

Rosuvastatin 5-10mg/day

OR

Fluva XL +/- ezetimibe

Then

Rosuvastatin Q48H

Rosuvastatin Qweek

Nonstatin therapy, Aggressive Lifestyle Modification

Stein, Am J Cardiol. 2008; Glueck Clin Ther. 2006; Backes, Pharmacotherapy 2006; Backes Am J Cardiol. 2007
Treatment of patients with MRSE

Fluvastatin XL 80 + Ezetimibe
- 199 patients randomized
- All with prior muscle related side effects (MRSE)
- Median time to first recurrent MRSE 0.4 to 3.7 weeks

Stein et al. Am J Cardiol 2008;101:490–496

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<tr>
<th></th>
<th>EZ</th>
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<tr>
<td>Δ LDL</td>
<td>15.6</td>
<td>32.8</td>
<td>46.1</td>
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<tr>
<td>Any MRSE</td>
<td>24%</td>
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<td>14%</td>
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<tr>
<td>Discon MRSE</td>
<td>8%</td>
<td>4%</td>
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Adjusting therapy
My personal practice

• Switch from one statin to second statin with best evidence at low dose

• Move next to fluvastatin 20 or 80 then add EZ
  – 20 for refractory patients (capsule)
  – 80 for non-refractory

• Next improvise
  – Rosuva or Atorva qod – minimal drop in efficacy
  – Rosuva weekly – reported 25% LDL lowering efficacy

• Finally niacin or fibrate +/- EZ or Colesevelam
Outcomes in patients with myopathy

45 patients with statin myopathy

- Mean time symptom onset was 6 mo
  - 9 month standard deviation
  - Faster in those recently hospitalized vs not
    - (1.3 mo vs 7.1 mo)

- Mean time to resolution of sx 3 mo - All resolved sx

- 37 rechallenged
  - 21 with recurrent sx
  - 16 without

Hansen et al Arch Int Med 2005
Summary

• Expect muscle symptoms in 10% of patients
  – Tell patients up front to stop if they get them
  – Severe syndromes usually genetic or iatrogenic

• Most individuals can be treated by switching statins or cutting back dose and days treated

• Seldom are symptoms permanent