Risk Underlying Statin-Induced Adverse Muscle Complaints

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What Is the Spectrum Of Statin-Associated Muscle Toxicity?

1. Myalgia
2. Myopathy
3. Myositis
4. Muscle injury with acute renal failure (Clinical “rhabdomyolysis”)


What Is The Definition Of Statin-associated Muscle Adverse Events?

- Myalgia – unexplained muscle discomfort often described as “flu-like” symptoms with normal CK level
- Myopathy – muscle weakness
- Myositis – muscle inflammation often with muscle enzyme elevations
- Myonecrosis – elevation in muscle enzymes, severity graded by elevation of CK level above pre-treatment baseline levels or ULN.
- Clinical rhabdomyolysis – muscle injury with myoglobinuria and/or acute renal failure

The Spectrum Of Myalgia Symptoms

• Muscle aches
• Muscle soreness
• Muscle stiffness
• Muscle tenderness
• Muscle cramps with or shortly after exercise. Not nocturnal cramping


What Clinical Scoring Index Should Be Used For The Accurate Diagnosis Of Statin Myalgia In Clinical Practice?

• Clinical symptoms (new or increased unexplained muscle symptoms
• Regional distribution/pattern
  – Symmetric pelvic/thigh aches
  – Symmetric calf aches
  – Symmetric upper proximal aches
  – Non-Specific asymmetric, intermittent
• Temporal pattern
  – Symptoms onset < 4 weeks
  – Symptoms onset 4-12 weeks
  – Symptoms-onset > 12 weeks
• Dechallenge
  – Improves upon withdrawal (< 2 weeks)
  – Improves upon withdrawal (2-4 weeks)
• Challenge
  – Same symptoms recurs upon re-challenge <4 weeks
  – Same symptoms recur upon re-challenge 4-12 weeks

What Is The Definition Of Myopathy?

• Muscle weakness (not attributed to pain) and not necessarily associated with elevated CK

What Are The Diagnostic Criteria For Myopathy?

Physical examination
  Proximal weakness in upper and lower extremities ≤ 4 by MRC definition

Standardized muscle testing with isokinetic dynamometer, aerobic capacity and respiratory exchange ratio with fasted patient and standardized procedure on metabolic cart (requires off drug/on drug comparison

Confirmation by EMG +/- muscle biopsy

What is the definition of Myonecrosis?

• CK elevation indicates severity of muscle damage:
  – Mild hyperCKemia: <10x ULN
  – Moderate hyperCKemia: 10-50x ULN
  – Marked hyperCKemia: >50x ULN

What Tests Are Available To Support Or Confirm The Diagnosis Of Statin-associated Muscle Adverse Events

• Muscle adverse event clinic index score
• Muscle enzymes (CK). Serum aldoase and myoglobin not recommended.
• If CK levels > 50 times ULN and/or dark brown, obtain urinary myoglobin
• Pain questionnaires (brief pain inventory [preferred because most widely used], McGill, adaptation of quality of life)
• Strength and aerobic testing
• Metabolic tests (MRS, O₂ uptake intake)
• Pharmacogentic testing
What Is The Indication For Muscle Biopsy?

- EMG myopathic discharges with fibrillations and/or positive sharp waves in affected muscles
- Threshold for biopsy - CK values should be adjusted >3 ULN above sex and racial norms


What Are The Rates Of Myopathy In Clinical Trials?

- Twenty-six of 42 trials (62%) reported the number of subjects with muscle complaints including myalgia, myositis, myopathy, muscle cramps, and muscle weakness
- Only one study specifically solicited muscle complaints (Kjekshus et al. 2007: Rosuvastatin in older patients with systolic heart failure)
- Detailed criteria for evaluating mild to moderate muscle complaints were not presented in the other 41 studies (98%)

Ganga, Slim and Thompson: A Systematic Review of Statin-Induced Muscle Problems in Clinical Trials; In Review
What Are The Best Estimates Of Rates Of Myopathy In Clinical Practice?

Muscle Complaints In Clinical Practice: PRIMO

- Examined the prevalence of mild to moderate muscle side effects among 7924 French patients on moderate to high dose statin therapy
- No control group (unblinded)
- 10.5% muscle complaints
- Median time of onset of 1 month following initiation of statin therapy

Bruckert et al. Cardiovasc Drugs Ther 2005
Muscle Complaints In Clinical Practice: STOMP

- 80 mg atorvastatin for 6 months
  - 9.4% value recently reported
  - 4.6% of the STOMP placebo subjects met the study definition of myalgia
  - True incidence of statin myalgia was 4.8%
  - Healthy, statin-naïve patients
  - No other overt CVD
  - Average time of onset 1 month in true myalgics vs. 2 months in placebo myalgics (p < 0.05)

Parker et al. 2013

Muscle Complaints In Clinical Practice: NHANES Data

- Cross-sectional analysis NHANES 1999-2002
  - Adults ≥40 years (n=3,580) without arthritis
  - Queried for musculoskeletal pain and medication use in last 30 days
  - 22% of 402 statin users reported musculoskeletal pain
  - 16.7% of non-statin users reported pain
  - Difference of 5.3% (odds ratio 1.50)

Buettner et al. 2008
Why are the rates of myopathy in clinical trials different from clinical experience?

- Failure to query study subjects
  - Only 26/42 clinical trials reported the frequency of muscle complaints
  - Only one study actually queried subjects systematically about muscle complaints
  - "Don’t ask, don’t tell" phenomenon?
- Failure to define muscle side effects
  - Myalgia, myositis, cramps, weakness, stiffness, soreness, tenderness, aching
  - With or without CK elevations?
  - Baseline CK measurements?

Difference Between Clinical Trials and Clinical Practice

- Placebo effect
  - Side effects mentioned in informed consent
- Effect of run-in phase
  - Typically one month to onset of symptoms
  - HPS: 5 week run-in period
- Different patient/subject populations
  - Clinical trials inclusion/exclusion criteria
- Differences between statin types
  - Fewer muscle complaints with fluvastatin

What Are The Predictors Of Statin Associated Adverse Muscle Events?

Clinical Predictors Of Risk

• Older age, Asian race and gender (F>M)
• Exercise
• Comorbidity (hypothyroidism, hyperuricemia, alcohol overconsumption)
• Statin dose
• History of muscle pain with another lipid-lowering therapy
• Family history of muscular symptoms with lipid-lowering agents
• Concomitant medications (CYP3A4 with simvastatin, inhibitors of CYP3A4 and SLCO1B1 includingazole antifungals, ritonavir, verapamil and diltiazem; gemfibrozil

Modified after Feng, Wilke and Baye. Pharmacogenomics 2012;13:579-594
Genetic Determinants of Risk

- Candidate gene studies
  - Pharmacokinetic candidate genes
  - Pharmacodynamic candidate genes
- Genome-wide studies
  - Linkage studies in families
  - Genome-wide association studies in unrelated individuals

What Are Treatment Options for LDL-C Lowering Among Patients With Statin Associated Muscle Events?

- Ezetimibe
- Bile acid sequestrants
- Niacin
- Red yeast rice
- PCSK9 inhibitors
- CETP inhibitors
- AMP kinase inhibitors

Modified after Feng, Wilke and Baye. Pharmacogenomics 2012;13:579-594

What is the Evidence Base for Treating Patients With Statin Associated Muscle Events?

Treatments Investigated As Adjunctive/Alternative in Patients with Statin Associated Muscle Adverse Events

- Ezetimibe
- Bile acid sequestrants
- Niacin
- Red yeast rice
- PCSK9 inhibitors
- CETP inhibitors
- AMP kinase inhibitors

Role Of Coenzyme Q10 Supplementation

- Equivocal for Treating Statin Myalgics
  - Treatment of 100 mg/day (n=18): Pain severity ↓ 40% and pain interference ↓ 38%
  - Treatment of 200 mg/day (n=44): No difference in myalgia score or adherence to simvastatin treatment
- With selenium
  - In 60 patients, decreased muscle pain intensity by 50%, cramps, weakness and fatigue by 60-82%
  - In 41 patients, no difference in symptom questionnaire scores or muscle function tests

Caso et al. 2007; Young et al. 2007; Fedacko et al. 2013; Bogsrud 2013

Randomized Trial of Coenzyme Q10 in Patients with Confirmed Statin Myopathy

- Statin myalgia was confirmed in 120 patients with prior symptoms of statin myalgia using an 8-week randomized, double-blind crossover trial of simvastatin 20 mg/d and placebo
- 41 subjects (36%) developed muscle pain with simvastatin but not with placebo, and were randomized to simvastatin 20 mg/d combined with CoQ10 (ubiquinol 600 mg/d) or placebo for 8 weeks
- Serum CoQ10 increased from 1.3±0.4 to 5.2±2.3 mcg/mL with simvastatin and CoQ10 but not with simvastatin and placebo (1.3±0.3 to 0.08±0.2 (p<0.005)
- No differences in muscle strength or VO2 max with simvastatin with or without CoQ10 (p>0.10)
- 24 subjects participated in both arms of the CoQ10 or placebo phase:
  - No differences in reports of muscle pain on CoQ10 (17/24 [71%]) vs. placebo (13/24 [54%]); p = 0.23
  - No differences in time to pain onset for CoQ10 (3.2±1.9 weeks) vs. placebo (3.2±2.0 weeks; p=0.53

**PCSK-9 Inhibitors: Alternative/Complimentary Therapy for Statin Associated Muscle Complaints**

**Entry Criteria:**
SAM complaints, unable to tolerate effective statin dose

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Duration (w)</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAUSS II</td>
<td>II</td>
<td>160</td>
<td>12</td>
<td>Ezetimibe</td>
</tr>
<tr>
<td>GAUSS III</td>
<td>III</td>
<td>300</td>
<td>12</td>
<td>Ezetimibe</td>
</tr>
<tr>
<td>ODYSSEY Alternative</td>
<td>III</td>
<td>500</td>
<td>24</td>
<td>Ezetimibe</td>
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</tbody>
</table>

**GAUSS-2 Study Design**

- **Screening and placebo run-in period**
- **Fasting LDL-C 5–10 days before randomization**
- **Subcutaneous injection of placebo**

**Randomization 2:2:1:1**

- Evolocumab 140 mg SC Q2W + Placebo PO QD
  - N = 103
- Evolocumab 420 mg SC QM + Placebo PO QD
  - N = 102
- Placebo SC Q2W + Ezetimibe 10 mg PO QD
  - N = 51
- Placebo SC QM + Ezetimibe 10 mg PO QD
  - N = 51

**End of Study**

- **Time points:** Day 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14
- **QM, Q2W, QD:** Quantum, every 2 weeks (biweekly), oral

*Phone call for AEs, SAEs, AEs, adverse events; EOS, end of study; LDL-C, low-density lipoprotein cholesterol; SAEs, serious adverse events; SC, subcutaneous; PO, oral; Q2W, every 2 weeks (biweekly); QM, monthly.

GAUSS-2: Biweekly Evolocumab LDL-C Response

<table>
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<tr>
<th>Treatment Difference vs Ezetimibe</th>
<th>Average at weeks 10 and 12</th>
<th>-37%</th>
<th>P&lt;0.001</th>
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<td>At week 12</td>
<td>-38%</td>
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Study Week
1: Ezetimibe (N = 51)  2: Evolocumab 140 mg Q2W (N = 103)

Study drug administration
Biweekly SC
BL, baseline. Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values. P values are multiplicity adjusted. Stroes E, et al. J Am Coll Cardiol 2014

GAUSS-2: Monthly Evolocumab LDL-C Response

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<th>Treatment Difference vs Ezetimibe</th>
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Study Week
1: Ezetimibe (N = 51)  2: Evolocumab 420 mg QM (N = 102)

Study drug administration
Monthly SC
BL, baseline. Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values. P values are multiplicity adjusted. Stroes E, et al. J Am Coll Cardiol 2014
GAUSS-2: Treatment Difference in Other Lipids at Week 12

- ApoB*
  - Error bars represent standard error.
  - Treatment difference vs ezetimibe: * P < 0.001; P value adjusted for multiplicity.
  - Treatment difference, Mean (%): -25% to -35%

- Lp(a)*
  - Treatment difference, Mean (%): -28% to -30%

- HDL-C
  - Treatment difference, Mean (%): 4% to 5%

- ApoA1
  - Treatment difference, Mean (%): 2% to 6%

- Triglycerides
  - Treatment difference, Mean (%): 2% to 5%


Evolocumab 140 mg Q2W vs ezetimibe
Evolocumab 420 mg QM vs ezetimibe

No notable difference in results for average at weeks 10 and 12.

ODYSSEY ALTERNATIVE: Study Design
Statin-Intolerant Patients

- Moderate- to very high-risk statin-intolerance
- Randomization
  - Alirocumab 75/150 mg SC Q2W + placebo PO QD
  - Ezetimibe 10 mg PO QD + placebo SC Q2W
  - Atorvastatin 20 mg PO QD + placebo SC Q2W
- 8 week follow up and open-label treatment period
- Primary endpoint

Summary

- The major cause of statin intolerance is adverse muscle events
- Imprecise definitions have impaired accurate diagnosis of statin associated adverse events and clinical trials designed to investigate alternative therapies
- The need for a validated clinical myalgia index is a crucial step for accurate diagnosis
- Research into diagnostic studies and procedures will further improve accurate diagnosis of statin associated adverse events, and provide the basis for evaluating other myopathic disorders and justifying alternative cholesterol lowering therapies