Prevention and Management of Statin-Induced Myopathy

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Objectives

- Define statin myopathy.
- Define key concepts in development of statin myopathy.
- List risk factors for development of statin myopathy.
- Define steps to prevent myopathy
- Develop a therapeutic plan to keep patients on their statin following development of myopathy.
Case Study - AJ

- AJ is a 63 yo male with chronic heart failure (EF = 25%), hx hypertension (106/66), gout, low activity, and poor diet. He is currently being treated with:
  - Furosemide 40 mg QD
  - Lisinopril 20 mg QD
  - Metoprolol XL 100 mg QD
  - Spironolactone 25 mg QD
  - Allopurinol 150mg qd

- LDL = 140 mg/dL, HDL = 36 mg/dL, Trigs 200

- Plan – start a statin

Statin Myopathy/Myalgia – Talking About?

- Mild – moderate muscle symptoms:
  - Myalgia
  - Fatigue/weakness (heaviness/stiffness/cramps)
  - Generalized aching
  - Cramps, Tendon Pain
  - With or without elevated CK

- Incidence – 11% (higher in your practice!)
- Onset ~ 4 weeks (median)
- Excluded other causes (working in the garden)

Primo Study. Cardiovasc Drugs Ther 2005;19:403
### Key Concepts

- **Class Effect**
  - Dose – dependent
    - Increase systemic bioavailability
  - LDL-c reduction – independent
- **Risk Factors**

### Prevention
Key Concepts

- Class Effect
  - Dose – dependent
    - Increase systemic bioavailability
  - LDL-c reduction – independent
- Risk Factors

Dose

- A-Z Trial (N ~ 4,500pts)
  - Simva 80mg: 9 patients developed myopathy
  - Simva <80mg: 0 patients developed myopathy
- IDEAL Study (N ~ 9,000pts)
  - Simvastatin 20mg: 1.1% myalgia
  - Atorvastatin 80mg: 2.2% myalgia
  - Simvastatin – DNE 40 mg

Risk Factors - Endogenous

- Advanced Age
- Low BMI
- Diabetes, HTN
- Renal disease
- Hepatic disease
- Hypothyroidism
- Genetic (SLCO1B1 – SNP rs4149056)
- Metabolic disease
Risk Factors - Exogenous

- Excessive alcohol consumption
- Heavy exercise
- Surgery with severe metabolic demands
- Increase systemic bioavailability – i.e.

DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Statin</th>
<th>CYP-450 Isozyme</th>
<th>Increased Concentration With 3A4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>3A4</td>
<td>Yes</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>3A4</td>
<td>Yes</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>3A4</td>
<td>Yes</td>
</tr>
<tr>
<td>Cerivastatin*</td>
<td>3A4/2C8</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>2C9</td>
<td>No (yes with 2C9 inhibitors)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Minor 2C9</td>
<td>No</td>
</tr>
</tbody>
</table>

## CYP3A4 Inhibitors

- **Inhibitors**
  - Amiodarone
  - Diltiazem/Verapamil
  - Macrolide Antibiotics – erythromycin, clarithromycin
  - Azole Antifungals (itraconazole, ketoconazole, fluconazole)
  - Grapefruit juice
  - Antiretroviral protease inhibitors (ritonavir, nelfinavir, indinavir)
  - Cyclosporin (Inhibits OATP1B1 Transporter)
  - Natural Products: Gingko, Goldenseal, Pomegranate, Kava, Resveratrol

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### Simvastatin (Zocor®) Drug Interaction Labeling Changes

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Previous Label</th>
<th>Updated Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4 Inhibitors</td>
<td>Avoid</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Gemfibrozil, CYA, Danazol</td>
<td>DNE 10 mg/day</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Amiodarone/Verapamil</td>
<td>DNE 20 mg/day</td>
<td>DNE 10 mg/day</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>DNE 40 mg/day</td>
<td>DNE 10 mg/day</td>
</tr>
<tr>
<td>Amlodipine/Ranolazine</td>
<td>No dose cap</td>
<td>DNE 20 mg/day</td>
</tr>
<tr>
<td>Grapefruit Juice</td>
<td></td>
<td>Avoid</td>
</tr>
</tbody>
</table>

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*Zocor® Package Insert 2011.*
Risk Factors - DI

- Gemfibrozil – interaction with all statins (except fluvastatin – one pk study?).
  - 8.6 cases rhabdo/million scripts
- Fenofibrate – no PK interactions.
  - 0.58 cases rhabdo/million scripts.
- Colchicine?
- Overall – Lowest DI potential
  - Rosuvastatin, Pravastatin, Fluvastatin

Am J Cardiol. 1995 Jul 13;76(2):80A-83A
Prevention Summary

- Lowest dose
- Risk Factors – lower dose
- Avoid Drug Interactions (variable)
- Drug Interactions – lower dose

Case Study - AJ

- AJ was started on 40mg simvastatin 6 weeks ago and now comes back to clinic complaining about generalized aching and some muscle cramping. Lipid profile shown below:
  - LDL=78 mg/dL, HDL=40 mg/dL, Trigs 140
- Plan?
Management

Key Concepts

- No EB Guidelines or Best Practice (many right answers) – minimal data overall
- Exclude other causes (physical activity)
- Number of approaches - Some common themes
  - Stop the Statin
  - Adjusting/Switching Statins
  - Alternate Schedules
  - Alternative Treatments
### 1\textsuperscript{st} Consideration: Stop The Statin?

- Intolerable muscle symptoms
- Tolerable muscle symptoms and CK > 10x ULN
  
  
  D/C statin wait until symptoms resolve and CK returns to baseline

- Consider stopping in patients with any CK > 3x but <10x ULN (higher more likely to stop)

- Consider stopping and wait for resolution in pts with normal CK

### 2\textsuperscript{nd} Consideration: Adjust the Statin

**Options (A or B)**

- **A.** Restart or continue the same statin at lower dose
- **B.** Switch statins
- **C.** A then B if needed
### Switching Statins

- Lipophilic (ATV, Simva, Lova) to hydrophilic (RSV, Prava) or vice-versa
  - No data – can make theoretical arguments for both.
- **Low dose of another statin** (more potent statin q.d.?)
  - Potency: RSV > ATV > Simva > Prava
- Last Line? - Fluvastatin XL 80mg (Randomized PBO Trial ± zetia). Meta-analysis – lower rate overall of myopathy. Primo Survey – 18% (Sim 40-80) v 5% (F 80XL)

Primo Study. Cardiovasc Drugs Ther 2005;19:403

### Muscles Still Ache Doc!

- Now What?
  - **3rd Decision point**
  - Alternative Schedules?
  - Alternative Treatments?
Alternative Schedules

- Rosuvastatin and Atorvastatin –
  - Alternative days (RSV 2.5–10mg, 74% tolerated)
  - Twice weekly (RSV 5-40mg, ATV 10-40mg, 80% tolerated)
  - Once weekly (RSV 2.5-20mg, 71% tolerated)
- May not get to goal -
  - Ezetimibe (Zetia) or Colesevelam (Welchol)
- Effect on hard outcomes unknown?
  - Use alternative treatment first???

Am J Health-Syst Pharm 2012;69:291-300

Alternative Treatments

- Vitamin D
- Coenzyme Q10

Consider before Alternative Schedules?
- Adv: continue everyday statin dosing (EBM)
Vitamin D

- Low vitamin D associated with muscle weakness.
- However, association studies between Vit D levels and myopathy are limited and inconclusive.
- Limited study showed benefit with supplementation.
- Cost – cheap
- Should treat Vit D deficiency or insufficiency
  - IOM recommended level (20-30 ng/mL)
  - Myopathy benefit? What level (>30 ng/mL)??


Fig 2. Distributions of serum 25 OH vitamin D in 128 statin-treated patients with myalgia at study entry and in 493 statin-treated asymptomatic patients.

(Translational Research 2009;153:11-16)
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Coenzyme Q10 & Statins

- Statins may or may not lower muscle CoQ10?
- **Meta-Analysis– insufficient evidence to recommend.**
- N = 32, 44, 41, 76 – 2 no effect and 2 improvement in pain score
- Dose? 100 – 300 mg/day for 1-6 months, or longer? (May affect INR with warfarin??)
- Cost consideration ($20-$60/month)
- Very last line? (after Vit D supplementation and alternative scheduling due to cost?)

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