My patient is statin intolerant..... now what?

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Dr. Scordo has no financial relationships with commercial interests to disclose
Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

In Any Given Diner Program

- In the first 15 min -60% is retained
- In the next 15 min -30% is retained
- In the next 30 min -10% is retained
- After 30 min - one starts having sexual fantasies

Objectives

- Discuss the incidence of statin induced myopathy
- Discuss the presentation of statin intolerance
- Discuss strategies to deal with individuals with statin intolerance

1 case/1000 with low dose statin
1 case/500 with high dose statin
The Case

52 year old male known HTN and CHD with PCI two months ago referred because of statin intolerance. Untreated TC 250 mg/dl; triglycerides 200 mg/dl; HDL 45 mg/dl; LDL 165 mg/dl. Two weeks after 40 simvastatin, he experienced moderately severe myalgias in his thighs and upper arms and muscle weakness. CK 420 IU/liter—statin stopped, atorvastatin 20 started with similar symptoms within 10 days. CK then 525 IU/liter—returned to normal with drug d/c. Other meds: ARB, ASA, beta blocker, diltiazem.

A Few Factoids

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the mainstay of lipid-lowering therapy.

Well-established efficacy for reducing cardiovascular disease (CVD) morbidity and mortality in various at-risk populations.

Cholesterol Synthesis Pathway

More Factoids

- Improvement of endothelial function
- Inhibition of vascular inflammation, platelet aggregation and thrombosis
- Amelioration of oxidative stress

In general statin therapy is associated with rare occurrences of serious adverse events & considered to be safe.

A significant proportion of subjects taking these drugs may experience some degree of intolerance.

Statin-induced myopathy (SIM) is the most common side effect.

Less common side effect of statin therapy is the increase of serum aminotransferase levels, which is considered the manifestation of hepatic toxicity.
### Terminology to Describe Muscle Injury

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias</td>
<td>muscle ache or weakness without creatine kinase (CK) elevation</td>
</tr>
<tr>
<td>Myopathy</td>
<td>muscle symptoms with increased CK levels &gt;10 x ULN</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>muscle symptoms with marked CK elevation (typically &gt;10 x ULN) and with creatinine elevation (usually with brown urine and urinary myoglobin)</td>
</tr>
</tbody>
</table>


### Incidence of Muscle Adverse Events from Clinical Trials

(180,000 patients in 21 major statin trials for average of 3 years)

<table>
<thead>
<tr>
<th>Muscle AE</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias</td>
<td>1.5% to 3%</td>
</tr>
<tr>
<td>Myopathy (Sc + inc CK)</td>
<td>5/100,000</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1.6/100,000</td>
</tr>
</tbody>
</table>

Law M et al. AmJCardiol. 2006;97(suppl8A):52C-61C

### Real Life

- Frequency of SIM often higher than reported in clinical trials
- Patients at increased risk for statin-induced adverse effects tend to be excluded prior to randomization
- Healthier patients in clinical trials
- Clinical practice patients have more severe comorbidities

### The Prediction of Muscular Risk in Observational Conditions (PRIMO)

- Observational studies of muscular symptoms in an unselected population
- 7,924 French outpatients with hypercholesterolemia, ages 18 to 75 years, on high-dose statins for 3 or more months before the study
- Atorvastatin 40 to 80 mg, fluvastatin 80 mg, pravastatin 40 mg, and simvastatin 40 to 80 mg
- 10.5% of patients reported muscle-related symptoms

### PRIMO: Risk of Muscular Symptoms Individual Statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dosage</th>
<th>Percentage of patients with muscular symptoms</th>
<th>Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>40 mg/day</td>
<td>10.9%</td>
<td>0.99 [0.74-1.31]</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40-80 mg/day</td>
<td>14.9%</td>
<td>1.28 [1.02-1.60]</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40-80 mg/day</td>
<td>16.2%</td>
<td>1.78 [1.39-2.29]</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80 mg/day</td>
<td>5.1%</td>
<td>0.33 [0.26-0.42]</td>
</tr>
</tbody>
</table>

*% values relative to the total number of patients with or without muscular symptoms.
†Odds ratios were calculated using pravastatin as the reference.
‡P values were determined by Pearson’s Chi-squared test.

### Risk Factors for Statin Myopathy
Patient factors that predispose to myopathy

- Exercise or increased physical activity
- Alcohol consumption and drug abuse (cocaine, amphetamines)
- Hypothyroidism
- Vitamin D deficiency
- Renal disease
- Baseline muscle disease (i.e. inherited metabolic muscle disease)

Factors That Increase the Risk of Statin-Induced Myopathy

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Statin Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>High systemic exposure</td>
</tr>
<tr>
<td>Female sex</td>
<td>Lipophilicity</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>High bioavailability</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>Limited protein binding</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Potential for drug-drug interactions metabolized by CYP pathways (particularly CYP450 3A4)</td>
</tr>
<tr>
<td>Diet (i.e. grapefruit juice)</td>
<td></td>
</tr>
<tr>
<td>Polypharmacy</td>
<td></td>
</tr>
</tbody>
</table>

National Lipid Association Statin Safety Task Force Statin Muscle-Related Diagnosis

Etiology of SIM

Unclear - mainly hypothesis

- Cholesterol reduction with statins may upset the integrity of the plasma membrane of myocytes - cholesterol plays a key role in cell membrane fluidity
- Statins favor the deficiency of coenzyme Q10 which is the metabolite of the HMG-CoA reductase pathway - result is abnormal mitochondrial respiratory function
- Statins induce apoptosis of myocytes or may impair intracellular calcium homeostasis by interfering with mitochondrial respiratory chain

Myalgias: Differential Diagnosis

- Continue Statin
  - Reduced Dosage, 5x as a Guide
- Discontinue Statin
  - If 5x Disappear
  - The 5 Approach Guide
- Reconsider Risk/Benefit of Statins
Statin Intolerance
Kristine A Scordo, PhD, ACNP-BC, FAANP

Physiological
- Exercise induced
- More common with increasing age

Metabolic
- Hypocalcemia, hypomagnesemia, renal failure, pregnancy

Ischemia
- Peripheral vascular disease

Endocrinopathies
- Hypothyroidism, hyperparathyroidism,
- Hypertension, diabetes, hypoglycemia

Drugs/Toxins
- Diuretics, statins, alcohol

Neurological
- Motor neurone disease, peripheral neuropathy, radiculopathy

Clinical Presentation
- Myalgia
- Fatigue
- Weakness
- Generalized aching
- Low back or proximal muscle pain
- Less frequent
  - Tendon pain
  - Nocturnal muscle cramps

Symptoms and Time Frame
- Temporal relationship between initiation of statin treatment and onset of symptoms is widely variable
- Most cases of SIM occur within the first 12 weeks of statin exposure
- Can occur up to 52 weeks after starting statin

Diagnostic Strategies
- Remember OLD CART?
  - Ask about timing, location, severity and duration of symptoms
  - Are symptoms precipitated by exertion
  - limit ADL, exercise
Vitamin D Treatment

- deficiency (<10 ng/ml)
  - oral dose of 50,000 IU of vitamin D3 once per week for 8 weeks (calciferol)
  - Recheck in 8 weeks
- Need 1000/day needed to satisfy the body's requirement

CK Levels: Monitoring and Surveillance

- Routine CK levels in asymptomatic patients is not recommended
- Baseline CK only in patients at high risk of myopathy
- CK levels should be monitored in symptomatic patients
- If symptomatic, rule out other etiologies of muscle symptoms or asymptomatic CK elevation
  - Increased physical activity, hypothyroidism, trauma, falls, seizures etc.

Further laboratory evaluation depends on the findings and will often be directed by subspecialists

EXAMPLES:

- ESR, anti-Ro and anti-La antibodies, and the myositis panel in patients with elevated CK whose other findings suggest an autoimmune or inflammatory process
- Serum carnitine levels (free, total, and esterified), fasting serum lactate levels, and serum cortisol in those with findings suggestive of metabolic myopathy
- Electromyography and nerve conduction studies in patients with possible myelopathy, peripheral neuropathy, or inflammatory myopathy.

OPTIONS

- Use low-dose, statin twice a week and gradually increase to three times a week or every other day
- Caution:
  - Need to carefully consider in light of the ideal LDL-C target for the patient
  - Dosing regimens lack data on cardiovascular mortality outcomes
Clinical pharmacokinetics of HMG-CoA reductase inhibitors

<table>
<thead>
<tr>
<th>Statin</th>
<th>Lipid lowering</th>
<th>Lipid lowering</th>
<th>Lipid lowering</th>
<th>Lipid lowering</th>
<th>Lipid lowering</th>
<th>Lipid lowering</th>
<th>Lipid lowering</th>
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</tbody>
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Limitations of Alternative Day Statin Dosing Trials

- Retrospective designs
- Lack of placebo control groups
- Small study populations
- Some trials allowed patients to continue other lipid lowering drugs
- Even reduction-unknown

Doing well-do I double dose?

![Adapted from Harper C, NLA National Meeting 2010 Chicago](image-url)
**Statin Intolerance**
Kristine A Scordo, PhD, ACNP-BC, FAANP

**Additional Therapies**

- **Coenzyme Q10**
  - Evidence of benefit lacking
  - 100-200 mg start prior to initiating the statin for a few weeks, then start statin

- **Ezetimibe alone**

- **BAS-bile acid sequestrant (can increase triglycerides)** (Colesvelem, cholestyramine or colestipol) can be used instead of statin-outcome mortality benefit??

- **Niacin, fibrates**

- **Omega 3FA**

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**USP Dietary Supplement Verification Program**

- Voluntary testing & auditing program
- Verifies what’s on the label is in the bottle
- No harmful contaminants
- Dietary supplement will break down and release ingredients in the body
- Dietary supplement has been made under GMP (good manufacturing practices)

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**Dietary Supplement Omega 3FA**

<table>
<thead>
<tr>
<th>Dietary Supplement</th>
<th># Capsules x 0.5 g EPA/DHA</th>
<th># Capsules x 3.6 g EPA/DHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirkland Signature™ Natural Fish Oil (Costco)</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Member's Mark™ Omega-3 Fish Oil (Sam’s Club)</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Spring Valley™ Natural Fish Oil Concentrate</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>CVS Pharmacy™ Natural Fish Oil Concentrate</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Walgreens Fish Oil Concentrate™</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>GNC Fish Body Oils™</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Nutri Advanced Natural Fish Oil™</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Eckerd Natural Fish Oil Concentrate™</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Nature’s Bounty™ Salmon Oil</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

Adapted from list of supplements tested in Consumer Reports 2003:  
Companies Participating in the USP Programs

Red Yeast Rice

- Made by fermenting rice with a specific strain of yeast *Monascus purpureus*
- Contains monacolins—naturally occurring HMG-CoA reductase
  - Monacolin K (mevinolin) became lovastatin (Mevacor) first statin approved in US
- Xuezhikang 1.2 g/d providing 13.5 mg total monacolins (Dose: 1200 or 2400 mg/day)
- Monitor LFTs
- Shown to decrease LDL, hsCRP, major coronary events

BEWARE
Citrinin found in some supplements is nephrotoxic

<table>
<thead>
<tr>
<th>Red Yeast Rice Products</th>
<th>Monacolin K</th>
<th>Monacolin L</th>
<th>Citrinin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Cholesterol®</td>
<td>3.35</td>
<td>&lt;0.006</td>
<td>4.07</td>
</tr>
<tr>
<td>B. Cholesterol®*</td>
<td>2.67</td>
<td>&lt;0.006</td>
<td>3.22</td>
</tr>
<tr>
<td>C. Cholesterol®</td>
<td>1.60</td>
<td>&lt;0.006</td>
<td>6.06</td>
</tr>
<tr>
<td>D. Cholesterol® &amp; Yeast</td>
<td>3.27</td>
<td>&lt;0.006</td>
<td>5.23</td>
</tr>
<tr>
<td>E. Beyond Cholesterol®</td>
<td>0.19</td>
<td>0.02</td>
<td>ND*</td>
</tr>
<tr>
<td>F. Hongqi®</td>
<td>2.46</td>
<td>&lt;0.059</td>
<td>11.92</td>
</tr>
<tr>
<td>G. Cholesterol Power®</td>
<td>2.51</td>
<td>&lt;0.007</td>
<td>0.47</td>
</tr>
<tr>
<td>H. IVRS®</td>
<td>1.56</td>
<td>&lt;0.006</td>
<td>4.87</td>
</tr>
<tr>
<td>I. Cholesterol®</td>
<td>2.46</td>
<td>0.05</td>
<td>ND*</td>
</tr>
</tbody>
</table>

*trace of phospholipids = 0.05 mg/g


Plant Sterols

- Inhibit the absorption of dietary cholesterol
- 2-3 g daily of phytosterols incorporated into margarine, mayonnaise, orange juice, olive oil, low-fat milk, yogurt, and tablets is associated with significant reductions in LDL (up to 15%)

What about the patient with elevated ALT at baseline that needs statin therapy?

Algorithm for managing statin therapy in patients with chronic liver disease

- Start statin at low dose
- Recommend cessation of alcohol drinking
- Check aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in 2 weeks
- AST or ALT level twice or more times the baseline value
- Discontinue statin therapy
  - Consider a trial of another statin or AST or ALT levels return to baseline
- AST or ALT level near baseline level or mildly elevated
  - Continue statin therapy
  - Monitor liver enzymes monthly for 3 months, then every 3 months to a year
- If dose needs to be increased
  - Check liver enzymes 2 weeks after dosing change, then monthly or every 3 months after change

How to use statins in patients with chronic liver disease

[Image of algorithm diagram]
Back to the case……

The Case

52 year old male known HTN and CHD with PCI two months ago referred because of statin intolerance. Untreated TC 250mg/dl; triglycerides 200mg/dl; HDL 45 mg/dl; LDL 165 mg/dl.

Two weeks after 40 simvastatin, he experienced moderately severe myalgias in his thighs and upper arms and muscle weakness

CK 420 IU/liter-statins stopped, atorvastatin 20 started with similar symptoms within 10 days. CK then 525 IU/liter-returned to normal with drug d/c

Other meds: ARB, ASA, beta blocker, diltiazem

Options

- Lab studies WNL
- Start co-enzyme Q10
- Start less potent statin, low dose q0d or TIW and gradually increase (fluvasatin or pravastatin 20 mg)
- Pitavastatin 2 mg
- Rosuvastatin 5 mg BIW or TIW
- Retest lipid/liver/ck 6-8 weeks

Approximate Dose Equivalency of Statin LDL-C Efficacy

<table>
<thead>
<tr>
<th>Dose of Agent (mg/d)</th>
<th>Rosuva*</th>
<th>Atorva*</th>
<th>Simva</th>
<th>Pitava</th>
<th>Lovoa</th>
<th>Prava</th>
<th>Fluva</th>
<th>Approx ΔLDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>10</td>
<td>1</td>
<td>20</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>28-34%</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>40</td>
<td>40</td>
<td>80</td>
<td>35-42%</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>39-47%</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>46-52%</td>
</tr>
<tr>
<td>40</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>51-55%</td>
</tr>
</tbody>
</table>

*Atorvastatin and rosuvastatin may be more effective [1% and 1 doubling, respectively].

Most commonly used dose in United States.
**Statin Intolerance**
Kristine A Scordo, PhD, ACNP-BC, FAANP

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**In asymptomatic patients, a CK should be measured only in patients at high risk of developing myopathy.**

**Effects of Drug Therapy and Diet on Lipids**

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**References**

- Fernandes G et al. Cleveland Clinic Journal of Medicine 2011;78:393-403