Statin Intolerance

2nd Annual CV Course for Trainees and Early Career Physicians: Current Concepts in the Diagnosis and Management of Coronary Artery Disease

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April 20th, 2018
Objectives

• Understand the clinical importance of statins and the implications of stopping statin therapy
• Define Statin Intolerance
• Discuss a management strategy for statin-associated adverse (muscle) events
• Case
Why Do we Care?

Reduction in LDL-C with Statin therapy leads to a reduction in events

*Throughout a wide range of LDL-C levels, in both primary and secondary prevention, statin therapy reduced the risk of CVD*

*For each ~1 nmol / L (39 mg / dL) reduction in LDL-C, statins reduce MACE by 20-25% (CTT)*

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**Meta-analysis of statin therapy in primary prevention trials**

**Meta-analysis of statin therapy in secondary prevention trials**

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AFCAPS= Air Force/Texas Coronary Atherosclerosis Prevention Study, ASCOT= Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm, LDL-C=Low density lipoprotein cholesterol, WOSCOPS= West of Scotland Coronary Prevention Study

Source: O’Keefe JH Jr et al. JACC 2004;43:2142-2146

CARE=Cholesterol and Recurrent Events Trial, CHD=Coronary heart disease, HPS=Heart Protection Study, LDL-C=Low density lipoprotein cholesterol, LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease, 4S=Simvastatin Survival Study, TNT=Treating to New Targets

Source: LaRosa JC et al. NEJM 2005;352:1425-1435
Why Do we Care?
Discontinuing statin therapy after an adverse effect was associated with worse outcomes

Retrospective cohort study on patients presumed to have an adverse reaction to statins. Outcomes were worse in patients in whom statin therapy was discontinued.

Statin therapy is discontinued at a high rate (sometimes prematurely or unnecessarily)

Statin intolerance – an attempt at a unified definition. Position paper from an International Lipid Expert Panel

*goal is optimizing the diagnosis and avoiding both over- and underrepresenting the condition*

*Intolerance can be due to any reason, but most commonly intolerance to due to muscle related symptoms*  

1) The inability to tolerate at least 2 different statins – one statin at the lowest starting average daily dose and the other statin at any dose
2) Intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities
3) Symptoms or biomarker changes resolve or significant improvement upon dose decrease or discontinuation
4) Symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of statin intolerance.
Effect of Statins on Skeletal Muscle Function

420 healthy, statin-naïve subjects. Atorvastatin 80 mg vs Placebo.

Myalgias are more common with statin therapy compared to placebo
- Patients in the placebo arm also get myalgias
- Mild CK elevations are seen frequent with statins (rhabdo rare)
- There were no significant changes in muscle strength with atorvastatin

Average CK increased 20.8 U/L.
No individual value exceeded 10 X ULN

Table 1. Subject Baseline Characteristics and Medication Use by Drug Assignment for All Subjects and Those Who Developed Myalgia

<table>
<thead>
<tr>
<th></th>
<th>Entire Sample</th>
<th></th>
<th>Myalgic Sample</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATOR (n=203)</td>
<td>PL (n=217)</td>
<td>ATOR (n=19)</td>
<td>PL (n=10)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9.4%</td>
<td>4.6%</td>
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<td></td>
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</table>

Parker BA, et al. STOMP study. Circ. 2013
New or Worsening Muscle Symptoms on Statin Therapy

Take a Detailed History
- Are symptoms and timing c/w statin myopathy?
- Associated conditions?
  Assess for:
  - Hypothyroidism
  - Vit D deficiency
  - Drug-Drug Interaction
  - CK elevation

Associated Conditions
- Advanced Age
- Female sex
- Asian Ethnicity
- Pre-Existing neuromuscular condition
- Known history of myopathy or family history of myopathy syndrome
- Pre-existing liver disease
- Pre-existing kidney disease
- Untreated hypothyroidism/↓vit D
- Genetic Polymorphisms regulating liver cytochrome enzyme pathways

Table 2: Proposed statin myalgia clinical index score

<table>
<thead>
<tr>
<th>Clinical symptoms (new or increased unexplained muscle symptoms)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric hip flexors/thigh aches</td>
<td>3</td>
</tr>
<tr>
<td>Symmetric calf aches</td>
<td>2</td>
</tr>
<tr>
<td>Symmetric upper proximal aches</td>
<td>2</td>
</tr>
<tr>
<td>Non-specific asymmetric, intermittent</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional distribution/pattern</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms onset &lt;4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms onset &gt;4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms onset 4–12 weeks</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms onset &gt;12 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temporal pattern</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves upon withdrawal (&lt;2 weeks)</td>
<td>2</td>
</tr>
<tr>
<td>Improves upon withdrawal (2–4 weeks)</td>
<td>1</td>
</tr>
<tr>
<td>Does not improve upon withdrawal (&gt;4 weeks)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same symptoms reoccur upon rechallenge &lt;4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Same symptoms reoccur upon rechallenge 4–12 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statin myalgia clinical index score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable</td>
<td>9–11</td>
</tr>
<tr>
<td>Possible</td>
<td>7–8</td>
</tr>
<tr>
<td>Unlikely</td>
<td>&lt;7</td>
</tr>
</tbody>
</table>

NLA. J Clin Lipidology. 2014
New or Worsening Muscle Symptoms on Statin Therapy

Take a Detailed History
• Are symptoms and timing c/w statin myopathy?
• Associated conditions?
Assess for:
• Hypothyroidism
• Vit D deficiency
• Drug-Drug Interaction
• CK elevation

Drug-Drug Interactions
-Increase risk for rhabdomyolysis

Watch for:
• Dose reductions with simvastatin
• Cyclosporine
• HIV medications
• Antifungals
• Gemfibrozil

Vit D supplementation in 146 HLD, Vit D deficient pts with previous statin-intolerance b/c of muscle symptoms

- Low vit D is a risk factor for statin intolerance
- Correction of vit D deficiency appears to improve muscle related symptoms
New or Worsening Muscle Symptoms on Statin Therapy

Take a Detailed History
• Are symptoms and timing c/w statin myopathy?
• Changes with physical activity?
Assess for:
• Hypothyroidism
• Vit D deficiency
• Drug-Drug Interaction
• CK elevation

Symptoms intolerable, muscle weakness, or CK > 3 x ULN?
No
Either continue or dose reduce or switch to alternative statin

Yes
Stop Statin for 2-4 weeks

• If Rhabdomyolysis is present, avoid statin medications unless clear secondary etiology, drug-drug inactions, or clear (removable) contributable factor has been identified.
• If statin restarted under these circumstances closely monitor symptoms / CK.
Re-challenging with Statin Therapy

*Despite proven efficacy, the rate of discontinuation of statin therapy is high*

*Statin discontinuation (by patient or provider) is many times unnecessary as symptoms may not be related to the statin*

*Observational data suggest that many patients tolerate the same drug or another statin when re-challenged.*

Stop Statin for 2-4 weeks

**Symptoms Improve**

Re-Initiate Statin:
- Starting at lower Dose or a
- Different statin medication

**Symptoms do NOT Improve**

- Consider alternative etiology s/as Inflammatory Myopathy
- Consider referral to neuromuscular specialist

Tolerating statin

**Increase dose as tolerated to:**
- achieved LDL goal or
- highest tolerated dose as used in RCT

**Symptoms Return**

- Alternative Statin / Dose
  - Hydrophilic statin if not previously tried
  - Low Dose
  - Non-daily dosing

**Tolerating statin**

Goals achieved

Continue therapy with periodic re-assessment of compliance, tolerance, efficacy.

Goals not met or statin not tolerated

**Consider additional non-statin therapy or switching to more potent statin**

**Not tolerating statin**

Consider non-statin Therapy
Ezetimibe (Zetia)

IMPROVE-IT trial, the addition of ezetimibe to statin therapy (simvastatin) was evaluated in patients after an ACS event.
- Combination therapy resulted in a reduction in the primary endpoint.
- Of note, the baseline LDL-C in the simvastatin therapy arm alone was well controlled.

Cannon et al. NEJM. 2015
Bile Acid Sequestrants

- Decreases LDL-C by ~12-25%
- Reduces the risk of fatal and nonfatal MIs in patients with hypercholesterolemia
- Can be used with statins with additional reduction in LDL-C
- Colesevelam (Welchol) can improve glycemic control in DMII
- Minimal systemic absorption

- Can increase triglycerides (due to increased VLDL production)
- Difficult to take (powder and pills)

*Use: second line agent, most commonly in patients who can’t tolerate ezetimibe*
The FOURIER Trial: 27,564 patients with ASCVD and LDL cholesterol levels of 70 mg / dL or higher who were receiving statin therapy +/- Zetia

67% reduction in LDL-C

Primary End Point: composite of CV death, MI, CVA, hospitalization for UA, or coronary revascularization. Median f/up 2.2 years
**ODYSSEY OUTCOMES Trial**

Randomized 18,924 pt with ACS 1-12 months prior to randomization

- 90% of patients were on high intensity statin therapy
- dose was adjusted to keep LDL-C target 15-50 mg / dL
- Baseline LDL-C: 87 mg/dl

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
<th>HR (95% CI)</th>
<th>Log-rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>903 (9.5)</td>
<td>1052 (11.1)</td>
<td>0.85 (0.78, 0.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2)</td>
<td>222 (2.3)</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>626 (6.6)</td>
<td>722 (7.6)</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>111 (1.2)</td>
<td>152 (1.6)</td>
<td>0.73 (0.57, 0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>37 (0.4)</td>
<td>60 (0.6)</td>
<td>0.61 (0.41, 0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Particular benefit, including a mortality benefit, was seen in patients with baseline LDL-C >100 mg / dL

Presented by Dr. Philippe Steg at the American College of Cardiology Annual Scientific
68 y/o presents to the lipid clinic for hyperlipidemia, secondary prevention, and statin intolerance.

PMHX:

- Coronary artery disease.
  - Stent placed in OM1 in 2003 at time of NSTEMI
  - Additional stent placed distal to this segment in 2017 for recurrent angina. Mild to moderate disease in the remaining vessels.
- PAF s/p RFA
- HTN: well controlled
- Mixed HLD
- Statin intolerance: Not currently on statin therapy (no h/o ↑ CK)
  - Atorvastatin: muscle aches. Unknown Dose
  - Lovastatin: muscle aches. Unknown Dose
  - Niacin ER: tolerated but stopped for unknown reasons

Vitals:

- BP 110/60, pulse 75 bpm. BMI 27. Waist 41 in.
- Physical exam is otherwise unremarkable

Social: non-smoker. Exercises, walking 1-2 miles per day.

FHX: Dad had an MI in his early 40s

Meds:

- Aspirin 81 mg daily
- Clopidogrel 75 mg daily
- Zetia 10 mg daily
- Ramipril 10 mg daily
- Triamterene-hydrochlorothiazide 37.5-25 mg daily

<table>
<thead>
<tr>
<th>Date</th>
<th>Total Chol (mg/dL)</th>
<th>HDL</th>
<th>LDL</th>
<th>TG</th>
<th>Total LDL Particle # (&lt;1000 nmol/L)</th>
<th>Small LDL Particles (&lt;527 nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/2017</td>
<td>200</td>
<td>38</td>
<td>141</td>
<td>223</td>
<td>2059</td>
<td>1388</td>
</tr>
</tbody>
</table>
68 y/o presents to the lipid clinic for hyperlipidemia, secondary prevention, and statin intolerance.

Plan:
• Continue Zetia 10 mg daily (recently started)
• Add Crestor 5 mg 3 days a week, with plans to titrate up as tolerated

Update after phone call 2 weeks after starting Crestor
• Significant myalgias. Not able to exercise.

Plan #2:
• Continue Zetia 10 mg daily (recently started)
• Add evolocumab (Repatha) 140 mg SC injection every 2 weeks

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<td>223</td>
</tr>
<tr>
<td>1/2018</td>
<td>103</td>
<td>45</td>
<td>36</td>
<td>109</td>
</tr>
</tbody>
</table>

74% LDL reduction
Initial flu-like symptoms but otherwise tolerating well
Conclusions

• Statin therapy improves outcomes
• Discontinuing statin therapy is associated with worse outcomes
• Take a detailed history to ensure symptoms are attributable to statin therapy
  • Check for associated conditions / RF like vit D def, hypothyroidism, and drug-drug interactions
• Most patients who have a side effect to one statin, can tolerate another
• If not at goal despite max tolerated statin therapy, consider Zetia and PCSK9 inhibitors
• Referral to the lipid clinic
Thank you!

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