Evaluating, Managing, and Treating Statin Intolerance

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Evaluating for Statin Intolerance
Statin Therapy: Monitoring Therapeutic Response and Adherence.

The management of statin intolerance

Current Guidelines Suggestions
1st Assess and Evaluate for:

• Less anticipated therapeutic response due to:
  – poor adherence
  – Myalgias
  – hair loss
  – malaise,
  – GI upset

• Individuals intolerant of the recommended intensity of statin therapy should use the maximally tolerated intensity of statin.
  – Establish the symptoms are statin related by a statin re-challenge.
  – Rule out secondary causes of statin intolerance.
2013 ACC/AHA Recommendations

- Refer to Table 8 in your briefing materials (pictured to the right)
- Obtain a history of muscle symptoms.
- Unexplained severe pain, discontinue and evaluate CK, UA for myoglobinuria for rhabdomyolysis.
- For mild to moderate musculoskeletal pain, re-challenge statin.
- If causal relationship with previous statin, use low dose different statin.
- Evaluate patient for other secondary causes.

Stone et al. ACC/AHA 2013 Blood Cholesterol Guidelines
Factors that Increase the Risk of Statin-Induced Myopathy

**Patient Characteristics**
- Increased age
- Female
- Renal insufficiency
- Hepatic dysfunction
- Hypothyroidism
- Diet - grapefruit and other juices potentiate statin
- Polypharmacy
- Rheumatologic disorders

**Statin Properties**
- High systemic exposure
- Lipophilicity
- High bioavailability
- Limited protein binding
- Potential for drug-drug interactions metabolized by the CYP pathways (especially CYP 450 3A4)

Stone et al. ACC/AHA 2013 Blood Cholesterol Guidelines
Clinical Evaluation of Statin Myopathies

• History:
  – Obtain h/o MSK complaints prior to statin initiation
  – Focus on timing of symptoms in relation to statin initiation/titration
  – Unusual physical activity or concurrent illness
  – Diet (daily grapefruit consumption)
  – Clues to suggest other causes of myopathy
    • Hypothyroidism
    • Vitamin D deficiency
    • Autoimmune disease
    • Neuromuscular disease
    • Systemic illness

• Medications
  – Drugs that inhibit cytochrome P450 3A4 (clarithromycin, HIV meds, voriconazole, etc)
  – Fibrates
  – Independently cause myopathy (steroids, cyclosporine, etc)

• Physical exam
  – Proximal LE weakness

Welcome to ACC’s Statin Intolerance Tool

This tool should be used by clinicians to assess, treat, and manage patients with possible statin intolerance.

Although muscle symptoms may occur, true statin intolerance is uncommon. Given the benefits of statins in ASCVD risk reduction, clinicians should partner with the patient to gain a thorough symptom history and determine if he or she is truly statin intolerant. Walk through the steps of treating and managing a patient who reports muscle symptoms, including cycles of statin discontinuation and rechallenge to identify a tolerated statin and dose.

1. Evaluate
Review of Statins

- There are 7 Statins Available
  - Atorvastatin
  - Fluvastatin
  - Lovastatin
  - Pitavastatin
  - Pravastatin
  - Rosuvastatin
  - Simvastatin
CYP450 Isoenzymes Known to Oxidize Clinically Used Drugs

• CYP2C9
  – alprenolol, diclofenac, fluconazole, **fluvastatin**, hexobarbital N-desmethyldiazepan, tolbutamide, **warfarin**

• CYP3A4
  – amlodipine, amiodorone, **atorvastatin**, clarithromycin, cyclosporine A, diltiazem, erythromycin, ketoconazole, itraconazole, **lovastatin**, mibefradil, midazolam, nefazodone, nifedipine, protease inhibitors, quinidine, **sildefanil**, **simvastatin** (including combos), terbinafine, verapamil, **warfarin**

**Rosuvastatin**: CYP2C19 and biliary excretion

**Pravastatin**: Sulphation, biliary excretion, urinary excretion

**Pitavastatin**: CYP2C8, CYP2C9 and lactonization and biliary excretion

2015 updated by Dr. Rhonda Cooper Dehoff
Safety Considerations with Dosing Statins

- Use reduced dosages of drugs when prescribing statins in the same CYP450 pathway.
  - Increased risk of toxicity
  - Increased risk of myopathy
  - Increased risk of rhabdomyolysis
Clinical Pearl…. 

• If a patient is achy on Simvastatin, they may also be achy on Atorvastatin as it uses the same CYP3A4.

• Try a Statin with a different CYP450 pathway such as Rosuvastatin, Fluvastatin, Pitavastatin and select based on your LDL reduction goal (If we still use goals???).
Lipid Clinic Treatment Strategies

- Avoid drug-drug Interactions
- Select a drug with less utilization of the CYP pathway
- Alternate Statin Dosing (Monday, Thursday dosing for 1 month add one day per week as tolerated).
- Daily Low Dose Statin
- Use Hydrophilic Statins (pravastatin, rosuvastatin, and fluvastatin)
- Plant Sterols 5-10% reduction
- Soluble Fiber
- Mediterranean Eating- PUFAs
- Less data- Vitamin D, Co Q 10
What if your patient is still not medically optimized?
Before considering alternate statin therapies,

• Reiterate adherence to lifestyle and statin therapy
• For patients who are completely statin intolerant, may consider the addition of a non-statin cholesterol-lowering therapy (remember there are 7 to try).
• Add on therapy
**IMPROVE-IT**

**Trial design:** Patients with recent ACS were randomized in a 1:1 fashion to either ezetimibe 10 mg/simvastatin 40 mg or simvastatin 40 mg. They were followed for 6 years.

**Results**
- Primary endpoint (CV death/MI/UA/coronary revasc./stroke/moderate/severe bleeding) for ezetimibe/simvastatin vs. simvastatin: 32.7% vs. 34.7%, HR = 0.94, 95% CI 0.89-0.99; p = 0.016
- MI: 13.1% vs. 14.8%, p = 0.002; stroke: 4.2% vs. 4.8%, p = 0.05; CVD/MI/stroke: 20.4% vs. 22.2%, p = 0.003
- Median LDL follow-up average: 53.7 vs. 69.5 mg/dl

**Conclusions**
- In patients with high-risk ACS, ezetimibe 10 mg/simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing adverse CV events
- This is the first study powered for clinical outcomes to show a benefit with a nonstatin agent
- Reaffirms the "lower is better" hypothesis with LDL-C

Presented by Dr. Christopher Cannon at AHA 2014
Safety and efficacy of PCSK9 inhibitors in patients with statin intolerance

Mean Percent Change in LDL-C from Baseline to Week 12 in Patients Who Received Evolocumab
- Patients who received evolocumab
  - (A) every 2 weeks
  - (B) monthly.

JACC.2014;63:2541–2548
GAUSS-2: Adverse events on placebo, ezetimibe, evolocumab

<table>
<thead>
<tr>
<th>Event</th>
<th>Ezetimibe</th>
<th>Evolocumab</th>
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<tbody>
<tr>
<td></td>
<td>QD = PBQ</td>
<td>QD = PBQ</td>
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<tr>
<td>Treatment emergent</td>
<td></td>
<td></td>
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<tr>
<td>Any</td>
<td>35 (69)</td>
<td>39 (77)</td>
</tr>
<tr>
<td>Serious</td>
<td>1 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Leading to discontinuation of investigational product</td>
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<td>9 (18)</td>
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<tr>
<td>Deaths</td>
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<td>0</td>
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<tr>
<td>Common treatment emergent:</td>
<td></td>
<td></td>
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<tr>
<td>Headache</td>
<td>3 (6)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7 (14)</td>
<td>11 (22)</td>
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<tr>
<td>Pain in extremity</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>3 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (8)</td>
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<td>Nausea</td>
<td>3 (6)</td>
<td>5 (10)</td>
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<td>Nasopharyngitis</td>
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<td>4 (8)</td>
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<td>Injection site erythema</td>
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<td>3 (6)</td>
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<tr>
<td>Paraphositis</td>
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<td>4 (8)</td>
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<tr>
<td>Influenza</td>
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<td>Pruritis</td>
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<td>3 (6)</td>
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<td>Abnormal laboratory tests:</td>
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<td>CK &gt;5 × ULN</td>
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<td>CK &gt;10 × ULN</td>
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<td>ALT or AST &gt;3 × ULN</td>
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<td>Muscle-related EMG</td>
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<tr>
<td>Myalgia</td>
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<td>11 (22)</td>
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<td>Increased plasma creatinine</td>
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<td>Anti-evolocumab antibodies</td>
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<td>Binding</td>
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<tr>
<td>Neurocognitive adverse events</td>
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ODYSSEY ALTERNATIVE

**Trial design:** Patients with statin intolerance were randomized in a 2:2:1 fashion to either self-administered alirocumab 75 mg SC Q2W, ezetimibe 10 mg daily, or atorvastatin 20 mg daily and followed for 24 weeks.

**Results**
- % decrease in LDL-C levels at 24 weeks from baseline for alirocumab vs. ezetimibe:
  - 45% vs. 14.6%, difference 30.4%, $p < 0.0001$
- Absolute ↓ in LDL from baseline:
  - 84 vs. 33 mg/dl
- LDL-C <100 mg/dl:
  - 61% vs. 10%, $p < 0.0001$
- Muscle-related side effects:
  - 32.5% vs. 41.1%, $p = 0.096$

**Conclusions**
- Alirocumab is superior to ezetimibe in lowering LDL-C levels and achieving target levels in statin-intolerant patients, with a lower risk of muscle-related side effects
- Trial adds to the growing body of literature with PCSK9 inhibitors

Moriarty PM at AHA Scientific Sessions. Chicago, IL. 2014. LBCT.02
### ODYSSEY ALTERNATIVE

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<th>Alirocumab</th>
<th>Ezetimibe</th>
<th>Atorvastatin</th>
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<td>Treatment emergent adverse event (%)</td>
<td>82.5</td>
<td>80.6</td>
<td>85.7</td>
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<td>Serious adverse events (%)</td>
<td>9.5</td>
<td>8.1</td>
<td>11.1</td>
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<td>Adverse events leading to discontinuation (%)</td>
<td>18.3</td>
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<td>25.4</td>
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<td>Skeletal muscle related adverse event (%)</td>
<td>32.5</td>
<td>41.1</td>
<td>46.0</td>
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<tr>
<td>Skeletal muscle related adverse event leading to discontinuation (%)</td>
<td>15.9</td>
<td>20.2</td>
<td>22.2</td>
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</table>
Final Thoughts

• Statin therapy is the gold standard for the management of the patient with ASCVD.
• There are several studies published on alternative dosing regimens however they are mainly small and observational but seem to be effective in the clinical setting.
• PCSK9 inhibitors are an exciting new therapy that may potentially become an addition/ alternative to statin therapy in patients who otherwise do not tolerate adequate statin dosing.
Thank you