Statin intolerance:
Does it exists? & How to manage?

By

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Agenda

- Introduction
- Epidemiology
- Definition and classification
- Risk factors and mechanism
- Diagnosis
- Management
- Take home messages

Introduction

- HMGCoA reductase inhibitors or statins have revolutionized the treatment of hypercholesterolemia and the management of patients with increased cardiovascular disease (CVD) risk.
- Statins are well tolerated, but are associated with skeletal muscle, metabolic, neurological, and other possible side effects.
- Such reports are labeled as statin associated symptoms (SAS) because there is no consensus that statins are actually causative.
- SAS is favored over the term statin intolerance because many patients with SAS can tolerate reduced doses of these drugs.
Epidemiology

- Statin associated muscle symptoms (SAMS), the most common statin side effect, are reported by 10% to 25% of patients receiving statin therapy in observation studies and clinical registries while it is 5% in clinical trials.
- Cessation of statin treatment is associated with worse CV outcomes.
- A metaanalysis of 15 statin studies observed a 45% increase in all cause mortality and a 15% increase in CVD events in patients taking <80% of their prescribed statin therapy versus patients who were more adherent.

Potential adverse effects of statin

**Good supportive evidence**
- Myopathy
- Hepatic enzyme elevation
- Incident DM

**Little or no supportive evidence**
- Cancer
- Intracerebral hemorrhage
- Psychiatric illness
- Erectile dysfunction
- Cataract
- Abdominal pain
- Permanent hepatic or renal injuries
**Definition & Classification**

- Statin intolerance is the inability to tolerate a dose of statin required to sufficiently reduce LDL C level and cardiovascular risk.
- A syndrome that has been verified, confirmed and documented that leads to suboptimal statin dosing, reductions in statin compliance, reductions in patient quality of life and function, statin cessation, and/or suboptimal LDL-C lowering.
- It may be:
  - Complete intolerance to any statin by any dose
  - Partial intolerance can tolerate statin in less than guideline recommended dose

**Definition & Classification**

- Myopathy any muscle symptoms related to statin
- Myalgia muscle pain with normal CK
- Myositis muscle pain with raised CK
- Myonecrosis
  - Mild > 3 ULN CK
  - Moderate 10-50 ULN CK
  - Severe > 50 ULN
- Rhabdomyolysis CK> 10 ULN, Myoglobinuria and + 0.5 mg creatinine above the basal
**Risk factors for statin intolerance**

**Patient related**
- Old age > 75 y
- Female sex
- Low BMI
- Positive FH of muscle disease
- Heavy exercise
- Associated comorbidities: severe hepatic or renal disease, vitamin D def. Disorders of calcium homeostasis, surgery and major trauma & hypothyroidism

**Drug related**
- Dose of statin
- Type of statin
- Food interaction grape fruit, alcohol
- Drug interaction amiodarone, cyclosporine, antifungal, diltiazem

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**Table 15** Drugs potentially interacting with statins metabolized by CYP3A4 leading to increased risk of myopathy and rhabdomyolysis

<table>
<thead>
<tr>
<th>Anti-infective agents</th>
<th>Calcium antagonists</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>Verapamil</td>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Diltiazem</td>
<td>Danazol</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Amlodipine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>Ranolazine</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Telithromycin</td>
<td></td>
<td>Nefazodone</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td></td>
<td>Gemfibrozil</td>
</tr>
</tbody>
</table>
**SAMS with different statin in PRIMO study**

<table>
<thead>
<tr>
<th>Drug</th>
<th>No of patients</th>
<th>SAMS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin 80 mg</td>
<td>3121</td>
<td>5.1</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>1844</td>
<td>14.9</td>
</tr>
<tr>
<td>Pravastatin 40 mg</td>
<td>1901</td>
<td>10.9</td>
</tr>
<tr>
<td>Simvastatin 40-80 mg</td>
<td>1027</td>
<td>18.2</td>
</tr>
</tbody>
</table>

**Mechanisms of SAMS**

- Reduced sarcolemmal or T tubule cholesterol is a possible mechanism
- Reduction of coenzyme Q
- Stimulation of myocyte apoptosis
- Activating the phosphoinositide 3kinase (PI3K)/Akt pathway.
- Statins also appear to impair mitochondrial function.
**Statin myalgia index score**

<table>
<thead>
<tr>
<th>Clinical symptoms—new or increased unexplained muscle symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regional distribution pattern</strong></td>
<td></td>
</tr>
<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>Nonspecific asymmetric—intermittent</td>
<td>1</td>
</tr>
<tr>
<td><strong>Temporal pattern</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms onset &lt; 4 wk</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms onset 4 - 12 wk</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms onset &gt; 12 wk</td>
<td>1</td>
</tr>
<tr>
<td><strong>Dechallange</strong></td>
<td></td>
</tr>
<tr>
<td>Improves on withdrawal—&lt; 2 wk</td>
<td>2</td>
</tr>
<tr>
<td>Improves on withdrawal—2 – 4 wk</td>
<td>1</td>
</tr>
<tr>
<td>Improves on withdrawal—&gt; 4 wk</td>
<td>0</td>
</tr>
<tr>
<td><strong>Challenge</strong></td>
<td></td>
</tr>
<tr>
<td>Same symptoms reoccur on rechallenge—&lt; 4 wk</td>
<td>2</td>
</tr>
<tr>
<td>Same symptoms reoccur on rechallenge—4 – 12 wk</td>
<td>1</td>
</tr>
</tbody>
</table>

**Probable** 9-11  
**Possible** 7-8  
**Unlikely** < 7

**Non-invasive tests for SAMS**

- Basal CK
  - Mild < 4ULN
  - Moderate 4-10 ULN
  - Severe > 10 ULN
- Post-exercise CK
- Muscle strength testing
- P 33 MRI
- Genetic testing
- Auto Antibodies to HMGcoA reductase for autoimmune statin myopathy
**Clinical approach to SAMS**

Rosenson, R.S. et al. J Am Coll Cardiol. 2017

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**CENTRAL ILLUSTRATION** Clinical Approach to Patient With SAMS

- Patient with suspected statin-associated muscle symptoms (SAMS)
- Clinical assessment: Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)

**Low SAMS-CI score**

- Evaluate for:
  - Other causes affecting musculoskeletal system
  - History of medication-related side effects
  - Depression and anxiety

- Statin discontinuation

- After symptom resolution, initiate:
  - Same dose of same statin (low likelihood that SAMS will reoccur)
  - Alternative high-intensity statin

- Address concerns about side effects
  - Promote a healthy lifestyle
Algorithm for treatment of muscular symptoms during statin treatment

**High SAMS-CI score**

Before establishing a diagnosis of statin intolerance:
- Review drug-drug interactions and co-morbidities
- Check for hypothyroidism and vitamin D deficiency which could increase SAMS

- Statin discontinuation
- After symptom resolution, initiate:
  - Lower dose of same statin
  - Alternative high-intensity statin
- Readminister SAMS-CI

If still high SAMS-CI score, initiate:
- Statin with different pharmacokinetic properties
- Consider non-statin LDL-C lowering therapy
- Address concerns about side effects
  - Promote a healthy lifestyle

**Consider if statin-attributed muscle symptoms favour statin continuation / reinitiation**

- Symptomatic & CK < 4 X ULN
  - 2-4 weeks washout of statin
    - Symptoms persist: statin re-challenge
    - Symptoms improve: second statin at usual or starting dose
      - Symptom-free: continue statin
      - Symptoms re-occur
- CK ≥ 4 X ULN +/- rhabdomyolysis
  - 6 weeks washout of statin until normalisation of CK: creatinine and symptoms
Algorithm for treatment of muscular symptoms during statin treatment

1. Low-dose third efficacious (potent) statin;
2. Efficacious statin with alternate day or once/twice weekly dosing regimen

Aim: achieve LDL-C goal with maximally tolerated dose of statin

Ezetimibe

A + bile acid absorption inhibitor
B + fibrate (not gemfibrozil)
A + B

If still not at goal: consider additional (future) novel therapies: PCSK9 monoclonal antibody therapy, CETP inhibitor

Non-statin Pharmacotherapy

- Ezetimibe
- Bile acid sequestrant
  - Colesevelam
  - Cholestyramine
  - Colestipol
- PSCK9 inhibitors
- Fibrates
- Niacin
- Bempedoic acid investigational drug
**ODYSSEY ALTERNATIVE: Alirocumab in Statin Intolerance**

- **ITT (primary endpoint)**
  - Alirocumab: n=126, -45.0%
  - Ezetimibe: n=122

  Alirocumab vs ezetimibe:
  - -30.4 (3.1); P < .0001

- **On-treatment (key secondary endpoint)**
  - Alirocumab: n=126, -17.1%
  - Ezetimibe: n=122

  Alirocumab vs ezetimibe:
  - -35.1 (2.8); P < .0001


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**GAUSS-3: Better LDL-C Lowering**

- **Baseline to Study Week**
  - **LDL-C Change From Baseline, %**

- **No. of Patients**
  - **Ezetimibe**
    - 73
    - 72
    - 70
    - 67
    - 67
    - 64
    - 60
    - 57
  - **Evolocumab**
    - 145
    - 142
    - 142
    - 139
    - 137
    - 127
    - 127
    - 117

Ezetimibe dose: 10 mg/d; evolocumab dose: 140 mg 3 × /mo (420 mg total dose/mo). GAUSS-3 indicates Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3. Error bars indicate 95% CIs.

**Nutraceuticals**

- Coenzyme Q 10
- Vitamin D
- Phytosterols
- Viscous fiber
- Red yeast rice
- Others: curcumin, fish oils and omega 3 FA

**Take home messages**

- Statin are a corner stone in prevention and management of ASCVD
- Statin associated side effects especially SAMS are an important cause for non-adherence to this important pharmacotherapy
- Up to 90% of patient diagnosed with SAMS can tolerate statin on stepwise approach
- Lower dose, alternate statin, use of long acting statin/2d or once or twice weekly can help in rechallenge therapy
- Non statin pharmacotherapy, nutraceutical, life style modifications, and psychotherapy are helpful in overcoming this problem
شكرا لحسن استماعكم
Thank you