Management of Patients Intolerant to Statins

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Statin Intolerance

Disclosures

- NONE -

Statin Intolerance

Gold standard Rx of elevated cholesterol in patients with elevated CV risk

Statin Intolerance

Effectiveness of Statins @ 5 years

- Reducing LDL-C by 1.0 mmol/L (38.7mg/dl)
  - 12% Reduction: all cause mortality
  - 23% Reduction MI
  - 24% Reduction in need for coronary revascularization
  - 17% Reduction fatal/non fatal stroke
  - 21% Reduction stroke and CV death

Cholesterol Treatment Trials
Lancet 2010;376:1670 Circulation 2016;133:256

Statin Intolerance

Statin Associated Muscle Symptoms

Treatment

- Important to understand -
  - Patients subjective assessment of perceived risks
  - Patients understanding of benefits of Rx

Definition: 2016

1. “A clinical syndrome, not caused by drug interaction or risk factors for untreated intolerance as characterized by significant symptoms and/or biomarker abnormalities that prevent long-term use of statins documented by challenge/dechallenge/rechallenge, using at least two statins, including Atorvastatin and Rosuvastatin, and that leads to failure of maintenance of therapeutic goals, as defined by national guidelines”

Mancini GB. et al
Can J Cardiol 2016;32:S35
Statin Intolerance

Symptoms

- Appear within 1st 3 months
- Improve after suspension
- Recur after reintroduction

Statin Intolerance

- Most commonly attributed to muscle related events

New onset diabetes: Rx 500 to see 1
Severe liver damage: NNH = 1M

True Statin Intolerance

Frequency

Complete statin intolerance requiring statin discontinuation affects <5% of patients with statin intolerance symptoms

Statin Intolerance

Statin Associated Muscle Symptoms

SAMS

- Myalgia: Discomfort, pain (Normal CK)
- Myopathy: Weakness, +/- Pain (Normal or Elevated CK)
- Myositis: Inflammation
- Myonecrosis: Elevated CK levels (>3x)
- Rhabdomyolysis: Myonecrosis with Myoglobinuria or acute renal failure
  (1.6 per 100,000 pt. years)

Statin Intolerance

Statin Associated Muscle Symptoms

Rhabdomyolysis: Rare

- FDA Database -

Associated with Concomitant Drugs in 58%

- Gemfibrozil- 38%
- Digoxin- 5%
- Cyclosporine- 4%
- Warfarin- 4%
- Macrolide ABX- 3%
- Azol Antifungal- 1%
**Autoimmune Myopathy**

- 2-3 per 100,000 -
  - Progressive proximal muscle weakness
  - Elevated CK levels (typically >10x)
  - Antibodies against HMG-CoA reductase
  - Muscle Bx - necrotizing myopathy without severe inflammation
  - Myopathy progresses despite d/c statins
  - Rx: Immunosuppression

**Statin Intolerance**

**Options for Care**

**Avoiding Statin Discontinuation**

- Step by step reduction in statin dose (de-challenge)
- Convert to different statin
- Alternate day RX
- New non statin agents (nutraceuticals)
- Re-challenge those who have discontinued

**Management**

**Alternative Drugs**

- Ezetimibe (Zetia) - Blocks intestinal absorption of cholesterol, both dietary and biliary
  (Lower LDL = 14%)
- Bile acid sequestrants
  - Cholestyramine (Questran)
  - Cholestipol (Colestid)
  - Colesevelam
  (Lower LDL 12-28%)
- PCSK-9 Inhibitors - Monoclonal Ab that inhibits PCSK-9 and exposes LDL Receptors
  - Evolocumab (Repatha)
  - Alirocumab
  (Lower LDL=60%)

**Prevalence of SAMS**

<table>
<thead>
<tr>
<th>Source</th>
<th>Prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>30% Randomized Trials</td>
<td></td>
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<tr>
<td>16.5% PRIMO Survey (France)</td>
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<tr>
<td>STOMP Study - Randomized Trial</td>
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<tr>
<td>Atorvastatin</td>
<td>9.4%</td>
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<tr>
<td>Placebo</td>
<td>4.6%</td>
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**Lipophilic vs Hydrophilic**

Change from hydrophilic to lipophilic statin ie: Rosuvastatin, Pravastatin to Atorvastatin
**Submassive P.E: Seattle II Study**

### Statin Intolerance Management

**Nutraceuticals**

- **Monacolins** - Inhibit HMG-CoA Reductase
  - Policosanols
  - Bergamot
  - Red Yeast Rice Extract (Armolipid Plus)
    - (Lowers LDL 15%-20%)
- **Icosapent Ethyl (Vascepa)**
  - (Lowers LDL 6%)
- **Chokeberry Extract**
  - (Lowers LDL 30-38%)

  *Spirulina, Curcumin, Berberine... Not Well Studied*

### Statin Intolerance Summary

**True statin intolerance requiring d/c of statin occurs in <0.5%**

- Severe hepatotoxicity or muscle injury is rare
- Dose reduction, de-challenge, re-hallenge, and changing statin are effective methods of mgt.

### Alternative Medications

- Nutraceuticals are options
- Mediterranean Diet - Effective but Difficult

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**Inova Heart and Vascular Institute**

**Thank You!**