A Practical Approach to Managing Statin Myalgias

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What is statin intolerance?

• Statin intolerance is an imprecise term
What is statin intolerance?

- Classically it refers to a symptom, most commonly diffuse muscle pain or arthralgia without known cause, or a biochemical abnormality that can be attributed temporally and unequivocally to the use of statin.
What is statin intolerance?

- **Re-challenge** is a cornerstone of this definition, however, this is often not undertaken, especially when initial problems have been particularly severe, when practitioners lack the confidence to re-challenge or when patients express incredulity or resistance about the value of re-challenge.
What is statin intolerance?

• Intolerance is also **not all or none**. It has a spectrum of severity that may be determined by the dose used and may be related to either a specific statin or sometimes more than one or all of them.
What is statin intolerance?

- The inability to achieve cholesterol targets with statin monotherapy due to inability to tolerate maximal doses of statins is sometimes also considered to be a form of statin intolerance even though a lower dose of statin is fully tolerated and cholesterol targets are met through adjuncitive therapies.
What is statin intolerance?

- There is no established biomarker for statin intolerance other than CK as an aid for evaluating frank myositis and rhabdomyolysis.
What is statin intolerance?

- Statin intolerance pre-supposes exclusion of predictable drug-drug interactions or predisposing circumstances (e.g., febrile illnesses).
What is statin intolerance?

• Thus, statin intolerance is defined within these **broad boundaries** and requires careful **empirical assessment** before applying the term.
Review

Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Proceedings of a Canadian Working Group Consensus Conference

G. B. John Mancini, MD, Steven Baker, MD, Jean Bergeron, MD, David Fitchett, MD, Jiri Frohlich, MD, Jacques Genest, MD, Milan Gupta, MD, Robert A. Hegele, MD, Dominic Ng, MD, and Janet Pope, MD

- Increasing numbers of patients are eligible for statin therapy
- In spite of safety, absolute number of cases of “intolerance” create a significant case load
- Needless tests and referrals are reaching a critical level
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Mancini GBJ et al: CJC 2011;27:635-662
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Mancini GBJ et al: Canadian Journal of Cardiology 2011;27:635-662
Consensus Terminology

• Myopathy: A general term referring to ANY disease of muscle
• Symptomatic Myopathy
  – Myalgia: CK \leq ULN
  – Myositis: CK > ULN
  • Rhabdomyolysis: CK > 10x ULN (>10,000 U/L), myoglobinuria, may have renal dysfunction and other systemic features, emergency situation requiring hydration, observation
Severity of “hyperCKemia” (With/without Symptoms/Complications)

- **SEVERE:** > 50x ULN
- **MODERATE:** > 10x, ≤ 50x ULN
- **Mild**
  - Grade 1: > 1x, ≤ 5x ULN
  - Grade 2: > 5x, ≤ 10x ULN

• Idiopathic/Benign/Chronic elevations may be seen (“black/brown”)

**GET HELP!**

**GET CONFIDENT!**
Can statin-associated muscle symptoms be prevented or relieved with vitamins, minerals, supplements?

• **NO!**
• Currently, there is no good evidence to support use of CoEQ10, Mg, quinine, Vitamin D
• Electrolyte and vitamin deficiencies should be treated but these are **RARELY** detected during work up of statin-associated muscle symptoms
• **Hypothyroidism** should be ruled out before using lipid lowering agents and treated appropriately during therapy as untreated hypothyroidism is associated with increased risk of statin intolerance
All effective approaches incorporate altered statin (type/dose/frequency) with/without non-statin supplements.

- Behavioural intervention takes on an even more critical role (diet/exercise/weight loss)
- Consider **phytosterols** as part of the dietary intervention (margarines, yogurts, capsules)
- Identify the highest dose and greatest frequency of dosing of the most potent statin that is tolerated (**atorvastatin**, **rosuvastatin**)
- Consider less potent statins (**simva** > **prava** > **fluva**)
- **Adjuncts/replacements**: **ezetimibe**, **niacin**, **resins**, **fibrates**
Figure 5. Management approach for muscle symptoms or hyperCKemia. CK, creatine kinase; ULN, upper limit of normal.
Table 4. Differential diagnosis of myopathy or creatine kinase elevations not due to lipid-lowering therapy

<table>
<thead>
<tr>
<th>Muscle Symptoms</th>
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<tbody>
<tr>
<td>● Physical exertion</td>
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<tr>
<td>● Viral illness</td>
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<td>● Vitamin D deficiency</td>
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<tr>
<td>● Hypo- or hyperthyroidism</td>
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<tr>
<td>● Cushing syndrome or adrenal insufficiency</td>
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<tr>
<td>● Hypoparathyroidism</td>
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<tr>
<td>● Fibromyalgia</td>
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<tr>
<td>● Polymyalgia rheumatica</td>
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<tr>
<td>● Polymyositis</td>
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<tr>
<td>● Systemic lupus erythematosus</td>
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<tr>
<td>● Tendon or joint disorder</td>
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<tr>
<td>● Trauma</td>
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<tr>
<td>● Seizure or severe chills</td>
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<tr>
<td>● Peripheral arterial disease (exertional buttock, thigh, calf symptoms)</td>
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<tr>
<td>● Medications (glucocorticoids, antipsychotics, antiretroviral drugs, illicit drugs [cocaíne or amphetamines])</td>
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</tbody>
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<table>
<thead>
<tr>
<th>CK Elevations</th>
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<tbody>
<tr>
<td>● Physical exertion</td>
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<tr>
<td>● Hypothyroidism</td>
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<tr>
<td>● Metabolic or inflammatory myopathies</td>
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<tr>
<td>● Alcoholism</td>
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<tr>
<td>● Neuropathy or radiculopathy</td>
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<tr>
<td>● Seizure or severe chills</td>
</tr>
<tr>
<td>● Trauma</td>
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<tr>
<td>● Medications (illicit drugs [cocaíne or amphetamines], antipsychotics)</td>
</tr>
<tr>
<td>● Ethnicity (black patients may have elevated baseline CK levels)</td>
</tr>
<tr>
<td>● Idiopathic hyperCKemia (high CK with no demonstrable cause)</td>
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</tbody>
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CK, creatine kinase.
Reproduced with permission from Joy and Hegele.⁶
<table>
<thead>
<tr>
<th>Type of interaction</th>
<th>Examples of drugs</th>
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<tr>
<td>Inhibition of CYP3A4</td>
<td>• “Azole” antifungals: itraconazole, ketoconazole, miconazole</td>
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<tr>
<td></td>
<td>• Macrolide antibiotics: erythromycin, telithromycin, clarithromycin</td>
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<td></td>
<td>• Protease inhibitors: amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir</td>
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<td></td>
<td>• Fibrates: gemfibrozil, bezafibrate, fenofibrate, ciprofibrate</td>
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<td></td>
<td>• Verapamil, diltiazem</td>
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<td></td>
<td>• Warfarin</td>
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<td>Inhibition of CYP2C9</td>
<td>• Amiodarone</td>
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<td></td>
<td>• Omeprazole</td>
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<tr>
<td>OATP1B1</td>
<td>• Gemfibrozil</td>
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<td></td>
<td>• Cyclosporine</td>
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<tr>
<td>Various mechanisms</td>
<td>• Digoxin</td>
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<tr>
<td></td>
<td>• Colchicine</td>
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<td>• Niacin</td>
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CYP, cytochrome; OATP, organic anion transporting polypeptide.
Adapted from Neuvonen et al.\textsuperscript{177}
Figure 5. Management approach for muscle symptoms or hyperCKemia. CK, creatine kinase; ULN, upper limit of normal.
Figure 6. Management approach for patients with liver disease and/or transaminitis. ULN, upper limit of normal.
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Conclusions

• Don’t count on vitamins, minerals, supplements to alleviate pain
• Don’t hesitate to seek help/refer patients with hyperCKemia > 10x ULN, with or without symptoms
• For lesser degrees of hyperCKemia and/or milder symptoms, systematically assess response to re-challenge, lower dose/frequency, different statin
• Use non-statin drugs as alternates/adjuncts to achieve targets