Clinical Pharmacology & Toxicology Pearl of the Week

Statin Intolerance

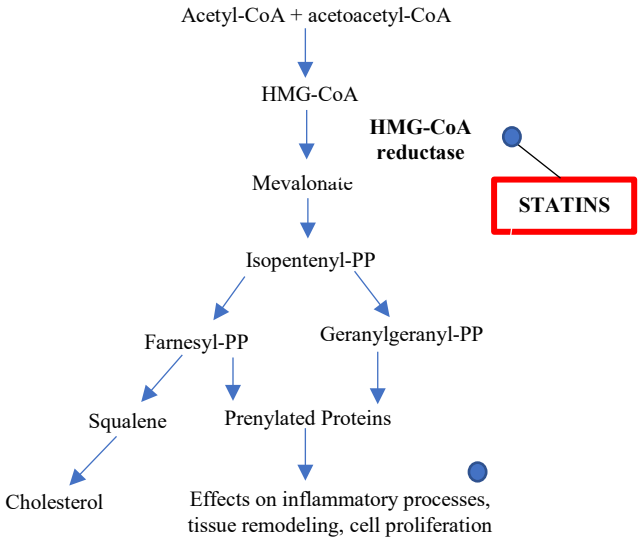
Case

- 54 yo M with hypertension, T2DM, obesity presents for assessment for dyslipidemia
- Myocardial perfusion scanning reveals large burden coronary calcium and Framingham Risk Score of 20.6% 10-year risk of MI or death
- Chronic mild elevations in CK noted on bloodwork
- Initiated on atorvastatin
- Re-presents to clinic 1-month later complaining of bilateral shoulder and upper back pain with on-going but unchanged elevations in CK

How would you manage this patient?

Statins

- 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor
- Reduce the plasma concentrations of total cholesterol, LDL-C, VLDL-C, triglycerides, apo-B, and increase the plasma concentrations of HDL-C
- Cardiovascular protective effects due to inhibition of the production of prenylated proteins



Statin associated adverse muscle events (SAMS)

- Currently no universally accepted definition of statin intolerance/toxicity exists
- Can be characterized by:

1. Asymptomatic CK elevation
2. Myalgia – muscle pain/weakness without CK elevation
3. Myositis – muscle pain/weakness with CK elevation <10x ULN
4. Rhandomyolysis – muscle symptoms with raised CK typically >10x ULN, renal injury

Prevalence

- Studies quote 1.5 – 3% of statin users in randomized controlled trials and up to 10-13% of participants enrolled in prospective clinical studies develop myalgia
- Differs for different classes of statins (discussed below)
- Studies have quoted average incidence of hospitalization for rhabdomyolysis was 0.44 for 10 000 patient years for patients treated with atorvastatin, pravastatin, or simvastatin monotherapy
- Estimated that 40% of people discontinue statins within 1 year of initiation, rates even higher for primary prevention

Risk Factors

- Female sex
- Age > 80
- Small body frame and frailty
- Low BMI
- Asian ethnicity
- Pre-existing neuromuscular disorders
- Hypothyroidism
- Vitamin D deficiency
- Concurrent Drug Therapy
- Exercise

Clinical Findings

- Typically presents as proximal, symmetric muscle weakness
- May be associated muscle tenderness and functional impairments such as raising arms above head
- Onset usually within weeks to months of after initiation of statin therapy
- Mean duration of therapy before symptom onset was 6.3 months for one study (range 0.25 to 48 months)

Laboratory testing

- Can be associated with mild elevations in CK (usually <10x ULN)
- Rarely, CK elevated above 10x ULN
- Can have associated increase in creatinine if patient developing rhabdomyolysis
- Asymptomatic elevations in liver enzymes can be seen in up to 3% of patients
    - Usually these are < 3x ULN and will self-resolve
    - If persistent and above 3x ULN, consider drug-induced liver injury

Proposed Mechanisms of Myopathy

- Genetic Factors
    - Single nucleotide polymorphism in SLCO1B1
    - Encodes orgnanin-anion transporting polypeptide (OATP)1B1 which regulates hepatic uptake of statins
    - Hydrophilic statins use (OATP)1B1 for statin uptake into hepatocytes
- Metabolic Factors
    - Mitochondrial dysfunction
    - Reduction of cholesterol in skeletal muscle membrane results in destabilization
    - Impaired calcium signaling
- Drug Factors
    - Hydrophilic statins use facilitated transport into hepatocytes using transporters (see "Genetic Factors")
    - Lipophilic statins can passively diffuse across membranes and thought to have uptake into extra-hepatic tissues such as skeletal muscle that can result in muscle toxicity
      Multiple medications that use a similar mechanism of metabolism e.g. CYP-mediated metabolism (see table below) can increase risk for toxicity due to higher plasma concentrations

Properties of Individual Statins

Statin	Lipophilicity	CYP-mediated metabolism	LDL-C reduction with maximal dose (%)	Intensity of Statin
Rosuvastatin	**No**	**2C9, 2C19**	**63**	**High**
Atorvastatin	**Yes**	**3A4**	**55**	**High**
Simvastatin	**Yes**	**3A4**	**41**	**Moderate**
Lovastatin	**Yes**	**3A4**	**41**	**Moderate**
Pitavastatin	**Yes**	**2C9, 2C8**	**41**	**Moderate**
Pravastatin	**No**	**None – sulphonation**	**38**	**Low**
Fluvastatin*	**Yes**	**2C9**	**38**	**Low**

Management

- Meta-analysis has shown 1 mmol reduction in LDL-cholesterol associated with significant reductions in major vascular and coronary events by up to 22%
- Treatment with statin still remains the gold standard so clinicians should attempt to continue statin therapy with the following management options:
    - Trial of discontinuation until symptoms resolve (2-8 weeks)

    - Step-by-step dose reduction (de-challenge)
    - If trial of discontinuation pursued:
        - If on high-intensity statin, switch to alternative high-intensity
        - Consider dose reduction OR switch to low-intensity statin
        - If on-going symptoms, consider alternate day dosing
        - If patient is on a hydrophobic statin, consider switching to a hydrophilic statin to theoretically avoid extra-hepatic uptake of statins
        - Review other medications and if patient on multiple medications metabolized by similar mechanism (e.g. CYP family of enzymes), consider switching to alternative
- Vitamin D
    - Interaction between vitamin D and statins unclear but appears to play role in lipid-lowering response to statins
    - Vitamin D deficient patients shown to have reduced response to statins and increased myalgia
    - Vitamin D deficiency can be corrected with supplementation

- Other LDL-lowering therapies
    - Statin remains the gold standard and all efforts to continue statin should be made
    - If unable to tolerate despite all attempts, consider non-statin alternatives
        - Ezetimibe
        - Proprotein convertase subtilisin/kexin (PCSK) 9 inhibitors ($$)

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

References

1. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovasc Drugs Ther. 2005 Dec;19(6):403-14.
2. Climent E, Benaiges D, Pedro-Botet J. Hydrophilic or Lipophilic Statins?. *Front Cardiovasc Med*. 2021;8:687585. Published 2021 May 20.
3. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005 Feb;19(1):117-25.
4. Pennisi M, Di Bartolo G, Malaguarnera G, Bella R, Lanza G, Malaguarnera M. Vitamin D Serum Levels in Patients with Statin-Induced Musculoskeletal Pain. *Dis Markers*. 2019:3549402.
5. Ward NC, Watts GF, Eckel RH. Statin Toxicity. Circ Res. 2019 Jan 18;124(2):328-350.
6. Zaleski, A.L., Taylor, B.A., Thompson, P.D., Coenzyme Q10 as Treatment for Statin-Associated Muscle Symptoms—A Good Idea, but…, *Advances in Nutrition*, Volume 9, Issue 4, July 2018, Pages 519S–523S,