



Clinical Pharmacology & Toxicology Pearl of the Week

~Statin Associated Muscle Symptoms (SAMS) ~

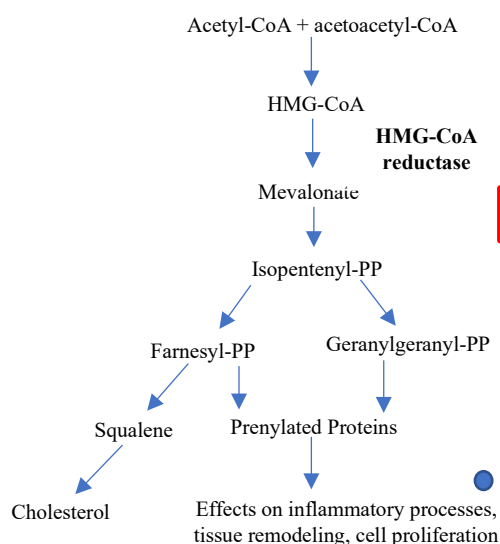
Case

- 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 muscle symptoms (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. Rhabdomyolysis - 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
 - o Usually these are < 3x ULN and will self-resolve
 - o If persistent and above 3x ULN, consider drug-induced liver injury

Proposed Mechanisms of Myopathy

- Genetic Factors
 - o Single nucleotide polymorphism in SLCO1B1
 - o Encodes organic-anion transporting polypeptide (OATP)1B1 which regulates hepatic uptake of statins
 - o Hydrophilic statins use (OATP)1B1 for statin uptake into hepatocytes
 - Metabolic Factors
 - o Mitochondrial dysfunction
 - o Reduction of cholesterol in skeletal muscle membrane results in destabilization
 - o Impaired calcium signaling
 - Drug Factors
 - o Hydrophilic statins use facilitated transport into hepatocytes using transporters (see “Genetic Factors”)
 - o 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 remains the gold standard so clinicians should attempt to continue statin therapy with the following management options:
 - o Trial of discontinuation until symptoms resolve (2-8 weeks)
 - o Step-by-step dose reduction (de-challenge)
 - o 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
 - o Interaction between vitamin D and statins unclear but appears to play role in lipid-lowering response to statins
 - o Vitamin D deficient patients shown to have reduced response to statins and increased myalgia
 - o Vitamin D deficiency can be corrected with supplementation
- Other LDL-lowering therapies
 - o Statin remains the gold standard and all efforts to continue statin should be made
 - o If unable to tolerate despite all attempts, consider non-statin alternatives
 - Ezetimibe
 - Proprotein convertase subtilisin/kexin (PCSK) 9 inhibitors (\$\$)

References

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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

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The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in [Alberta Referral Directory](#) (ARD) by searching “Toxicology” from the ARD home page.

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