# Prevention and Management of Statin-Associated Myopathy:

A practical approach for pharmacists

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#### Today's Speaker

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### Disclosure

- I have **no** current or past relationships with commercial entities
- I have **not** received a speaker's honourarium for this learning activity
- I am a member of the primary panel of the Canadian Cardiovascular Society (CCS) guidelines for the management of dyslipidemia for the prevention of CVD in the adult



# Learning Objectives

- 1. Differentiate the terms myopathy, myalgia, myositis, hyperCKemia, and rhabdomyolysis;
- 2. Define goal-inhibiting statin intolerance and goal-inhibiting statin resistance;
- 3. Identify six key principles in the management of patients with suspected statin-associated myopathy (SAM);
- 4. Develop an approach to patients with suspected SAM with a focus on patients with statin-induced myalgia.



# Prevention and management of statin adverse effects: A practical approach for pharmacists

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Canadian Journal of Cardiology 32 (2016) S35-S65

#### **Special Article**

#### Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Canadian Consensus Working Group Update (2016)

G.B. John Mancini, MD,<sup>a</sup> Steven Baker, MD,<sup>b</sup> Jean Bergeron, MD,<sup>c</sup> David Fitchett, MD,<sup>d</sup> Jiri Frohlich, MD,<sup>a</sup> Jacques Genest, MD,<sup>e</sup> Milan Gupta, MD,<sup>b</sup> Robert A. Hegele, MD,<sup>f</sup> Dominic Ng, MD,<sup>d</sup> Glen J. Pearson, PharmD,<sup>g</sup> Janet Pope, MD,<sup>f</sup> and A. Yashar Tashakkor, MD<sup>a</sup>

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### **Poll Question**

- Have you ever encountered a patient with muscle symptoms that may have been caused by a statin?
- 1. Yes (100%)
- 2. No
- Statin-associated is common in clinical practice (7-30% of patients)



# Terminology

#### TABLE 1 Terminology for statin-associated myopathy\*

Term	Laboratory characteristics	Clinical characteristics
Myalgia	CK≤ULN	Muscle ache or weakness
Myositis	CK > ULN	Muscle ache or weakness
Rhabdomyolysis	CK > 10× ULN	Muscle ache or weakness ± myoglobinuria
Mild (grade 1) hyperCKemia	$CK > ULN but \le 5 \times ULN$	May or may not have myositis
Mild (grade 2) hyperCKemia	$CK > 5 \times ULN but \le 10 \times ULN$	May or may not have myositis
Moderate hyperCKemia	$CK > 10 \times ULN but \le 50 \times ULN$	May or may not have rhabdomyolysis
Severe hyperCKemia	CK >50× ULN	May or may not have rhabdomyolysis

\*Adapted from Mancini et al.<sup>3</sup> with permission from Elsevier. CK, creatine kinase; ULN, upper limit of normal.



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# Terminology

- <u>Goal-inhibiting statin intolerance</u> (GISI): defined as a syndrome characterized by symptoms or biomarker abnormalities that prevent the long-term use of and adherence to indicated statin therapy, which includes a trial of at least 2 statins (including atorvastatin and rosuvastatin, as appropriate) and precludes reversible causes of statin adverse effects (e.g., drug interactions, untreated hypothyroidism)
- <u>Goal-inhibiting statin resistance</u> (GISR): defined as patients who are unable to achieve the expected lipid- lowering effect with maximally tolerated statin dose.



#### Case

- 62 yo M presents to refill his Rx
- PMHx: T2DM, HTN, dyslipidemia, chronic back pain
- Atorvastatin 20 mg PO daily
- Other Rx: metformin, ACE inhibitor, DHP CCB, acetaminophen PRN
- Does not want to refill his statin
- C/o leg pains (read on Internet this is a side effect of statins)
- "Can diet and exercise replace my statin?"
- "Should I be taking coenzyme Q10 and/or vitamin D?"



#### Approach to Patients with SAM





### Step 1

#### Ensure your patient has a valid indication for statin therapy

- Statin indicated conditions
- High-risk primary prevention
- ± Intermediate-risk primary prevention
- Baseline bloodwork: lipid profile, A1c, SCr, ALT, TSH, CK

Can J Cardiol 2016;32:1263-82



#### Case

• Statin indicated condition (T2DM and >40 yr of age)



# Step 2

#### Identify factors that may limit or preclude use of statins

- Advanced age (>80 yr of age)
- Female sex
- Asian ethnicity
- Low BMI
- Hx of preexisting/unexplained muscle/joint pain
- FamHx of myopathy

- Neuromuscular diseases
- Severe renal/hepatic impairment
- Untreated hypothyroidism
- Diabetes mellitus
- Genetic polymorphisms
- Drug interactions



#### Case

- Risk factors for SAM:
  - Preexisting chronic back pain
  - T2DM
- No drug interactions
- Does not drink grapefruit juice



# Step 3

# Ensure your patient is fully informed regarding the benefits and risks of statin therapy

- Unmet opportunity for pharmacists to discuss benefits vs risks
- Focusing only on possible adverse effects may be detrimental
- ++ unsubstantiated/misleading information on Internet



- Primary prevention:
  - Statin vs placebo x 4 yr
  - Major coronary events NNT=77
  - All-cause mortality NNT=167
  - Stroke NNT=250
- Secondary prevention:
  - High-intensity vs moderate- or low-intensity statin x 2-5 yr
  - Death and adverse CV events NNT=26-44

BMJ 2009;338:b2376 N Engl J Med 2004;350:1495-504 N Engl J Med 2005;352:1425-35



- "Nocebo effect"
  - Patients with negative expectations about a therapy are more likely to experience an adverse effect
- Retrospective analysis of ASCOT-LLA
  - "These analyses illustrate... an excess rate of muscle-related adverse event reports only when patients and their doctors were aware that statin therapy was being used and not when its use was blinded."

Lancet 2017;389:2473-81



#### Case

- You discuss the potential benefits vs risks of therapy
- Collaborative Atorvastatin Diabetes Study (CARDS)
  - Patients aged 40-75 yr with T2DM and ≥1 other CV risk factor
  - Atorvastatin 10 mg PO daily vs placebo
  - Adverse CV events NNT=32
  - All-cause mortality NNT=67
  - Muscle-related symptoms similar between groups (about 5%)
- "These results seem important enough to continue my statin, but not if I'm going to have ongoing leg pain"

Lancet 2004;364:685-96



### Step 4

Encourage dietary interventions and exercise to lower your patient's CV risk and do not advocate supplements to reduce the risk of SAM

- Diet and exercise should augment (but not replace) statin therapy
- Mediterranean diet
- 150 minutes of moderate-to-vigorous exercise per week



- Coenzyme Q10:
  - Evidence is inconsistent
  - Meta-analysis of 5 RCTs did not show any benefit
  - No evidence of improved clinically meaningful outcomes
- Vitamin D:
  - No RCTs

Mayo Clin Proc 2015;90:24-34



#### Case

- Discuss importance of diet and exercise, but not as replacement for his statin
- Recommend against use of coenzyme Q10 or vitamin D



# Step 5

# Use a systematic challenge/dechallenge/rechallenge approach to patients with SAM

- Assess for other causes (e.g., exercise, trauma, infection)
- Address modifiable risk factors
- Typical clinical presentation:
  - Heaviness/cramping/weakness, larger muscle beds
  - Intermittent and bilateral
  - Onset often <4 weeks



Parameter	Points
Distribution	
Symmetric hip or thigh aches	3
Symmetric calf or upper arm aches	2
Nonspecific, asymmetric or intermittent	1
Transient during statin use	0
Timing of symptom onset	
≥2 days but <4 weeks	3
4-12 weeks	2
>12 weeks	1
<2 days	0
Dechallenge	
Improves upon withdrawal in 2 days to <2 weeks	2
Improves upon withdrawal in 2-4 weeks	1
Does not improve upon withdrawal in >4 weeks†	0
Asymptomatic after 1 day	0
Rechallenge	
Same symptoms recur in ≥2 days but <4 weeks	3
Same symptoms recur in 4-12 weeks	1
Response to nonstatin therapy	
Same symptoms as with statin occur with nonstatin lipid-lowering drug	
Probability	
Probable	≥9
Possible	
Unlikely	<7

<sup>1</sup>Symptoms may persist or worsen despite discontinuation of statin in rare cases of immune-mediated necrotizing myopathy.





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- Myalgia:
  - If symptoms tolerable  $\rightarrow$  could continue therapy
  - If symptoms intolerable → reduce dose, switch statins or temporarily discontinue
  - Intermittent non-daily dosing strategies (e.g., q other day dosing, q weekly rosuvastatin)
- Myositis:
  - Stop statin and follow CK until ≤ ULN and asymptomatic
  - Restart at lower dose or switch statins



- Rhabdomyolysis:
  - Stop statin
  - Referral to acute care
  - Prompt assessment of renal function (SCr, urine myoglobin)
  - ± IV rehydration and/or dialysis
- Not necessarily a contraindication to future therapy
- Restart statin at low dose



- 70-90% of patients with SAM will tolerate another statin
- Factors not useful for rechallenge:
  - Symptoms are plausible and resolve with statin cessation
  - Severe with objective weakness and/or hyperCKemia
  - Patient refusal



#### Case

- Bilateral muscle cramping in thighs
- Taking atorvastatin x 8 weeks
- Symptoms started 2 weeks ago
- No other identifiable cause
- CK < ULN
- Dose reduced to 10 mg PO daily
- 2 weeks later, symptoms not improved  $\rightarrow$  stop atorvastatin
- 1 week later, symptoms are resolved
- Start rosuvastatin 10 mg PO daily



## Step 6

*If necessary, recommend non-statin therapy to achieve the therapeutic goal* 

- See previous webinar on non-statin therapy
- Two small RCTs of ezetimibe vs PSCK9 inhibitor in patients with statin intolerance
  - Not powered to adequately assess CV outcomes
  - Muscle-related symptoms similar in each group (about 20-30%)

JAMA 2016;315:1580-90 J Clin Lipidol 2015;9:758-69



#### Case

- 6 weeks later, his non-HDL-C is 2.8 mmol/L
- Target non-HDL-C <2.6 mmol/L
- Recommend to increase rosuvastatin to 20 mg PO daily
- 6 weeks later, no muscle-related symptoms and non-HDL 2.5 mmol/L



### **Real-Life Case**

- 56 yo M with dyslipidemia
- Previous severe muscle aches with rosuvastatin
- Labs: non-HDL-C 6.46 mmol/L, CK 152 U/L
- Step 1: high-risk primary CV prevention
- Step 2: no risk factors for SAM
- Step 3: Discussed benefits vs risks, patient agreeable
- Step 4: Encouraged diet and exercise
- Step 5: rechallenge with atorvastatin 10 mg PO q other day
- Step 6: N/A



### **Real-Life Case**

- 8 weeks later:
  - Some minor myalgias (?secondary to RA)
  - Labs: non-HDL-C 4.98 mmol/L (23% reduction)
  - Increase atorvastatin to 10 mg PO daily
- 16 weeks later:
  - Diffuse muscle aches  $\rightarrow$  limiting physical activity
  - Diffuse aching in upper thighs
  - Labs: non-HDL-C 4.67 mmol/L (6% reduction), CK 300 U/L (1.8x ULN)
  - Myositis  $\rightarrow$  discontinue atorvastatin



#### **KNOWLEDGE INTO PRACTICE**



- In 2016, a Canadian Consensus Working Group published the third iteration of a statement to evaluate the diagnosis, prevention and management of statin adverse effects and intolerance.
- Goal-inhibiting statin intolerance is defined as a syndrome characterized by symptoms or biomarker abnormalities that prevent the long-term use of and adherence to indicated statin therapy, which includes a trial of at least 2 statins and precludes reversible causes of statin adverse effects.
- There are 6 key principles in the management of patients with goalinhibiting statin intolerance: ensuring a valid indication, identifying risk factors for intolerance, ensuring the patient is informed of the benefits and risks, encouraging nondrug therapies/not advocating for supplements to prevent statin-associated myopathy, using a systematic challenge/dechallenge/rechallenge approach and recommending nonstatin therapy, if necessary.



#### Questions

Please type your questions in the "Questions" window in the control panel and click **Send** 





# Thank you!

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archive/

