Statin-Associated Muscle Adverse Events

Introduction

- Statin is a commonly used medication in CV disease.
- It is generally safe but the s/e may include hepatotoxic, muscle injury, proteinuria, new dx of DM, cognitive dysfunction and memory loss, etc.
- When comparing between statins, equipotent doses with regard to LDL-C reduction should be consider.

Comparison of the efficacy of statin drug

% ↓LDL-reduction	Atorva statin	Simva statin	Lova statin	Pitava statin	Rosuva statin	Fluva statin	Prava statin
Usual dose	10-80	10-40 (80)	10-80	1-4	5-20	20-80	10-80
20%			10			20	10
25%		10	20	1		40	20
30%	10	20	40	2		80	40
40%	20	40	80	4	5		80
50%	40	80			10		
55%	80				20		
excretion	3A4	3A4	3A4	Limited 2C9	Limited 2C9	2C9	-

*In Asian population may need lower dose to achieve target LDL reduction.

Muscular side effect

- The exact pathophysiology remains unclear but may include decreased levels of coenzyme Q10, decreased bioavailability of isoprenoids, or mitochondrial dysfunction.
- More common in daily clinical practice than in RCTs. (Am Heart J 2014;168:6-15)
- Typically manifested as large symmetry proximal muscle (lower > upper)
- Usually within wks-months after initiation, but can happen anytime.
- Improve with stopping statin and may occur again with rechallenge.
- No consistent definition between guidelines.

Term	Incident	Description
Myalgia	5-10%	Muscle discomfort, ache, sore, stiff, cramps with normal CK
Myopathy	< 0.5 %	Muscle weakness with or without ↑CK
Myositis/myonecrosis	< 0.5 %	↑CK; mild (3-10x), moderate (10-50x), severe (>50x)
Rhabdomyolysis	Very rare < 0.01 %	Myonecrosis + myoglobinuria + ARF Primarily seen when given concurrently with cyclosporine, gemfibrozil, or protease inhibitors

Suggested readings

PRIMO (Cardiovasc Drugs Ther. 2005;19:403–414)
STOMP (Circulation. 2013;127:96–103.

Risk Factors

- High-dose statin
  - Rate of simvastatin related myalgia = 0.02, 0.07 and 0.3% at 20, 40 and 80 mg/day, respectively.
- Different statin
  - The risk of myopathy appears to be lowest with fluvastatin and pravastatin.
  - Pravastatin: pool data from WOSCOPS, CARE and LIPID – 20,000 patients for 5 years of pravastatin 40 mg/day, when compares to placebo: 8.8% vs. 8.2% for AST > 50% of ULN. 2.1% vs 1.9% of CK > 3xULN. No cases of myositis or rhabdomyolysis. (Circulation. 2002;105:2341-6)
  - Lipophilic statins (simvastatin and lovastatin) are more likely to produce muscular effects?
- Patient related factors (Ann Intern Med.2009;150:858-868)
  - Elderly, female, low BMI, DM, alcoholism, perioperative period, FH of myopathy
  - Comorbidity: Hypothyroidism, vit D def., neuromuscular disorders (ALS, MG, mitochondrial myopathy), renal failure, obstructive liver disease
- Drug-drug interaction
  - Fibrates
  - CYP3A4 inhibitor: Cyclosporine, macrolide (eg. erythromycin), -azole, protease inhibitor (ritonavir), diltiazem/verapamil, amiodarone, grapefruit juice
  - Drugs that are competitive CYP3A4 substrates: Colchicine, amlodipine.
  - Pravastatin, rosuvastatin, fluvastatin, and pitavastatin are less likely to have drug interactions since they are not mainly metabolized via CYP3A4.
  - Others: steroid, daptomycin
- Vigorous exercise
- Patient perception: 25-60% of pts have muscle s/e in a survey (J Clin Lipidol. 2012;3:208-15)

Management (J Clin Lipidol. 2014;8:S58-71)

- Routine checking CK levels in asymptomatic patient is not recommended.
- If symptomatic:
  - Consider checking CK, TSH
  - Check risk factors, assess drug interactions
  - Search for other causes of symptoms and/or ↑CK
  - Stop statin if intolerable symptoms or CK > 10xULN
  - Restart another statin (fluvastatin and pravastatin), once symptoms resolve and normal CK.
  - Most patients (70-90%) tolerated statins on repeat challenge. These pts may not have a "real" statin induced myopthy (Ann Intern Med. 2013;158:526–534)
  - Alternate day? coenzyme Q10?
- If rhabdomyolysis: stop statin ASAP, if no other causes identified → do not restart statin.

Rhabdomyolysis (JAMA 2004;292:2585-90)

- The most fearful muscle related s/e of statin.
- Very rare (24 of 252,460 pts (0.0044%) of monoRx with statin had rhabdomyolysis.
- The same incident between atorva- and simvastatin
  - Significant higher with cerivastatin (already withdraw from the market)
- Significant higher incident when using higher dose than recommend (simvas 80, rosuvas 40)
- Significant higher incident when combine with fibrate (Gemfibrozil >>> fibrate) but still low (atorvastatin + gemfibrozil = < 0.2%)