THE STATIN “INTOLERANT” PATIENT

DIAGNOSIS and MANAGEMENT

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ASCVD Risk Reduction

• Primary and secondary prevention
• Set LDL-C and non-HDL-C treatment goals considering intermediate, long-term/lifetime risk
• Maximize lifestyle intervention and management of non-lipid risk factors
• Select drug Rx on basis of lipid phenotype
STATIN SIDE EFFECTS

Depend on dose, ethnicity, age, concomitant drugs
- Muscle and Liver toxicity
- Elevation of fasting plasma glucose
- Rashes; Gastrointestinal side effects
- Hypersensitivity syndromes
- (Cognitive impairment)
- (Peripheral neuropathy)

CASE 1

- 63 year old African American woman has hypertension controlled on medication and untreated combined pattern hyperlipidemia. Resuvastatin 20 mg is prescribed. Three months later she has a thromboembolic stroke.
- Was this caused by the statin?
Stroke and Statin Rx

• Statins have been associated with a decreased risk of thromboembolic stroke but with an increased risk of hemorrhagic stroke
• Evidence is considered insufficient in the latter case to attribute cause/effect

CASE 2

• 52 year old Caucasian man (he does not live in Flint, MI) who had taken 40 mg of atorvastatin for 9 years complains of slowly progressive symptoms of peripheral neuropathy with onset 2 months prior to his visit. He has no other symptoms.
• Is this caused by the statin?
PERIPHERAL NEUROPATHY and STATIN RX

Cohort studies

Incidence: 12/100,000 person years
Prevalence: 60/100,000 persons

If symptoms do not resolve on discontinuing the statin, cause/effect is unlikely
Diabetes and folic acid/B12 deficiency are more common causes

CASE 3

- 72 year old man has been treated for 15 years with a statin for his familial hypercholesterolemia. His wife tells you that his cognitive function is declining and he is concerned about recent memory loss.
- Is the statin to blame?
- Should you obtain an Apo E genotype?
Cognition and Statins

- Patient complaints should be taken seriously and appropriate neuropsychological testing done if symptoms persist after stopping the statin.
- If no other causes of cognitive dysfunction are identified, discontinuation of the statin should be considered only after careful review of the benefit-risk ratio.

Statins and Cognitive Function

- Evidence supporting a causal effect is very weak or nonexistent. There is some suggestion that there may be improvement with statin Rx.

Statins and Cognitive Function

• No difference in rate of development of cognitive impairment with simvastatin vs placebo (HPS: 20,536 patients over 5 yrs)
• No difference in rate of cognitive decline in patients age 70-82 (PROSPER: pravastatin)
• Statin benefit in Alzheimer disease and risk (?) (placebo controlled trial; case control and cohort studies)

Management of Neurological Disorders Associated With Statin Rx

• Routine monitoring for these disorders is not recommended
• If symptoms are reported, rule out secondary disorders (e.g., diabetes, renal disease, alcohol abuse, B12 deficiency, Lyme disease, heavy metal intoxication, cancer, hypothyroidism, etc.)
• If no secondary cause is identified and symptoms are “real” and troublesome, stop statin Rx for 3 to 5 months
• If symptoms resolve, resume Rx based on risk-benefit analysis with a different statin/lower dose
• If symptoms do not resolve, resume Rx based on risk-benefit analysis
CASE 4

• 34 year old South Asian man at high risk for CAD is treated with 40 mg of atorvastatin and marine omega 3s for his combined pattern hyperlipidemia. Prior to starting the statin, his HgbA1c was 5.9 and FBS was 108. Two months into statin Rx, his FBS was 114 and HgbA1c 6.0
• Should the statin be stopped?

Statins and Diabetes

• New onset DM2 is more frequent in persons taking a statin but the association is weak
• In absence of DM, FBS is increased 3 mg/dL (345,000 persons to see this difference)
• In patients with DM and A1c near 7.5% at baseline, statin Rx increased A1c by 0.3%

Shah, Goldfine. Circulation 2012:126;e282
Statins and Diabetes

- Meta-analysis of statin trials indicate a modest but statistically significant increase in risk for development of DM2 (about 10%)
- This may be limited to those with risk factors for DM
- Screen A1c prior to Rx if 1 or more risk factors are present

CASE 5

- 48 year old Asian woman with CAD is treated with 5 mg of resuvastatin for 2 years. The dose is increased to 10 mg to achieve her LDL-C treatment goal
- Two months later her AST level is about 3.5 times normal and ALT 4 times normal
- Was this due to the increased statin dose?
**Statins and Liver Function**

- Elevated aminotransferase levels of 2 to 3 times normal are not rare with statin Rx
- Liver disease attributable to statins is rare
- An abrupt fall in lipid levels could indicate liver toxicity
- NAFLD/NASH, alcohol consumption, and polypharmacy may be contributing

**Statins and Abnormal Liver Function**

- Minor, asymptomatic increases in ALT and AST are common (< 3X ULN); not a reason to stop Rx
- Elevated ALT (most specific test for drug-related hepatotoxicity) correlates with higher doses
- Levels persistently > 3X the ULN (1% of study participants taking maximal doses) are an indication to stop the statin or reduce the dose, and allow the level to return to baseline
- Baseline liver enzymes should be assessed
Statins in Asian Individuals

• At each statin dose, LDL-C may be reduced significantly more in Asians and serum levels of the statin tend to be higher
• Initial statin doses should be lower in Asians, especially women (start with no more than 5 mg resuvastatin or 10 mg atorvastatin)

CASE 6

• A 62 year obese woman is hospitalized with ACS. She has type 2 DM; A1c 8.4
• Lipid panel averages on simvastatin 20: Chol 180; TG 550; HDL 39; Dir. LDL 52
• Among other treatments, 80 mg of atorvastatin is started before discharge
• 6 weeks later she has nausea, poor appetite, and bilateral thigh aching and weakness
CASE 6

- AST is 3 times ULN
- ALT is 5 times ULN
- CK is 4 times ULN

STATIN MYOPATHY
FACTORS THAT INCREASE RISK

- Age > 70 years
- Multisystem diseases especially involving impaired renal (creatinine clearance < 30 mg/dL) or liver function; diabetes; hypothyroidism
- Certain drug interactions dependent on cytochrome metabolism or glucuronidation
- Ethnicity/race - Asian; Asian-Indian
- Female gender; small body frame
- Serious concurrent illness or surgery (anecdotal)
- Positive family Hx of statin myopathy
STATIN INDUCED MYOPATHY
Possible Contributing Mechanisms

- Decreases in mevalonate pathway products (dolichol, prenylation intermediaries, CoQ)
- Changes in sarcolemma related to calcium ion flux
- Alteration in gene expression related to inflammation, protein degradation and apoptosis
- Mitochondrial dysfunction
- Genetic predisposition (Gene loci associated with myopathy: SLC01B1, CoQ2, CYP2D6, ATP2B1, DMPK, CLN8, others)

STATIN MYOPATHY
Definitions vary in clinical trials

- Myopathy: refers to all muscle complaints
- Myalgia: a nonspecific, common complaint
- Myositis: muscle symptoms associated with increased CK levels
- Myositis: muscle symptoms associated with normal CK (Ragged red muscle fiber disease)
- Rhabdomyolysis: severe muscle damage usually associated with renal dysfunction
STATIN MYOPATHY
Suggested Categories-NLA

• Classes of absolute CK elevation:
  – Mild: CK > ULN but < 10 times ULN
  – Moderate: CK >10 times ULN but < 50 times ULN
  – Marked: CK > 50 times ULN

Any class can result from muscle-damaging exercise or other conditions

DRUG INTERACTIONS

• About 50% of all drugs are metabolized by the cytochrome 3A4 isoenzyme of the P-450 system; these include lovastatin, atorvastatin, and simvastatin
• Pravastatin (renal excretion), fluvastatin, pitavastatin, and resuvastatin (CYP2C9) may be preferred statins for some patients receiving multiple drugs
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Statin Myopathy Case

- 26 yo man with FH has taken 80 mg of atorvastatin for the past 4 years. His baseline CK was 750. It has been as high as 1300 following more vigorous exercise. Niacin was recently added to his regimen. A repeat CK was 680. He has never reported muscle symptoms.
MUSCLE SYMPTOMS OR INCREASED CK COINCIDENT WITH STATIN RX

- Etiologies other than the statin are likely
- These include: primary elevation, increased physical activity, sciatica, falls, accidents, trauma, seizure, febrile illness, infections, polymyositis, dermatomyositis, carbon monoxide poisoning, hypothyroidism, drug or alcohol abuse, sleep apnea, etc.
- Consider baseline CK if exercise is vigorous

EVALUATION OF MUSCLE SYMPTOMS Possibly Related to Statin Therapy

- Symptoms can include: aching, pain (neuropathy may mask pain), soreness, cramping, tenderness, weakness
- Are the symptoms persistent? (Intermittent or only nocturnal complaints less commonly associated)
- Are they bilateral?
- Proximal muscles in extremities most commonly affected
EVALUATION OF MUSCLE SYMPTOMS
Possibly Related to Statin Therapy

• Have there been recent changes in type or level of exercise or work (new activity that might involve stairs, lifting, gardening, etc.)?
• New prescribed or OTC drugs?
• Did the same or similar symptoms ever occur prior to starting the statin?

Managing Muscle Symptoms

• Rule out other causes of muscle symptoms and consider factors that increase risk
• Coenzyme Q10 (100 to 200 mg/day) improves symptoms in some patients; no convincing outcome data
• Vitamin D (no randomized trials)
• Red rice yeast is not recommended as a substitute for a prescribed statin; warn patients also about concomitant use
Managing Muscle Symptoms

- Consider fluvastatin
- Consider combined hypolipidemic drug therapy keeping doses of each agent low (choice of agents dependent on lipid phenotype)
- Consider alternate dosing strategies with up-titration of statin dose as tolerated
  - Alternate day
  - Weekly

Managing Muscle Symptoms

- If symptoms are mild to moderate, discontinue the statin, allow the symptoms to resolve; then re-challenge with the same or another statin, beginning at a reduced dose
- If symptoms are moderate to severe, measure CK level, stop the statin and allow the symptoms to resolve (and the CK to fall to < 10 times ULN). Resume as above
- If CK is > 50 times normal, stop the statin; check for myoglobinuria; rule out renal dysfunction
- CK levels that remain very high, and muscle symptoms that do not resolve after 2 months off therapy, are usually not due to the statin
Hypersensitivity Syndromes and Statin Myopathy

- These are very rarely reported
  - Lupus-like syndromes
  - Dermatomyositis
  - Autoimmune myopathy

Statins and Autoimmune Myopathy

Proximal, bilateral weakness and pain
- CK levels > 10 times upper normal persist after discontinuing statin
- HMG-CoA reductase antibody positive
- Refer to rheumatologist or neurologist
- EMG; Muscle biopsy; MRI (muscle edema)
- Immunosuppressive Rx
- Outcome usually good

CONSIDER RISK VS BENEFIT

- Average risk reduction for atherosclerotic vascular disease with statin Rx is 33.8% (? greater in the long term)
- Incidence of muscle complaints in clinical practice is 5 to 15% but serious myopathy is unusual

SUMMARY

- Side effects are generally dose-related
- Some patients are identifiably at higher risk
- Most side effects can be managed
- Lowest effective doses of each agent should be used in combination therapy
- The initiation and continuance of drug treatment should be based on a risk/benefit analysis
References

Rosenson R et al. J Clin Lipidol; 2014:8 (suppl)
NLA Statin muscle safety task force