

Managing Statin Intolerance

Background

- Though muscle symptoms are commonly reported, when managed appropriately, over 70% of these patients end up tolerating a statin
- Statin-induced myalgias are rarely serious – rhabdomyolysis is the exception, but is also very uncommon
- Consider downloading the ACC Statin Intolerance App

Review of Statin-related Side Effects

- Most commonly reported: pain, tenderness, stiffness, cramps, weakness, fatigue
- Usually involve large, proximal muscle groups (legs, back), bilaterally/symmetrically
- Usually occur within 4-6 weeks of starting therapy, but can show up years later
- Definitions
 - Myopathy – general term for muscle disease, may or may not be associated with elevated CK
 - Myalgia – muscle symptoms + CK WNL
 - Myositis – muscle symptoms + CK > ULN; muscle inflammation
 - Rhabdomyolysis – muscle symptoms + myoglobinuria + CK > 10x ULN
- In clinical trials, low-to-moderate intensity regimens did NOT increase risk for muscle symptoms
 - BUT, in practice, up to 30% of patients complain of side effects
- In clinical trials, rhabdomyolysis occurred in < 0.06% of patients over 5 years
 - BUT, in real life, may be up to 0.2% of statin users
- Risk factors for developing muscle symptoms w/ statin use:
 - Multiple disease states
 - Polypharmacy
 - History of MSK symptoms or CK elevation, neuromuscular disease, personal or family history of statin myopathies
 - Use of drugs or foods (grapefruit) that interact with statins
 - 75+ years old
 - Asian ancestry
 - Female gender
 - Low BMI, small frame
 - Frailty
 - Physical activity
 - EtOH or drug abuse
- Biggest offenders:
 - Lovastatin, simvastatin

Statin selection

- MOST patients who do not tolerate one statin will tolerate a different one

- Up to 50% of patients tolerate the SAME statin upon rechallenge (same or higher dose)
- If patient is high risk for statin side effects (see list above), consider selecting a product with fewer known drug-drug interactions
 - E.g. rosuvastatin, pravastatin
- There is NO evidence (in humans) to suggest that lipophilicity/hydrophilicity directly affects muscle symptoms

Preventing Statin Intolerance

- Before starting
 - Review expectations with patients – remind them that in most cases side effects can be managed if they occur
 - Review previous history of intolerances – ensure that this list is correct/up-to-date
 - Screen for potential drug-drug interactions
 - Do NOT combine statins w/ gemfibrozil
 - Ask about intake of grapefruit juice
 - Consider baseline measurement of CK in patients at risk
- When starting
 - Ensure dose is appropriate for renal function
 - Start with minimum intensity dosing based on patient's risk
 - Avoid simvastatin 80 mg

Monitoring

- Consider baseline measurement of CK in patients at risk
 - Otherwise, evidence does NOT support routinely checking CK or LFTs
- Check CK with significant muscle symptoms

Managing Patients Reporting Intolerance

- Initial Assessment
 - Assess for possible rhabdomyolysis if severe muscle pain, generalized weakness, dark urine
 - Check CK, urine for myoglobin, SCr
 - If confirmed, treat and *DO NOT RECHALLENGE*
 - Consider other possible causes of muscle symptoms
 - E.g. hypothyroidism, vitamin D deficiency, rheumatologic/MSK disease, strenuous exercise, steroid myopathy, antipsychotics, immunosuppressants, bisphosphonates, EtOH/drug abuse, drug or food interactions, nocturnal leg cramps
 - Consider checking renal function/lytes, vitamin D, TSH/FT4
 - If weakness present, consider triage to PCP for physical assessment

- Taking Action
 - If symptoms are mild and/or low suspicion for statin involvement, consider reducing dose or continuing as is (monitor closely)
 - If symptoms are intolerable, patient reports weakness, or CK > 3x ULN → hold statin for 2-4 weeks (washout)
 - If symptoms persist, triage to PCP for further assessment/testing (e.g. biopsy)
 - If ends up being unrelated to statin therapy, follow steps below to restart
 - Assuming no contraindications (i.e. NOT confirmed rhabdomyolysis):
 - RECHALLENGE with same statin at lower dose
 - Increase as tolerated, slowly
 - If symptoms return, discontinue
 - OR--
 - Start low-or-target dose of DIFFERENT statin
 - Increase as tolerated
 - If symptoms develop, hold 2-4 weeks and repeat steps with new agent
 - OR--
 - If low CV risk or no longer in statin benefit group, could consider lifestyle interventions in lieu of statin
 - Consider trying extended dosing intervals (e.g. once weekly, twice weekly) – see below
 - If unable to tolerate statin at any dose, or if LDL goal cannot be attained without intolerance, consider adding ezetimibe in high risk patients (e.g. prior CV event).

Extended Interval Dosing of Statins

- Rosuvastatin is first choice due to long half-life, high potency, favorable drug interaction profile
 - 5 mg dosed 2-3x/week can still reduce LDL by > 30%
 - 5-10 mg dosed 1x/week may reduce LDL by 10%
- Atorvastatin is next best option, also has a long half-life
 - 20 mg every other day might be as effective as 20 mg daily (re: LDL reduction)
- Keep in mind: extended interval dosing has not been prospectively studied (no CV morbidity or mortality data)

Role of Coenzyme Q10 (ubiquinol)

- Evidence to support use in patients with statin-related myopathies is limited/mixed
- Anecdotally, some patients have reported a noticeable improvement in side effects
- No formal recommendations exist in any of the guidelines
- Generally well-tolerated; OK for patients to try it if they are able to afford it (can be expensive)
- Dose: 100-200 mg daily (divide dose BID if > 100 mg)