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
  o E.g. rosuvastatin, pravastatin
• There is NO evidence (in humans) to suggest that lipophilicity/hydrophilicity directly affects muscle symptoms

Preventing Statin Intolerance

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

Monitoring

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

Managing Patients Reporting Intolerance

• Initial Assessment
  o 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
  o 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
  o Consider checking renal function/lytes, vitamin D, TSH/FT4
  o 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)