STATIN MYOPATHY

Self-limited statin associated myopathy
- 20% of users have myalgias, cramps, a mildly elevated CK, and rarely mild proximal muscle weakness that resolves upon discontinuation of statin
- more severe myotoxicity can present with rhabdomyolysis; 0.44 per 10,000 patient-years
- discontinuation of medication results in resolution of symptoms on average in 2 months (range 1 week to 14 months)
- Risk factors: advanced age, hypothyroidism, obesity, pre-existing liver disease
- Relative risk of medication: fluvastatin/pravastatin >> rosuvastatin
- Higher dose of medications increases risk
  eg. 98/6031 (1.6%) of subjects taking simvastatin at 80mg/d compared to 8/6033 (0.1%) of subjects taking 20mg/d (SEARCH Collaborative Group, NEJM, 2008)
- these pts do NOT have the anti-HMGCR antibodies (described below)

Anti-HMG CoA Reductase Necrotizing Autoimmune Myopathy (HMGCR NAM)
- incidence 2 per million/year (Mohassel P, Mammen AL. Muscle & Nerve. 2013)
- DIFFERENT entity from self-limited statin associated myopathy
- no clear correlation with any specific subtype of statin or dose of statin
- period of statin exposure before developing HMGCR NAM can range from weeks to years

Clinical presentation:
- slowly progressive proximal muscle weakness
  - eg. Difficulty walking, climbing stairs, getting off toilet or chair, getting out of bed, raising arms above head (to wash hair or place item on top shelf)
- myalgias especially in large muscles (thighs)—described as an “ache"

Laboratory:
- markedly elevated CK, with a mean value of 10,000 IU/L (range 958-45,000)
- check TSH, CBC with diff, ESR/CRP on 1st visit
  - hypothyroidism must be excluded
  - rarely, leukemias have been shown to invade myofibers and cause a progressive weakness with high CK
- EMG—should show an “irritable” myopathy
  - “irritable” means that on the needle EMG portion of test, that the muscle membranes are spontaneously depolarizing due to immune mediated attack on myocytes
- muscle biopsy—essential for making a diagnosis
  - will show necrotic muscle cells—this is the hallmark of this disease
    - necrosis can be found in many other conditions as well such as scleroderma-, SLE-, Sjogren’s-, paraneoplastic-, and neoplastic-associated myositis; so, its not a specific finding
    - necrotic cells are pale on H&E (because of protein breakdown)
- minimal invasion of inflammatory cells, consisting of mostly macrophages, who will enter muscle tissue to “clean up” the dying myocytes = myophagia; relative scarcity of T cells between or invading the muscle fibers (unlike polymyositis)
- biopsy helps exclude other diseases on DDx, such as polymyositis, dermatomyositis
Figure: H&E stain of thigh muscle biopsy from a patient with statin myopathy (my actual patient). #s below:

1. Better preserved muscle fiber (a muscle cell) in cross section. Dark evenly pink stain indicates that internal actin/myosin contractile apparatus has not broken down. The round shape of the cell is indicative of a myopathy (it should be polygonal, like a hexagon, bee-hive)
2. Two muscle fiber undergoing “myophagia”—a normal turnover process of dying muscle but its happening too often in this biopsy specimen (only shown twice in this specific photo however)
3. All the pale fibers are necrotic fibers (hallmark of this disease). Many more pale fibers shown are not labeled.

-send for anti-HMGCR antibody in serum
   -via RDL (Rheumatology Diagnostic lab) reference laboratories—Google it
   -sensitivity of 94.4%, specificity 99.3%

Diagnosis:
-definitive diagnosis of HMGCR NAM: clinical history & exam consistent with diagnosis + Anti-HMGCR antibodies + necrotic muscle biopsy + exclusion of other mimics

Pathophysiology (theorized):
-immune-mediated destruction of muscle
-see below for proposed mechanism
Differential diagnosis:
- medication induced toxic myopathies: concomitant use of statins & fenofibrates, colchicine, steroids, alcohol, propofol, chloroquine, valproate, TNF-alpha
- polymyositis—need to see T cells invading non-necrotic fibers to diagnose this
- dermatomyositis—look for classic rash; also requires muscle biopsy with either perifascicular atrophy or classic biopsy findings
- malignancy associated necrotic myopathy—leukemias in particular are known to invade muscle fibers, cause elevated CK and cause proximal muscle weakness with myalgias
  - screen for breast cancer
- necrotizing myopathies associated with connective tissue diseases including SLE, Sjogrens, RA, scleroderma

Treatment:
- Stop statin immediately
  - can do fibrate or even consider ezetimibe instead
- PLEASE CONSIDER CONSULTING NEUROLOGY
- prompt diagnosis and treatment can minimize disability
- TRIPLE THERAPY = PREDNISONE + IVIG + METHOTREXATE
  - triple therapy is often needed to stabilize a patient

Steroid:
- start prednisone 60mg/d (max recommended to prevent steroid induced myopathy) x 2 weeks, then reduce by 5mg every 5 days to 40mg/d
-maintain 40mg/d until clinical improvement in strength is seen
-if a patient is very mild or diagnosed early, 40mg/d of prednisone may be sufficient

**IVIG:**
-give max dose 2g/kg over 2-5 days every month until strength is fully restored
-may be necessary to give IVIG for over a year
-check kidney function regularly

**Methotrexate:**
-used as a steroid-sparing agent, but also as a 1st line drug to stabilize disease
-will take 4-6 months to see full effect on muscles
-most patients will need ~10mg/week; titrate up as needed based on CK
-follow CK serially (once a month or less) as lower CK correlates with exam and pathology
-should CK return to normal
-follow exam serially
-wean off 1 drug at a time starting with prednisone
-wean off prednisone GRADUALLY after full strength or near full strength is achieved—this can take >6 months
-recommend weaning off my increments of 2.5mg/month (very slow taper) to prevent relapses
-wean off IVIG next
-maintain on lowest dose of MTX needed indefinitely