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Statin Myopathy

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Background and Clinical Features

Myopathies are either acquired or inherited, and the most common acquired myopathies include the idiopathic inflammatory myopathies (IIMs), those associated with medications and toxins, or infectious myopathies. Medication-related myopathies have been reported with various drugs, including statins.

Statins, inhibitors of hydroxy-methyl-glutaryl-CoA reductase (HMGCR), are the most common prescribed medications used to lower serum cholesterol for both primary and secondary prevention of coronary artery disease and stroke. Although generally safe and well-tolerated, statins have been associated with a variety of muscle-related symptoms, including myalgia, muscle weakness, elevated creatine kinase (CK) levels, and in rare instances, rhabdomyolysis.[1,2] These statin-related symptoms characteristically improve and resolve weeks to months after cessation of the statin. More recently, a subset of myopathy termed statin-associated immune-mediated necrotizing myopathy (IMNM) has been described.[3] This more serious complication is characterized by significant proximal muscle weakness and very high CK levels. According to the 2014 National Lipid Association Statin Muscle Safety Task Force[2]

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and the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute Clinical Advisory Committee, the spectrum of statin-associated adverse muscle events includes:

- Asymptomatic hyperCKemia
- Myalgia without CK elevation
- Myopathy/myositis (objective muscle weakness with or without an elevation in serum CK level), which includes statin-associated self-limited myopathy and statin-associated IMNM
- Myonecrosis/rhabdomyolysis

With the introduction of the 2013 American College of Cardiology and American Heart Association guidelines for the reduction of blood cholesterol, an additional 30% of patients not currently receiving statin therapy will now require such treatment.[4] In this review, we will discuss statin-associated myopathy focusing on self-limited statin myopathy, and statin-associated IMNM.

Statin-Associated Immune-Mediated Necrotizing Myopathy (IMNM)

Statin-associated IMNM is characterized by a marked elevation of the serum CK, and persistent muscle weakness even after discontinuing statins. The autoimmune nature of this complication is supported by the response to immuno-suppressive medication and the frequent relapse of symptoms following the tapering of such therapies.[3,5] Eight cases of statin-associated myopathy that persisted or progressed after stopping the drug were initially reported in 2007.[5] Improvement occurred in seven of the eight patients with prednisolone and methotrexate, and up-regulation of MHC-I expression on myofibers was also reported. Subsequently, a report of 25 patients with proximal muscle weakness with an elevated CK, occurring during or after statin treatment, also noted persistent symptoms after discontinuation of the statin. Interestingly, these patients also improved with immuno-suppressive therapies,[3] supporting the aforementioned autoimmune pathogenesis. Most patients presented with severe symmetric proximal upper and lower extremity weakness along with generalized myalgias, arthralgia, and dysphagia. Symptoms often flared when the immunosuppressive agents were tapered, and the muscle tissue demonstrated a necrotizing myopathy with scant inflammation.

Epidemiology

Self-Limited Statin Myopathy

Statins are one of the most commonly prescribed worldwide medications for the management of elevated cholesterol, and studies show that muscle-related side effects are common. These include benign muscle problems in approximately 10% to 25% of patients, or the rare and serious finding of rhabdomyolysis.[6-8] However, in a recent meta-analysis of 42 randomized clinical trials of statin therapy, the muscle problems were only slightly higher with statins (12.7%) compared to placebo (12.4%, p=0.06).[9] The noted differences may be related to specific inclusion and exclusion criteria in randomized clinical trials that limit the ability to provide generalizable results.

The frequency and severity of muscle problems vary among the different statins. Complaints are lowest with pravastatin and fluvastatin.[10] In a prospective analysis, pravastatin therapy (40 mg/day) was associated with no laboratory or clinical evidence of myositis during more than 112,000 patient-years of experience in three large controlled trials, The West of Scotland Coronary Prevention Study (WOSCOPS), the Cholesterol and Recurrent Events (CARE), and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) studies.[11] With more than 243,000 serum samples, liver function test abnormalities were similar for pravastatin and placebo groups. Similarly, the safety of rosuvastatin (20 mg/day) was confirmed in a trial of 17,802 apparently healthy men and women (with low-density lipoprotein [LDL] cholesterol levels of less than 130 mg per deciliter) in which rates of muscle toxicity were similar between rosuvastatin and placebo.[12] Pravastatin, fluvastatin, rosuvastatin, and pitavastatin are not extensively metabolized by CYP3A4 and are less likely to be associated with drug interactions.

Statin-Associated IMNM

Statin-associated IMNM has a prevalence of 1 in 100,000 persons, along with female predominance (58%) and a mean age of onset greater than age 50.[13,14] A recent single-center experience reported an increasing incidence.[11] Statin-related IMNM is more common with statins metabolized via the cytochrome P450 3A4 (CYP3A4) and non-CYP3A4 pathways, which includes simvastatin, atorvastatin, lovastatin, pravastatin, and fluvastatin.[15] Although statin-related IMNM generally occurs within 1 year of the statin initiation, it may be delayed for years in half of the cases.[16]

Pathogenesis of IMNM

Anti-HMGCR Autoantibody

In 2010, an antibody directed against a 100 and 200 kd doublet protein was characterized in a subset of myositis patients previously considered to be autoantibody negative, suggesting an autoimmune mechanism.[17] In a series of elegant experiments, the 100 kd autoantigen was found to be HMGCR.[13] It was later discovered that high levels of HMGCR in regenerating muscle cells perpetuated the ongoing autoimmune attack on muscle tissue, thus contributing to persistent symptoms even after the discontinuation of the statin.[13] Our center later reported a similar significant association between anti-HMGCR positivity and necrotizing myopathy with a similar spectrum of clinical features, including severe muscle weakness, exposure to statin, high CK levels (90% ≥ 5,000), and a lack of other organ manifestations.[18] An interesting finding has been that approximately 20% of anti-HMGCR antibody-positive patients report no history of statin use (although exposure to statins may occur with ingestion of cholesterol-lowering supplements not appreciated by the patient or their physician).[19]

Anti-HMGCR autoantibodies are highly specific for patients with IMNM. In a sub-study of the community-based Atherosclerosis Risk in Communities that included 1,966 participants (763 current statin users), no patient had anti-HMGCR autoantibodies.[20] Similarly, none of 51 patients with self-limited statin intolerance or 47 statin-tolerant patients on high-dose statin therapy were anti-HMGCR positive. In another cohort, initial anti-HMGCR levels correlated with disease activity.[21] The anti-HMGCR levels decreased but did not normalize with immunosuppressive treatment and improvement of muscular strength. Statin-exposed anti-HMGCR-positive patients had significant improvements in strength and serum CK levels, whereas statin-unexposed anti-HMGCR-positive patients did not, suggesting a phenotypic difference between statin-exposed and statin-unexposed patients.

An anti-HMGCR ELISA test is now commercially available with a sensitivity of 94.4% and specificity of 99.3%, but the high 10.5% false-positive rate makes this ELISA test unsuitable for screening in the asymptomatic patient receiving statins.[20]

Genetic Risk Factors in Statin-Associated Self-Limited Myopathy and IMNM

There are some identifiable genetic factors, including single nucleotide polymorphisms, associated with statin-associated myopathies.[22-26] Ethnic variations in the susceptibility to statin myopathy, at least with simvastatin, have also been reported, with Chinese patients experiencing more side effects than Europeans.[27] Similar to other autoimmune conditions, statin-related IMNM is thought to occur in genetically susceptible individuals exposed to environmental triggers, with statins serving as that trigger. Statins cause overexpression of HMGCR, promoting production of anti-HMGCR autoantibodies in genetically susceptible individuals.[28]

Other Risk Factors in Statin-Associated Self-Limited Myopathy and IMNM

Concurrent therapy with a variety of medications enhances the risk for myopathic side-effects in statin-treated patients. Drugs that inhibit cytochrome P450 3A4 (CYP3A4) increase the susceptibility to statin myopathy in patients treated with lovastatin, simvastatin, and to a lesser extent atorvastatin, as they are metabolized by CYP3A4.[29] These medications include macrolide antibiotics (e.g., erythromycin), systemic-azole antifungals (e.g., ketoconazole), HIV/HCV protease inhibitors (such as ritonavir), and cyclosporine.[29-31] Statins that are not metabolized through the CYP3A4 system (e.g., pravastatin or low-dose atorvastatin) are appropriate choices for patients receiving the aforementioned medications who require statin treatment. Medications that are competitive CYP3A4 substrates (e.g., colchicine and calcium channel blockers – amlodipine and verapamil) also may increase the risk of statin myopathy.[32]

Although grapefruit juice inhibits intestinal CYP3A4, it does not increase the risk of muscle injury with statin use. Patients given atorvastatin (10, 20, or 40 mg day) at a stable dose received 300 mL a day of 100% grapefruit juice for a period of 90 days with only slight elevation of serum atorvastatin concentrations and no detectable liver or muscle adverse effects.[33]

Underlying neuromuscular disorders may increase the risk of statin myopathy. In a prospective cohort of 164 ALS patients, statin therapy was associated with an increased rate

of functional decline and muscle cramp frequency and severity.[34] Similar findings are reported to exacerbate myasthenia gravis.[35]

Statin use may potentiate muscle injury with prolonged vigorous exercise, but the injury is typically mild and subclinical[37] and increases with age.[37]

Approach to Statin Myopathy

Monitoring

A baseline CK level should be obtained prior to initiating statins, particularly in susceptible patients such as those with underlying neuromuscular disorders, hypothyroidism, a personal or family history of stain intolerance, and those receiving concomitant medications known to increase the risk of myopathy.[38] In the future, some more specific genetic testing may identify high-risk patients. Elevated CK levels need to be interpreted with caution, particularly in African Americans and younger men as "laboratory normal limits" vary according to a patient's age, gender, and ethnicity.[39-41] The National Lipid Association's Muscle Safety Expert Panel recently recommended a graduated training program for metabolic adaptation and prevention of exercise-induced muscle injury in those who plan to have regular physical exertion while taking statins.[2] Patients beginning statins are encouraged to report new myalgia or muscle weakness, but routine monitoring of CK levels is not recommended during statin treatment[42] and should be checked if new muscle-related symptoms develop.[43]

Diagnosis of Self-Limited Statin Myopathy

The diagnosis of a self-limited statin myopathy is based on the temporal association of statin use with an elevated CK, and the resolution of symptoms or normalization of biochemical abnormalities with statin withdrawal. A scoring system has been proposed for assessment of statin-associated muscle adverse events.[2] Trials of cessation and re-challenge of statin may be required when the diagnosis of a statin myopathy is in doubt. To compare the effect of statin re-challenge with placebo in patients with prior statin-related myalgia, a study used n-of-1 trials in eight patients.[44] Seven patients completed three treatment pairs, and one completed two treatment pairs, with each treatment pair consisting of three weeks of statin therapy. No statistically significant difference was noted in pain scores between statin and placebo treatment periods. Five patients resumed open-label statin therapy, with a median post-trial follow-up of 10 months. The role of muscle biopsy for the diagnosis of self-limited statin myopathy is unknown and is rarely employed in practice. Muscle biopsy obtained during acute rhabdomyolysis generally shows non-specific myonecrosis.[45]

Diagnosis of Statin-Associated IMNM

Establishing the diagnosis of statin-associated IMNM is essential in patients failing to improve after 3 to 6 months of discontinuing statins, or in those with progressive muscle weakness and elevated serum CK levels. The anti-HMGCR autoantibody should be ordered and electromyographic findings should be similar to those seen in other forms of inflammatory myopathy.[3] Magnetic resonance imaging (MRI) generally reveals muscle and fascial edema, atrophy and fatty replacement.[17] Statin-related IMNM patients demonstrate a necrotizing myopathy on muscle biopsy, and unlike classic polymyositis (or inclusion body myositis), there are minimal inflammatory cell infiltrates with no evidence of myofiber invasion.[5,16] MHC class I expression on the sarcolemma of muscle fibers is variable as well as complement deposition on capillaries.[5,16]

Management

Self-limited statin myopathy generally resolves with the cessation of statins, and statins must be stopped and never again administered in the setting of statin-associated IMNM.[47] IMNM patients have been treated with glucocorticoids and a variety of immunomodulatory or immunosuppressive therapies, including IVIG, methotrexate, azathioprine, mycophenolate, mofetil, tacrolimus, rituximab, and cyclophosphamide.[3,47] In particular, IVIG has been reported to be very effective in the management of statin-associated IMNM.[21,47-48] The efficacy of IVIG in statin-associated IMNM also has been our anecdotal experience at the University of Pittsburgh Myositis Center, however this needs to be assessed in larger cohorts.

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