Expanding our understanding of statin myopathy: when is it autoimmune?

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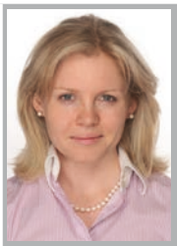
KEYWORDS: muscle inflammation ■ myopathy ■ myositis ■ myotoxin ■ necrotizing myopathy ■ statin ■ toxic myopathy



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Statins: the good, the bad & the ugly

Marketed as both single agents or as combination products (e.g., with niacin or ezetimibe), statins are a class of prescription drugs used together with diet and exercise to reduce blood levels of low-density lipoprotein cholesterol. Lipid-lowering agents, including statins, were among the top five classes of drugs prescribed in the USA in 2010 with US$18.7 billion in expenditures according to the IMS Health, National Sales Perspectives [101]. Touting known cardiovascular benefits, statins contribute to the reduction of cardiovascular morbidity and mortality and are thus widely prescribed. What may be underappreciated by clinicians is that in stark contrast to the lower discontinuation rates seen in clinical trials, although these drugs are believed to be underprescribed, in the 'real-world' approximately one-quarter of older adults who start taking statins for primary prevention stop taking them within 6 months, and greater than 50% stop within 2 years [1]. Thus, patients may never derive the cardiovascular benefit due to premature cessation. Statins carry with them rare, but well-known, side effects, including liver and muscle toxicity. The incidence of side effects in clinical practice likely exceeds that reported in clinical trials where patients are carefully selected and have a lower chance of potentially experiencing side effects. There was a time that clinicians believed that, while we did not understand the mechanism by which statins caused myotoxicity, statins were direct myotoxins that only caused a self-limited myopathy.

'Traditional' statin myopathy, where statins are believed to be direct myotoxins, appears to be genetically linked in some circumstances. The most eloquent study to date to demonstrate this link to a single-nucleotide polypeptide, and show biologically plausibility for this association, was the SEARCH group study that showed that a single-nucleotide polypeptide within the *SLC01B1* gene is strongly associated with an increased risk of statin-induced myopathy in simvastatin users [2]. The toxic myopathy resolved after statin discontinuation. Testing for *SLC01B1* prior to initiating statin therapy at the moment is not cost effective. This study was limited in that it only utilized a European cohort of patients, the majority of whom were caucasian.

It has also been posited that some patients may be predisposed to statin myopathy by underlying metabolic muscle disorders. In a study by Vladutiu and colleagues, of 110 patients who underwent mutation testing, 10% were heterozygous or homozygous for mutations causing three metabolic myopathies (carnitine palmitoyltransferase II deficiency, McArdle disease and myoadenylate deaminase deficiency) compared with 3% testing positive among asymptomatic patients on therapy suggesting that statins 'unmask' metabolic defects in some predisposed individuals [3]. These investigators recommend mutation screening for McArdle disease, carnitine palmitoyltransferase II deficiency, and myoadenylate deaminase deficiency for symptomatic statin users and any patients with a baseline serum creatine kinase (CK) level four-times the upper limit of normal [2,4].

But what about the times when myopathy persists despite statin cessation? Sir William Osler is reputed to have said, "Listen to your patient, he is telling you the diagnosis." We have been listening to patients tell us for years that they were convinced that the statins were responsible for their clinical myopathic signs and symptoms when they persisted even after statin withdrawal.

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While we listened carefully, we were at a loss to find a biologic mechanism for these persistent myopathic symptoms. We did not have any conclusive evidence that statins themselves were associated with immune-mediated myotoxicity; however, there was a growing body of literature that began to explore that link closely.

Statins & immune-mediated necrotizing myopathy

There are numerous case reports and small series that suggest that statins may be associated with idiopathic inflammatory myopathies in the traditional sense – dermatomyositis (DM), and polymyositis (PM), for example [5]. There has been no conclusive proof of causality, and often the temporal relationship between the commencement of the statin and the development of DM or PM is the main reason a link between the two is suspected. In recent years, however, there has been mounting evidence pointing to an immune-mediated necrotizing myopathy associated with statin use that persists even in spite of statin withdrawal. Needham and colleagues were the first to report these findings [6]. They investigated muscle pathology of eight patients with persistent myopathy despite statin withdrawal. All had myofiber necrosis. Only three had an inflammatory infiltrate, but MHC-I was upregulated. Following this case series, Grable-Esposito *et al*. reported on 25 patients from two neuromuscular centers (2000–2008) who met the following criteria:

- Proximal muscle weakness occurring during or after treatment with statins;
- Elevated CK;
- Persistence of weakness and elevated CK despite discontinuation of the statin;
- Improvement with immunosuppressive agents;
- Muscle biopsy showing necrotizing myopathy without significant inflammation [7].

We at the Johns Hopkins Myositis Center (MD, USA) read these papers with great interest, recognizing this clinical phenotype among our own patients. At the same time, we began to note a novel autoantibody specificity at 200 and 100 kd respectively by immunoprecipitation using HeLa cells in several of the patients with clinical and histopathologic myopathic features we evaluated at our center. We initially noted the strong association of this autoantibody with an immune-mediated necrotizing myopathy [8]. We also recognized that these patients had a significant association with statin use. The percentage of patients exposed to a statin differed in the patients with the novel autoantibody when compared with the larger clinical cohort of patients with DM and PM. When looking only at those patients over 50 years old, statin use was significantly higher in the autoantibody group compared with those in the DM, PM or inclusion body myositis subgroups. Our group later went on to identify the autoantigen as HMG-CoA reductase (HMGCR), the rate-limiting step in cholesterol synthesis and the pharmacologic target of statins [9].

Can we differentiate those who have the self-limited form of statin myopathy from those who have the immune-mediated variety?

In our experience, most patients with autoimmune statin myopathy had markedly elevated muscle enzymes at presentation to our clinic. Dramatic and persistent CK elevations are more likely in the autoimmune form of statin myopathy; however, perhaps earlier recognition and diagnosis of this select patient population may lead to better outcomes.

Mammen and colleagues have demonstrated that the anti-HMGCR autoantibody is very rare among statin users, even among those with self-limited muscle symptoms [10,11]. This study explored the prevalence of anti-HMGCR antibodies by using two groups of statin users – 1966 participants from a substudy of the community-based ARIC cohort as well as 98 French–Canadian patients with a history of familial hypercholesterolemia, 51 of whom had documented statin intolerance. Remarkably, not a single patient from either group of patients studied tested positive for anti-HMGCR antibodies. This suggests that the autoimmune type of statin myopathy associated with anti-HMGCR autoantibodies is most likely rare, and anti-HMGCR antibodies are thus highly specific for those with a statin-associated autoimmune myopathy. Given the screening on a much larger population than the original myositis cohort population tested, the investigators were able to better define the normal range of anti-HMGCR titers and thus determine the sensitivity and specificity of the anti-HMGCR ELISA, which is 94.4 and 99.3%, respectively. If we assume that anti-HMGCR autoimmune myopathy is rare (one in 100,000), the negative predictive value of the ELISA test in an unselected population is greater than 0.999.

As previously stated, genetics appears to play a role in the traditional self-limited type of statin myopathy. Similarly, there is now strong evidence that there is a genetic predisposition to developing anti-HMGCR-associated myopathy [11]. The association of anti-HMGCR myopathy with HLA class I and II antigens was investigated. HLA antigens were determined in: 20 Caucasian and eight African–American anti-HMGCR patients; 487 Caucasian and 167 African–American controls; and 51 Caucasian subjects with mild self-limited statin intolerance. DRB1*11:01 was associated with an increased risk of anti-HMGCR myopathy. This study, therefore, suggests a mechanistic link between statin exposure, increased HMGCR expression and the potential presentation of HMGCR-derived peptide(s) by DRB1*11:01.

A brief comment on statin rechallenge

Statin rechallenge with a different member of the statin class has been studied [12]. The proportion developing myopathy on introduction of other statins among patients with known simvastatin-induced myopathy ranged between 61% (for fluvastatin) and 81% (for rosuvastatin). No data yet exists regarding success of rechallenge in patients with the autoimmune type of statin myopathy.

The new US FDA recommendations may have unintended consequences

Recently, the US FDA announced the elimination of the recommendation that patients on statins undergo routine periodic monitoring of liver enzymes. Under these new guidelines, clinicians are advised to perform liver enzyme tests before initiating statin therapy in patients and only as clinically indicated thereafter. Interestingly, in our experience, in some instances, it was routine liver enzyme monitoring that prompted a further work-up in otherwise asymptomatic patients. When there was no obvious sign of liver toxicity, astute clinicians ascertained a CK level to determine if the source of the elevated liver function tests was skeletal muscle injury rather than injured hepatocytes. We are concerned that the lack of routine liver enzyme monitoring will have the unintended consequence of failing to prompt early skeletal muscle injury recognition.

Conclusion & future perspective

Our understanding of statin-induced myotoxicity is continually expanding. Nevertheless, it would be helpful to predict the likelihood of developing statin myopathy in an individual patient. Genetic predisposition seems to play a large role in this regard; however, the practical incorporation of such knowledge in day-to-day statin prescribing habits is unclear. Similarly, it would be helpful to predict which statin-intolerant patients can be treated merely with statin withdrawal and which ones will also need immunosuppressive therapy. When the anti-HMGCR antibody assay becomes commercially available, we believe that it will be potentially quite useful in delineating between these two populations. Except for scant data, it remains largely unknown whether patients at high risk for cardiovascular events in either group of patients can and should be rechallenged with a statin.

Financial & competing interests disclosure

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