Statin-Induced Anti-HMGCR-Associated Myopathy

In addition to self-limited myotoxicity, statins have recently been shown to trigger an immune-mediated necrotizing myopathy (IMNM), which is distinguished from polymyositis (PM) and dermatomyositis (DM) by the absence of primary inflammation on muscle biopsy. Previously, we have shown that patients with statin-associated necrotizing myopathy express an autoantibody targeting 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the pharmacological target of statins (1,2). We conducted a case-control study to characterize the comorbidities and detailed individual statin history and to investigate the possible clinical associations that could contribute to the development of anti-HMGCR-positive myopathy in statin-treated patients.

Within our longitudinal cohort, we identified 58 anti-HMGCR-positive statin-exposed myositis patients and 37 comparator myositis patients who were exposed to a statin and were anti-HMGCR negative. All patients met the Bohan and Peter criteria for PM or DM (3,4). Of note, the Bohan and Peter criteria do not distinguish PM or DM from IMNM by muscle biopsy characteristics; thus, all patients in the IMNM category meet the Bohan and Peter definition for PM.

The average duration of follow-up was 29 months (range from 0 to 100 months). Anti-HMGCR-positive patients were slightly older (mean age 59.9 vs. 55.4 years, p = 0.025), and there was a trend for women to be more likely to have anti-HMGCR antibodies (52% vs. 35%, p = 0.113). They had a higher prevalence of non-steroid-induced type 2 diabetes (47% vs. 17%, p = 0.003). All patients with diabetes were taking oral hypoglycemic agents and/or insulin.

Anti-HMGCR-positive patients had higher median creatine kinase values at the time of diagnosis (6,800 vs. 1,990 IU/l, p < 0.001). They also had lesser median hip flexor strength at presentation (14.5 vs. 18 on a 20-point scale, p = 0.005), but interestingly, median arm abduction strength was not significantly different (18 vs. 20 on a 20-point scale, p = 0.21) (The method used for scoring the muscle strength has been described elsewhere [5]). Dysphagia was also more frequently reported by anti-HMGCR-negative patients (60% vs. 40%, p = 0.059).

The interval from statin start date to 2014, the year of data review, did not differ between anti-HMGCR-positive (mean 11 years before 2014, SD ± 6) and anti-HMGCR-negative patients (mean 10 years before 2014, SD ± 5, p = 0.65). The median duration of statin therapy before the onset of muscle symptoms was 38 months in anti-HMGCR-positive patients. More patients in the anti-HMGCR-positive group were exposed to atorvastatin (86% vs. 43%, p < 0.001). Twenty-four patients, with equal frequency in both groups, had a history of treatment with multiple statins/combination therapy. In order to identify whether individual statins were associated with anti-HMGCR myopathy, in the multiple regression analysis, these patients were excluded. The data regarding the exact dose of statins were available for only 27 patients. However, there was no significant

![FIGURE 1 Multiple Regression Analysis of Variables Potentially Associated With Statin-Induced Anti-HMGCR Myopathy (n = 69)](chart)
difference in the proportion of patients who underwent high-intensity statin therapy in the 2 groups (38% and 27% of anti-HMGCR-positive and -negative patients, respectively, \( p = 0.69 \)). Given the limited sample, no conclusions regarding the association of statin intensity and anti-HMGCR-associated myopathy could be made.

We employed multiple regression analysis for the analysis of 69 patients who had been treated with a single statin to identify independent variables that may be associated with the risk for the development of anti-HMGCR myopathy in statin-exposed patients. After adjusting for age and sex, type 2 diabetes mellitus and atorvastatin use (vs. rosuvastatin and simvastatin) were significantly associated with anti-HMGCR myopathy (odds ratio [OR]: 15.6, \( p = 0.006 \), and OR: 14.3, \( p = 0.005 \), respectively; both with notably wide confidence intervals) (Figure 1). In addition, we repeated the analysis with all participants and individual statins entered into the model as dichotomous variables. Again, atorvastatin and type 2 diabetes remained significant independent predictors of anti-HMGCR-associated myopathy (OR: 7.4, \( p = 0.001 \), and OR: 3.8, \( p = 0.023 \), respectively).

Notably, the median duration of statin therapy before the onset of muscle symptoms in the anti-HMGCR-positive group was 38 months. This finding suggests that long-term exposure to statins is likely to trigger an autoimmune response in most cases (85% >6 months). Therefore, medical providers should be aware that statin-induced anti-HMGCR myopathy may occur even after several years of continuous uneventful statin exposure.

Our results indicate that statin-exposed patients with anti-HMGCR antibodies have severe skeletal muscle manifestations, specifically, hip flexor muscle weakness at presentation. In addition, type 2 diabetes mellitus and atorvastatin may be associated with a higher risk of development of this myopathy. This study was exploratory with small numbers of patients. Further studies need to be better characterized the risk factors for statin-induced anti-HMGCR-associated myopathy.

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REFERENCES

Effects of Prasugrel Versus Clopidogrel on Coronary Microvascular Function in Patients Undergoing Elective PCI

Microvascular impairment has been reported in patients on clopidogrel undergoing elective percutaneous coronary intervention (PCI) (1). The related potential mechanisms might include the high residual platelet reactivity observed in a substantial proportion of these patients pretreated with clopidogrel at the time of PCI (2,3). Alternatively, microvascular constriction could occur possibly as consequence of transient endothelial dysfunction related to impaired platelet response to clopidogrel (4). It is unknown whether prasugrel might exert a protective effect on microcirculation during elective PCI in patients with...