CLINICAL/SCIENTIFIC NOTE

Statins in Genetic Myopathies

A Retrospective Analysis of Safety and Tolerability

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Abstract

Objectives

Statins are widely prescribed lipid-lowering agents, but their safety and tolerability in patients with underlying genetic myopathies remain uncertain. We aimed to study statin safety and tolerability in genetic myopathies using a large retrospective cohort.

Methods

We conducted a retrospective study in patients with myotonic dystrophy type 1 (DM1) and type 2 (DM2), facioscapulohumeral dystrophy (FSHD), limb-girdle muscular dystrophy (LGMD), and metabolic or mitochondrial myopathies who were exposed to statins.

Results

We included 135 patients (36 with DM1, 46 with DM2, 22 with FSHD, 6 with LGMD, 17 with mitochondrial myopathy, 6 with glycogenosis, and 2 with disorders of fatty acid oxidation or carnitine transport). A total of 44 patients discontinued statins, most often for statin-associated muscle symptoms (SAMS; n = 20). SAMS occurred in 36 of 135 patients (26.67%; 8 with DM1, 10 with DM2, 7 with FSHD, 3 with LGMD, 4 with mitochondrial myopathy, and 4 with metabolic myopathy). Myalgias were the most frequent SAMS (n = 29). Rhabdomyolysis occurred in 4 patients (1 with mitochondrial myopathy and 3 with McArdle disease). Statins unmasked myopathy in 6 of 36 patients. No patient developed immune-mediated necrotizing myopathy.

Discussion

SAMS are generally mild and occur at a frequency similar to the general population in common genetic myopathies, except increased rhabdomyolysis in mitochondrial myopathies and McArdle disease. Statins are generally safe, though not well tolerated, and could be used when closely monitored in several genetic myopathies. In mitochondrial and metabolic myopathies, their use should be approached with caution because of the potential risk of rhabdomyolysis.

PRACTICAL IMPLICATIONS

Statins are generally safe but not well tolerated in genetic myopathies. In mitochondrial and metabolic myopathies, caution is warranted because of a potential risk of rhabdomyolysis.

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Supplementary Material

Introduction

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibitors and often recommended for treatment of dyslipidemia.[1] Statin-associated muscle symptoms (SAMS) are the most common adverse events, including self-limited myotoxicity (ranging in severity from myalgias to rhabdomyolysis) and anti-HMGCR immune-mediated necrotizing myopathy (HMGCR-IMNM) requiring immunotherapy.[2,3] The Effect of Statins on Skeletal Muscle Function and Performance trial showed increased myalgia without weakness or reduced exercise performance in patients treated with statin compared with placebo.[4] Proposed mechanisms of statin-associated myotoxicity may interact with those of genetic myopathies, such as reduced coenzyme Q10 synthesis and mitochondrial myopathies or

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sarcolemmal disruption, and certain subtypes of limb-girdle muscular dystrophies (LGMDs).[2] Reports of LGMD due to biallelic loss-of-function variants in HMGCR support a direct role for HMGCR in muscle health and disease.[5,6] A recent review concluded that evidence exists for avoiding statins in myotonic dystrophy type 2 (DM2), mitochondrial myopathies, and McArdle disease; however, data are limited in other genetic myopathies.[7] No large studies examining statin safety and tolerability in genetic myopathies exist while studies have evaluated this question in non-HMGCR immune-mediated myopathies and found statins to be generally safe and well tolerated.[8-10] We aimed to address this knowledge gap with a retrospective study on statin exposure in adults with common genetic myopathies, including myotonic dystrophy types 1 (DM1) and 2 (DM2), facioscapulohumeral dystrophy (FSHD), LGMD, mitochondrial myopathies, and metabolic myopathies.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Mayo Clinic Institutional Review Board.

Study Methodology

We screened electronic medical records of patients evaluated from January 2013 to December 2023 using ICD-10 diagnostic codes G71, E71, and E74 (eFigure 1), with medical record mention of "statin" or common trade names for atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin. Inclusion criteria were age older than 18 years; confirmed genetic diagnosis of DM1, DM2, FSHD, or LGMD; confirmed genetic or myopathological diagnosis of mitochondrial or metabolic (fatty acid oxidation defects or glycogen storage disorders) myopathy; and statin exposure.

SAMS were categorized into 4 subtypes[7]: (A) side effects: typical symptoms of myalgia that improve after discontinuation and are distinct from the symptoms of the underlying myopathy; (B) unmasking: manifestation of myopathy in an asymptomatic patient with clear temporal association with statin; (C) exposing: SAMS lead to diagnosis of myopathy in a previously symptomatic patient not investigated earlier, e.g., when creatine kinase (CK) levels remain elevated after statin discontinuation in patients with preexisting myalgia; and (D) aggravating: increased severity of existing myopathy with clear temporal association with statin. Rhabdomyolysis could be classified under B, if it occurs as a new manifestation of the myopathy that then persists, or under D, if it is already a characteristic of the myopathy that becomes more frequent. Rhabdomyolysis was confirmed if there was an increase in CK >10× the upper limit of normal or, in the case that CK values were not available in our electronic record, by chart record confirmation from a myologist at our institution (M. M. or T. L.) after external record review.

Creatine kinase values are reported in U/L and were recorded closest to the time of starting and stopping statin therapy. Statin doses were converted into equivalents of rosuvastatin for comparison and are reported in mg.[11]

Statistical Analyses

Statistical analyses were performed using International Business Machines (IBM) Statistical Product and Service Solutions (SPSS) Statistics. Comparisons of categorical data were performed with the Pearson χ^2 test. Comparisons of continuous variables between samples were performed using the *t* test and within samples were performed using the paired-samples *t* test.

Data Availability

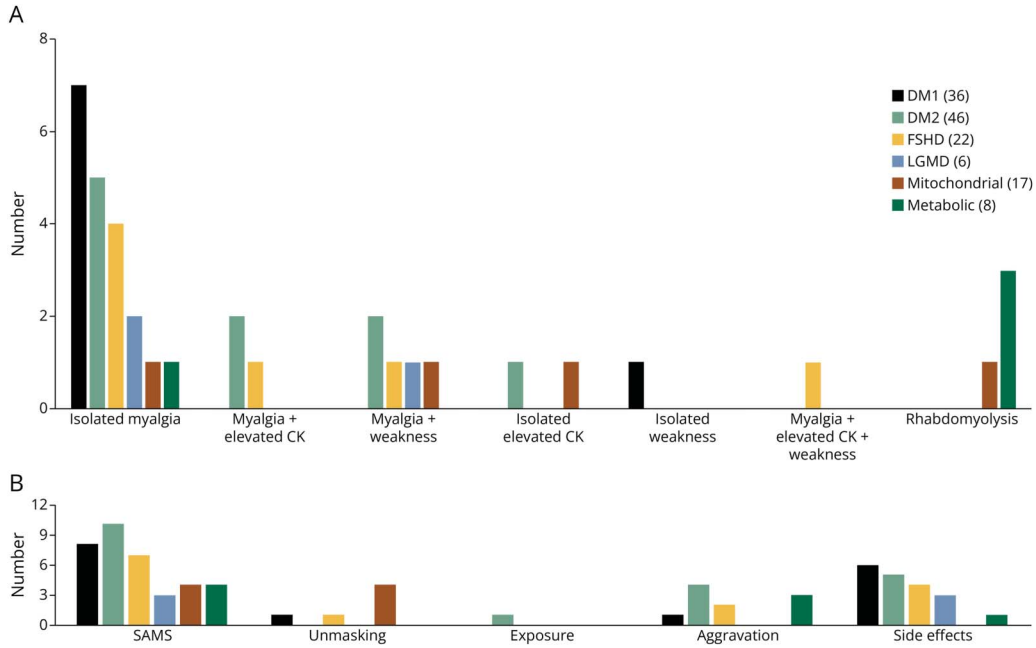
Anonymized data not published within this article will be made available by request to the corresponding author from any qualified investigator.

Results

We screened 574 individuals and included 135 patients (36 with DM1, 46 with DM2, 22 with FSHD, 6 with LGMD, 17 with mitochondrial myopathies, 6 with glycogenosis, and 2 with disorders of fatty acid beta-oxidation and carnitine transport system) who were exposed to statins. Demographic and clinical characteristics are given in eTable 1. At the last follow-up, 91 of 135 patients remained on statin therapy. SAMS occurred in 36 of 135 patients (26.7%; 8 with DM1, 10 with DM2, 7 with FSHD, 3 with LGMD, 4 with mitochondrial myopathy, and 4 with metabolic myopathy). Of these, 14 continued statin therapy while 22 discontinued statins (20 due to SAMS and 2 due to a new diagnosis of myopathy). An additional 22 patients without SAMS discontinued statins, most frequently for a new diagnosis of myopathy (n = 13; 7 without alternative dyslipidemia therapy). Myalgias were the most common symptom of SAMS (Figure 1A), occurring in isolation (n = 20) or in combination with hyperCKemia or weakness (n = 9). Mild worsening weakness was reported in 8 patients (1 with DM1, 2 with DM2, 2 with FSHD, 1 with LGMD-D4, and 2 with mitochondrial myopathy), but this did not result in any functional limitations beyond their preexisting status. Rhabdomyolysis occurred in 4 patients: 3 with McArdle disease, who had an increased frequency of rhabdomyolysis above baseline, and 1 with mitochondrial myopathy, with unmasking of the first episode of rhabdomyolysis occurring shortly after statin initiation and further episodes occurring in the setting of systemic illness after statin discontinuation. No patient in the cohort developed HMGCR-IMNM.

Side effects were the most common category of SAMS, occurring in 19 of 36 (Figure 1B). Statins unmasked the

Figure 1 Patterns of Statin-Associated Muscle Symptoms and CK Changes by Diagnosis



Patterns of statin-associated muscle symptoms (SAMS) and changes in creatine kinase (CK) levels. (A) Symptoms of SAMS stratified by diagnosis; the total number in each diagnostic category shown in parentheses for reference. (B) Total SAMS and category of symptoms stratified by diagnosis; the total number in each diagnostic category shown in parentheses for reference. Note: categories in panel B reflect how each of the symptoms in panel A was classified for each patient. CK = creatine kinase; DM1 = myotonic dystrophy type 1; DM2 = myotonic dystrophy type 2; FSHD = facioscapulohumeral muscular dystrophy (type 1 or type 2); LGMD = limb-girdle muscular dystrophy.

myopathy in 6 of 36 (1 with DM1, 1 with FSHD, and 4 with mitochondrial myopathy), exposed the myopathy in 1 of 36 (DM2), and aggravated the myopathy in 10 of 36 (1 with DM1, 4 with DM2, 2 with FSHD, and 3 with McArdle disease who had an increased frequency of rhabdomyolysis).

Among the 22 patients (11 with SAMS, none with rhabdomyolysis) who had CK levels measured both on and off statin therapy, none had a significant difference in CK values on and off statin (Figure 2A). Only 4 patients (3 with DM2 and 1 with FSHD) had an increase in CK levels >250 U/L from their pre-statin baseline (range 341–436 U/L), all of whom developed SAMS (Figure 2B). CK values, available in our electronic records during rhabdomyolysis in 3 patients, ranged from 5,324 to >20,000 U/L (baseline CK while on statin 591–1021 U/L).

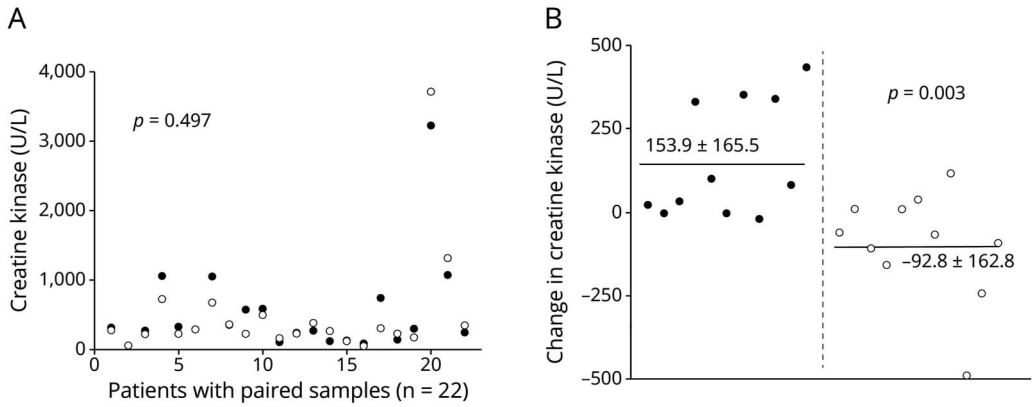
The mean statin dose in rosuvastatin equivalents was not different between those with SAMS (11.4 ± 10.9 mg) and those without (12.1 ± 10.3 mg, p value = 0.640). The proportion of patients on high-intensity statin regimens[11] was not different between those with SAMS (7/36) and those without (24/99, p value = 0.550).

Discussion

In our cohort, 36 of 135 patients (26.67%) experienced SAMS, which is within the range reported in general population.[2] In addition, there was no correlation between high-intensity statin regimens[11] or mean statin dose and SAMS. This underscores the importance of carefully assessing SAMS, even in patients taking the lowest possible dose of statin. None of the patients with non-rhabdomyolysis SAMS in our cohort showed a CK elevation >500 U/L above their pre-statin baseline values. Therefore, in patients with genetic myopathies, a CK rise exceeding 500 U/L from baseline after statin initiation should prompt consideration of additional pathology, such as evolving rhabdomyolysis or HMGCR-IMNM, although the latter was not observed in our cohort. In our cohort, statins were discontinued in 44 of 135 patients (32.6%), half attributed to SAMS, which is higher than the 10% reported in the general population.[12] Statins were discontinued in 13 of 135 patients (9.6%) after a new diagnosis of myopathy without SAMS, 7 of whom were not prescribed an alternative lipid-lowering strategy, highlighting a missed opportunity for cardiovascular risk factor modification.

Unmasking of an underlying myopathy is the third most common pattern of SAMS (6/36) after side effects and aggravation. Therefore, persistent muscle symptoms after statin discontinuation should prompt consideration of not only IMNM but also genetic myopathies. Rhabdomyolysis is a rare form of SAMS, occurring in 0.01% of statin users in the general population.[13] However, in our cohort, it was observed in 4 of 25 patients (16%) with mitochondrial myopathies or McArdle disease. This raises a safety concern that

Figure 2 Changes in CK Levels With Statin Use in the Genetic Myopathy Cohort With and Without Statin-Associated Muscle Symptoms



(A) Creatine kinase on (black) and off (white) statin in all patients with paired samples (N = 22); *p* value for the paired-samples comparison. (B) Change in creatine kinase on statin in those with muscle-associated symptoms (black) and those without (white). Mean and SD are written, and mean is indicated by solid horizontal lines; *p* value for independent-samples comparison between those with SAMS and those without. The median time to CK value from statin initiation was 10.5 months (range 1–108 months).

supports the recommendation[7] to avoid statins in these 2 subtypes of genetic myopathies when considering the availability of alternative lipid-lowering agents. We found no increased incidence of SAMS in the DM2 cohort compared with our other patient groups; however, there is a previous report of a patient with DM2 and statin-associated rhabdomyolysis.[14] This heterogeneity in observed outcomes suggests the need for caution and careful observation in patients with DM2.

Our study is limited by its retrospective nature, whereby patients were not systematically examined for SAMS, including severity or contributing factors, such as exercise. In addition, the numbers of patients with LGMD and metabolic myopathies were small because of the relatively younger age of patients and related lower prevalence of dyslipidemia.

In conclusion, the overall rates of SAMS in our cohort were comparable to those seen in the general population, except for a concern for increased frequency of rhabdomyolysis in individuals with mitochondrial myopathies and McArdle disease. While statin use should be avoided in patients with mitochondrial or metabolic myopathies, it seems to be generally safe, though not always well tolerated, in those with other forms of genetic myopathies. In these cases, careful monitoring for muscle symptoms, periodic CK measurements, and consideration of alternative lipid-lowering therapies may help improve tolerance and support cardiovascular risk management. A new diagnosis of genetic myopathy should not necessarily preclude initiation nor prompt discontinuation of statin therapy.

Author Contributions

B.N. Putko: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Milone: drafting/revision of the manuscript for content, including medical writing for content. T. Liewluck: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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