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# Absence of anti-HMG-CoA reductase autoantibodies in severe self-limited statin-related myopathy

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## Abstract

**Introduction—**Patients with self-limited statin-related myopathy improve spontaneously when statins are stopped. In contrast, patients with statin-associated autoimmune myopathy have autoantibodies recognizing 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) and usually require immunosuppressive therapy to control their disease. On initial presentation, it can sometimes be difficult to distinguish between these two diseases since both present with muscle pain, weakness, and elevated serum creatine kinase (CK) levels. The goal of this study was to determine if patients with severe self-limited statin-related myopathy also make anti-HMGCR autoantibodies.

**Methods—**We screened 101 subjects with severe self-limited cerivastatin-related myopathy for anti-HMGCR autoantibodies.

**Results—**No patient with severe self-limited cerivastatin-related myopathy had anti-HMGCR autoantibodies.

**Conclusion—**Anti-HMGCR autoantibody testing can be used to help differentiate whether a patient has self-limited myopathy due to cerivastatin or autoimmune statin-associated myopathy; these findings may apply to other statins as well.

### Keywords

rhabdomyolysis; statins; adverse drug reaction; autoimmune; myopathy

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**POTENTIAL FINANCIAL CONFLICTS OF INTEREST**

BMP serves on the DSMB of a clinical trial of a device funded by the manufacturer (Zoll LifeCor) and on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson. ALM is co-inventor of an anti-HMGCR test that is now commercially available; however, he receives no royalties or other compensation for this.

## INTRODUCTION

Statin-associated autoimmune myopathy is a rare complication of statin therapy characterized by muscle weakness and pain, elevated creatine kinase (CK) levels, and autoantibodies recognizing 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR), the pharmacologic target of statins.[1] Even after discontinuing statins, these patients develop a progressive myopathy that requires immunosuppressive therapy. In contrast, most patients with statin-related rhabdomyolysis have self-limited disease that resolves after statins are discontinued. Because the initial clinical presentations are similar, distinguishing between autoimmune and self-limited forms of statin-related muscle injury in the acute setting may be challenging. We have previously shown that anti-HMGCR antibodies are not present among individuals with mild self-limited muscle symptoms related to statins, few of whom had high CK elevations or weakness, but whether these antibodies are found in severe forms of self-limited statin-related muscle injury is unknown.[2] To address this question, we evaluated anti-HMGCR titers in a large population of individuals who suffered severe self-limited statin-related rhabdomyolysis.

## MATERIALS AND METHODS

### Subjects

Subjects were recruited through attorneys representing cerivastatin users who developed rhabdomyolysis from 1998 to 2001.[3,4] Telephone interviews were conducted with subjects who consented to join the study and copies of their medical records were obtained. Trained abstractors conducted medical record reviews to confirm the relationship between statin use and muscle injury, and to exclude other potential etiologies for muscle injury, such as genetic or autoimmune myopathies, acute myocardial infarction, severe infection, trauma, alcohol use, overexertion, and hyperthermia. Statin-related rhabdomyolysis was defined as muscle pain or weakness with no apparent etiology other than statin use and a CK level >10 times the upper limit of normal (ULN). Subjects with validated rhabdomyolysis provided blood specimens. This study was approved by the University of Washington Institutional Review Board.

### Experimental Procedures

Plasma samples were screened by enzyme-linked immunosorbent assay (ELISA) for anti-HMGCR autoantibodies and positive samples were confirmed by immunoprecipitation.[1]

### Statistical Analysis

The 95% confidence interval (CI) for the prevalence of positive anti-HMGCR titers was estimated using STATA, version 11.0 (StataCorp, College Station, TX).

## RESULTS

101 subjects provided a blood sample; most were hospitalized and experienced both muscle pain and weakness (Table 1). The median peak CK level was 35,064 international units per liter (IU/L) and 84% had CK levels > 50 times the ULN.

One subject was anti-HMGCR positive by ELISA, but negative by immunoprecipitation. Therefore the prevalence of anti-HMGCR autoantibodies in our population was 0% (95% CI, 0%–4%).

## DISCUSSION

Statin-associated autoimmune myopathy associated with anti-HMGCR autoantibodies often progresses slowly over weeks or months, whereas statin-related rhabdomyolysis tends to progress more quickly; indeed, most neuromuscular specialists only use the term rhabdomyolysis to describe acute elevations in CK level. Furthermore, statin-associated autoimmune myopathy has not been associated with renal failure, whereas a significant number of patients with statin-related rhabdomyolysis experience kidney dysfunction. In this study, for example, 23% of those with rhabdomyolysis had renal failure and 6% required hemodialysis. Thus, in a patient with an acute CK level elevation, and especially in those with renal failure, statin-related rhabdomyolysis is a more likely diagnosis than statin-associated autoimmune myopathy. However, nearly 90% of patients with statin-associated autoimmune myopathy have CK levels > 2000 IU/L, which meets some definitions of rhabdomyolysis.[5,6] Occasionally, these patients present with rapidly progressive disease that can mimic statin-related rhabdomyolysis[1] or lack of a reliable history to estimate how quickly CK levels have risen. Here, we show that in a large population of severe statin-related rhabdomyolysis patients, none had anti-HMGCR autoantibodies. Therefore, when the diagnosis remains in doubt, this finding supports the use of anti-HMGCR testing to help distinguish between those with statin-associated autoimmune myopathy, who require immunosuppressive therapy, from those with severe self-limited rhabdomyolysis, who require supportive care. Furthermore, together with the lack of genetic associations with autoimmune loci,[4,7] this study suggests that statin-related rhabdomyolysis is not mediated through autoimmunity to HMGCR.

One subject had a positive ELISA test for anti-HMGCR but was negative by the gold-standard immunoprecipitation test. This is consistent with the published 0.7% false-positive rate of the anti-HMGCR ELISA.[2] Since most commercial anti-HMGCR testing is currently performed by ELISA, a few patients with self-limited rhabdomyolysis could be misclassified as autoimmune by this method. This underscores the importance of only testing for anti-HMGCR autoantibodies in patients with a high pre-test probability of statin-associated autoimmune myopathy. Our recommendation would be to test for anti-HMGCR autoantibodies only in those who are weak, have markedly elevated CK levels, and who fail to improve or worsen following statin discontinuation. Testing large numbers of patients who do not fulfill these criteria would likely result in an unacceptably high number of false positive anti-HMGCR tests and subject patients to the harms of immunosuppressive therapy with no expectation of benefit.

This study has 4 main limitations. First, we recruited subjects and collected blood samples years after the rhabdomyolysis event, raising the possibility that these patients may have had transient autoimmunity in the acute setting. However, our prior studies have shown that anti-HMGCR autoantibodies persist even after statin-associated autoimmune myopathy has been well controlled.[8,9] Furthermore, we have now evaluated serial autoantibody titers in more

than 50 statin-associated anti-HMGCR positive subjects followed for an average of about 3 years (range 0–10 years). Although the majority of these have recovered full strength with treatment, they continue to have elevated autoantibody titers (unpublished data). Second, although there are no reports of patients with myopathy converting from anti-HMGCR negative to anti-HMGCR positive status, we cannot exclude the possibility that some patients with statin-associated autoimmune myopathy might test negative for these antibodies in the acute setting. Third, it is possible that some patients with statin-associated autoimmune myopathy never develop anti-HMGCR autoantibodies; however, there are currently no published studies to support this concern. Fourth, the rhabdomyolysis in our study subjects was caused by cerivastatin, which was removed from the market in 2001. Although muscle injury is a class effect for all statins, findings from our study may not generalize to users of other statins. These caveats notwithstanding, this study suggests that testing for anti-HMGCR autoantibodies may help to discriminate between self-limited rhabdomyolysis and statin-associated autoimmune myopathy.

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ALM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

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## ABBREVIATIONS

| | |
|---|---|
| **CI** | confidence interval |
| **CK** | creatine kinase |
| **ELISA** | enzyme-linked immunosorbent assay |
| **HMGCR** | 3-hydroxy-3-methyl-glutaryl-CoA reductase |
| **IQR** | interquartile range |
| **IU/L** | international units per liter |
| **SD** | standard deviation |
| **ULN** | upper limit of normal |

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**TABLE 1**

Characteristics of statin-related rhabdomyolysis subjects

| | **Subjects N=101** |
|---|---|
| Age, mean (SD) | 61 (9) |
| Women, count (%) | 55 (54%) |
| Race, count (%) | |
| White | 87 (86%) |
| African-American | 3 (3%) |
| Asian | 2 (2%) |
| Other/unknown | 9 (9%) |
| Muscle symptoms, count (%) | 101 (100%) |
| Pain | 96 (95%) |
| Weakness | 85 (84%) |
| Concomitant gemfibrozil use (%) | 75 (74%) |
| Hospitalized | 86 (85%) |
| Renal failure, count (%) | 23 (23%) |
| Required hemodialysis, count (%) | 6 (6%) |
| Highest creatinine kinase level, IU/L, mean (SD) | 62,701 (72,172) |
| Highest creatinine kinase level, IU/L, IQR | 14,643–85,636 |