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Case 22-2019: A 65-Year-Old Woman with Myopathy.

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Case 22-2019: A 65-Year-Old Woman with Myopathy

TO THE EDITOR: The case reported by Freeman et al. (July 18 issue)[1] contains conclusions that may perpetuate misconceptions. The patient had acute rhabdomyolysis and necrotizing autoimmune myositis, but the connection with statins is unlikely.

In this patient, myopathy started 2 weeks after coryza and cough; this suggests a preceding viral infection, which is a more likely trigger of necrotizing autoimmune myositis[2] than atorvastatin, which had been initiated 6 months previously. Statins can rarely lead to acute myotoxicity, but the contention that they induce anti-HMGCR (3-hydroxy-3-methylglutaryl coenzyme A reductase)–mediated autoimmunity is unsubstantiated and disputed.[3] HMGCR is normally expressed in regenerating rather than necrotic fibers, and there is no evidence that it induces muscle-fiber necrosis or triggers autoimmunity, especially since HMGCR is a ubiquitous cytoplasmic antigen that is not accessible to anti-HMGCR antibodies.[4] HMGCR is expressed in normal myotubes, but anti-HMGCR IgG does not induce myotubular necrosis[5] and does not explain pathogenicity.[4] Most important, anti-HMGCR autoantibodies are not statin-specific because they are most frequently seen in patients with paraneoplastic, viral, or other forms of necrotizing autoimmune myositis who have not received statins.[6]

In the few patients in whom necrotizing autoimmune myositis does develop after receipt of statins for years, the association is more of a chance phenomenon, considering that necrotizing autoimmune myositis is now the most common inflammatory myopathy[2,4] and that 25% of Americans older than 40 years of age take statins. The authors' conclusions could deprive the patient, as well as others with a similar presentation, of a helpful drug.

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TO THE EDITOR: We would like to expand on the discussion by Freeman et al. on statin-associated autoimmune myopathy with autoantibodies against HMGCR in a patient who had been prescribed a statin medication. First, we would note that this disease may also be associated with a dietary source of statins, such as red yeast rice or oyster mushrooms.[1] Second, since at least 25% of patients with anti-HMGCR–associated autoimmune myopathy have no known exposure to statins,[2] testing for anti-HMGCR autoantibodies may be considered in other patients with myopathy. This includes adults and children with clinical presentations that are consistent with genetic muscle disease but no known genetic defect; some of these patients have anti-HMGCR–associated autoimmune myopathy that responds to treatment.[3] Third, reinitiation of statins is con-

traindicated in patients with statin-associated autoimmune myopathy. However, the use of proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors appears to be safe in this patient population and may be considered in patients with clinically significant cardiovascular risk factors.[4]

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THE DISCUSSANTS REPLY: Dalakas raises an important point about the relationship between statin use and necrotizing autoimmune myopathy. There is considerable epidemiologic evidence of an association between statin use and necrotizing autoimmune myopathy; however, data to establish statins as causal agents of the illness are lacking. In a large series involving 1947 patients with suspected myopathy who were evaluated at the Johns Hopkins Myositis Center, 104 (5.3%) were positive for anti-HMGCR autoantibodies.[1] Of these 104 patients, 75% had a history of statin use. Widespread use of statins, as seen in the United States, can lead to ascertainment bias, linking a rare myopathy with a commonly used drug class. Nevertheless, in the Johns Hopkins cohort, there was a strong association between antibodies and statin use. However, 25% of the patients with anti-HMGCR autoantibodies did not have a history of statin use; thus, necrotizing autoimmune myopathy can occur in the absence of statin exposure. As Dalakas suggests, anti-HMGCR autoantibodies may not necessarily be pathogenic, but they could be biomarkers of the immune-mediated process. Although viral illness is a potential trigger, we did not find compelling literature linking viral illness with anti-HMGCR autoantibodies. Although the duration of statin use before anti-HMGCR myopathy is variable, 2 or more years of exposure is frequently reported. Thus, the time course in this patient is consistent with a statin-associated event.[2,3] We agree that Koch's postulates for causality are not satisfied with regard to the role of statins or HMGCR autoantibodies in causing necrotizing autoimmune myopathy; until there is stronger evidence, it may be better to view the condition as statin-associated rather than statin-induced. We do not agree, however, with rechallenging patients with statins; this perspective was supported in a recent review article stating that all five patients who were rechallenged had adverse effects.[4] In our opinion, rechallenging a patient with a statin would require conclusive proof that a statin was not implicated in the disorder. Given the very refractory nature of necrotizing autoimmune myopathy, we think alternative cholesterol-lowering therapy with the use of PCSK9 antibodies or ezetimibe should be the recommended treatment for a patient after the development of a statin-associated anti-HMGCR myopathy.

We thank Pinal-Fernandez and Mammen for their comments. These letters raise important issues in understanding this rare immune-mediated myopathy.

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Since publication of their article, the authors report no further potential conflict of interest.

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