REVIEW ARTICLE

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Statin-Associated Autoimmune Myopathy

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Statins significantly reduce the incidence of cardiovascular disease, are generally safe, and have an acceptable side-effect profile. Indeed, a recent meta-analysis confirmed that mild musculoskeletal problems, such as myalgia, occur in approximately equal numbers of persons treated with statins and those given placebo.[1] Only in rare cases, in approximately 1 of 10,000 treated persons per year,[2] do statins cause serious muscle damage, with weakness and elevated levels of creatine kinase. In the majority of such cases, the patients recover spontaneously after the statin treatment is discontinued.[3,4] It is now recognized, however, that in very rare cases, an autoimmune myopathy develops in patients treated with statins; this disorder is characterized by muscle weakness, evidence of muscle-cell necrosis on biopsy, and the presence of autoantibodies against 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.[5-16] In contrast to most patients who have side effects from statin therapy, those with statin-associated autoimmune myopathy may have progressive weakness that must be controlled with immunosuppressive therapy. This review describes the clinical characteristics, diagnosis, proposed pathologic mechanisms, and treatment of statin-associated autoimmune myopathy.

EPIDEMIOLOGIC AND GENERAL CLINICAL FEATURES

Statin-associated autoimmune myopathy is an exceptionally rare side effect of statin use. Its incidence is not known with certainty, but it is estimated to occur in approximately 2 or 3 of every 100,000 patients treated with statins (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Although the onset of myopathy may occur very soon after the initiation of statin therapy, treatment with any one of the available statins may have no side effects in a given patient for years before causing such symptoms as muscle pain and difficulty rising from a chair, ascending steps, or lifting heavy objects.[5,6,10,16] After weakness is noticed, it usually persists or worsens even if statin therapy is discontinued. In most cases, patients have only mild-to-moderate weakness. However, cases in which patients have severe weakness have also been reported. Although the myopathy primarily affects skeletal muscles, mild joint pain or rash may also be present.[7,17]

DIAGNOSIS

On physical examination, patients with statin-associated autoimmune myopathy usually present with symmetric proximal weakness. The creatine kinase levels are universally and persistently elevated in persons with active disease; in nearly 90% of cases, the level exceeds 2000 IU per liter, which is more than 10 times the upper limit of the normal range of 0 to 150 IU per liter[8] (although it should be noted that normal ranges of creatine kinase levels may vary according to sex and

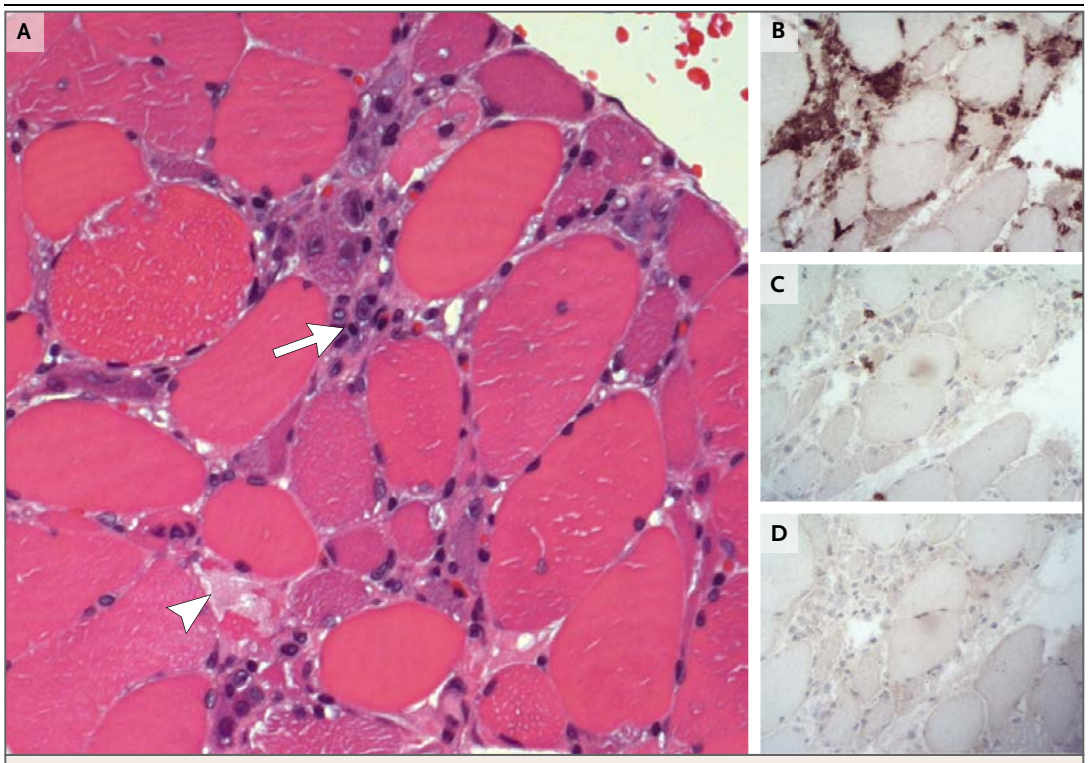

Figure 1. Muscle-Cell Necrosis and Macrophage Infiltration in Statin-Associated Autoimmune Myopathy.

Muscle-cell necrosis and infiltration of macrophages are characteristic features of muscle-biopsy specimens from patients with statin-associated autoimmune myopathy. Hematoxylin and eosin staining of a paraffin-embedded specimen reveals muscle-fiber necrosis (arrowhead) and myophagocytosis (arrow) in a patient with the condition who is positive for anti–3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase autoantibodies (Panel A). Serial frozen sections from the same patient were immunostained with antibody against CD68 (a macrophage marker) (Panel B), CD8 (a cytotoxic T-cell marker) (Panel C), and CD20 (a B-cell marker) (Panel D); antibody-positive cells are stained brown. Macrophages are the predominant type of infiltrating cell. Panels B, C, and D are reproduced, with permission, from Chung et al.[19]

race[18]). Electromyography shows small-amplitude motor-unit potentials with increased spontaneous activity characteristic of an active myopathic process, and muscle edema is evident on magnetic resonance imaging (MRI).

Muscle-cell necrosis and regeneration are the most prominent histologic features in muscle-biopsy specimens from patients with statin-associated autoimmune myopathy (Fig. 1).[8,10,17,19] Cellular infiltrates, found predominantly in endomysial and perivascular regions, are composed largely of macrophages, which probably play a role in tissue repair.[19-22] Small numbers of CD4+ and CD8+ lymphocytes, as well as CD123+ plasmacytoid dendritic cells, may also be present. Diffuse or multifocal up-regulation of major histocompatibility complex class I molecules is common.[5,7,17,19,23] Taken together, these histologic features are consistent with a diagnosis of immune-mediated necrotizing myopathy.[24,25] Only a small fraction of biopsy specimens show lymphocytes invading non-necrotic muscle cells or rimmed vacuoles; these features are characteristic of polymyositis and inclusion-body myositis, respectively.[8,17,19,24,26]

Autoantibodies against HMG-CoA reductase, the pharmacologic target of statins, are found predominantly in biopsy specimens from patients with necrotizing myopathy and much less frequently in specimens from patients with other muscle conditions[8,10,16,17,23]; these autoantibodies are associated with statin exposure.[8,16,27] One study found that 24 of 26 patients (92%) who were positive for anti–HMG-CoA reductase autoantibodies and were older than 50 years of age had taken statins before the onset of the disease.[8] Moreover, to date, anti–HMG-CoA reductase autoantibodies have not been detected

in statin-treated patients who do not have muscle disease or in those in whom self-limited statin-related myopathy develops.[28] Thus, in patients who have myopathy after statin exposure, a positive test for anti–HMG-CoA reductase autoantibodies strongly supports the diagnosis of an autoimmune process. In antibody-negative patients, alternative diagnoses should be considered. Commercial enzyme-linked immunosorbent assays for anti–HMG-CoA reductase autoantibodies may have a rate of false positive results of approximately 0.7%.[28] To avoid erroneous diagnoses, only patients with markedly elevated levels of muscle enzymes should be tested for these autoantibodies (Fig. 2).

Anti–HMG-CoA reductase autoantibodies may also be present in patients with autoimmune myopathy who have never been prescribed statin therapy.[8,10,17,23] Such patients, who made up one third of patients who were positive for anti–HMG-CoA reductase in the largest cohort studied to date, tend to be younger and to have myopathy that is less responsive to therapy than the statin-exposed patients.[29]

PATHOGENESIS

The mechanisms underlying the development of HMG-CoA reductase autoimmunity remain unknown. However, several observations support a hypothetical model. First, the class II HLA allele DRB1*11:01 is strongly associated with the development of anti–HMG-CoA reductase autoantibodies, even in patients without known exposure to statins, with odds ratios of 25 and 57 in white patients and black patients, respectively.[27,30] Second, the expression of HMG-CoA reductase is low in most tissues, but it is markedly increased when muscle and other types of cells are exposed to statins.[31,32] Third, regenerating muscle cells express high levels of HMG-CoA reductase protein,[8,23] which is required for normal muscle-cell differentiation.[33,34] Taken together, these observations suggest that statin-induced overexpression of HMG-CoA reductase in genetically susceptible patients may cause autoimmunity against HMG-CoA reductase. The binding of statin to HMG-CoA reductase might also change the conformation of the protein, leading to the generation of cryptic epitopes to which the immune system is not tolerant.

Once tolerance is broken and an autoimmune response is activated, high HMG-CoA reductase levels in regenerating muscle cells could continue to drive autoimmunity, even after statin therapy is discontinued. Because autoimmunity does not develop in the majority of patients with the DRB1*11:01 allele (who make up, e.g., approximately 7% of white persons in the United States) after treatment with statins, additional genetic risk factors, environmental triggers, or both are also likely to have a causal role. However, the prevalence of rs4363657, a single-nucleotide polymorphism known to be associated with self-limited statin-related myopathy,[35] is not higher among patients with statin-triggered autoimmune myopathy than among those without it.[8]

The cause of muscle damage in statin-triggered autoimmune myopathy is also not understood. Given the paucity of infiltrating lymphocytes, the presence of membrane attack complex on non-necrotic muscle-cell membranes[7] raises the possibility that anti–HMG-CoA reductase autoantibodies are pathogenic. This hypothesis is supported by the observation that autoantibody levels are correlated with both creatine kinase levels and the degree of muscle weakness.[10,17,29] However, HMG-CoA reductase is not known to reside on the surface of muscle cells, where it could be targeted by autoantibodies. Alternatively, anti–HMG-CoA reductase autoantibodies might cross-react with a different, unidentified antigen. Whether autoantibodies, some other soluble factor, or infiltrating immune cells cause the muscle damage remains to be determined.

TREATMENT

A few patients with statin-triggered autoimmune myopathy and anti–HMG-CoA reductase autoantibodies have had spontaneous improvement of their condition without treatment after the discontinuation of statin therapy.[5,10] This finding suggests that, in patients with very mild weakness, statin therapy can be stopped and the patients closely observed, with immunosuppressive therapy initiated only if the muscle disease fails to improve or continues to worsen. In most patients, however, treatment with statins should be discontinued and the patients treated with immunosuppressive medications similarly to those with other forms of autoimmune muscle disease.[26,36] Although no clinical trials of treatment

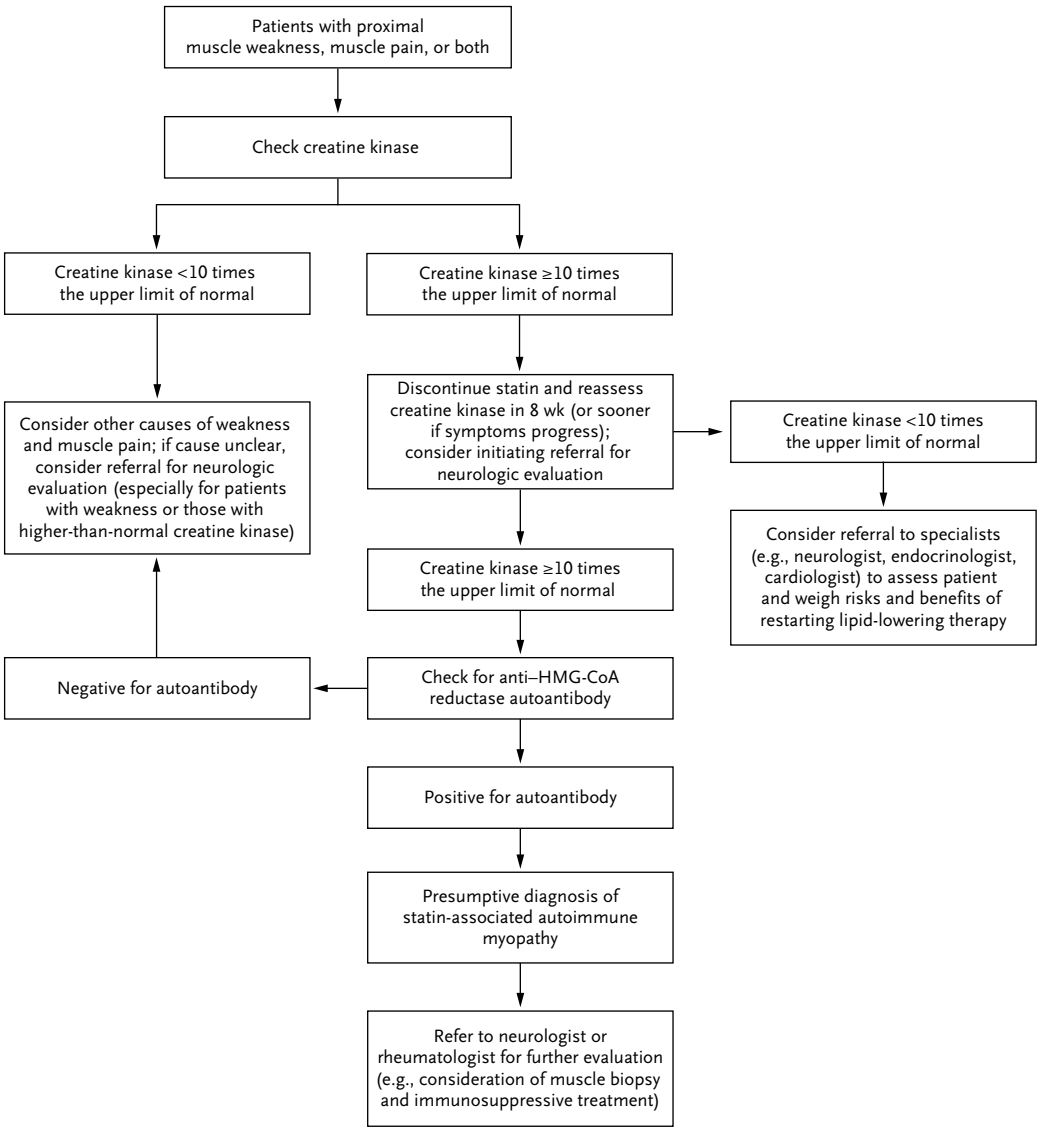

Figure 2. Algorithm for the Evaluation of Potential Cases of Statin-Associated Autoimmune Myopathy.

Patients receiving statin therapy who present with proximal muscle weakness, muscle pain, or both should undergo evaluation. The upper limit of normal for creatine kinase levels is 150 IU per liter; however, it should be noted that the normal range can vary according to race and sex.[18]

for statin-associated autoimmune myopathy have been conducted, clinical experience suggests that initial therapy should usually include oral prednisone at a dose of 1 mg per kilogram of body weight per day. Unless the patient has only mild weakness, another agent, such as methotrexate, azathioprine, or mycophenolate mofetil, should be included at the outset. In those in whom severe weakness develops or in whom the condition does not respond to the initial combination of medications after 8 to 12 weeks, intravenous immune globulin or another agent, such as rituximab, may be added. Triple therapy, usually including intravenous immune globulin, has been used to treat nearly half of all patients with statin-triggered autoimmune myopathy described in the literature.[6,9,10,23,29] Intravenous immune globulin has also been used successfully as

monotherapy[37] and may be considered as first-line therapy for selected patients, such as those with preexisting diabetes.

After patients recover full strength, immunosuppressive medications should be tapered while ensuring that symptoms do not return, with the recognition that some patients will have a relapse and require long-term treatment.[6,7] Some treated patients recover full strength even though their creatine kinase levels remain markedly elevated,[6,7,29,37] a finding that suggests an attenuated but still active process in which muscle regeneration outpaces muscle destruction. Whether therapy should be escalated in this situation remains the subject of controversy. In some patients, muscle weakness persists even after the muscle enzyme levels have returned to normal. Such persistence of symptoms may occur in patients who have received long-term undertreatment and in whom permanent damage, with fatty replacement of muscle tissue, develops; this can be investigated with MRI of the muscles.

CONCLUSIONS

For the overwhelming majority of patients, statins have a good side-effect profile. Only in those in whom markedly and persistently elevated muscle-enzyme levels develop should the very rare side effect of statin-associated autoimmune myopathy be considered. Confirmation of the diagnosis with a test for anti–HMG-CoA reductase autoantibody should lead to the discontinuation of treatment with statins and the initiation of immunosuppressive therapy. Fortunately, when this disorder is recognized and treated, patients with statin-associated autoimmune myopathy usually have very good outcomes, with marked improvements in muscle strength.

Dr. Mammen reports issued and pending patents related to compositions and methods for characterizing a myopathy (U.S. patent number 8778618, application numbers 20130040308 and 20140377784), licensed to INOVA Diagnostics. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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