Statin-Associated Autoimmune Myopathy

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Review Article

Statin-Associated Autoimmune Myopathy

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INTRODUCTION

- Statins significantly reduce the incidence of cardiovascular disease, are generally safe, and have an acceptable side-effect profile.
- Indeed, 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
- 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

- This review describes the clinical characteristics, diagnosis, proposed pathologic mechanisms, and treatment of statin-associated autoimmune myopathy.

- 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

Epidemiologic and General Clinical Features

- 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
- 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

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 liter8

- 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).

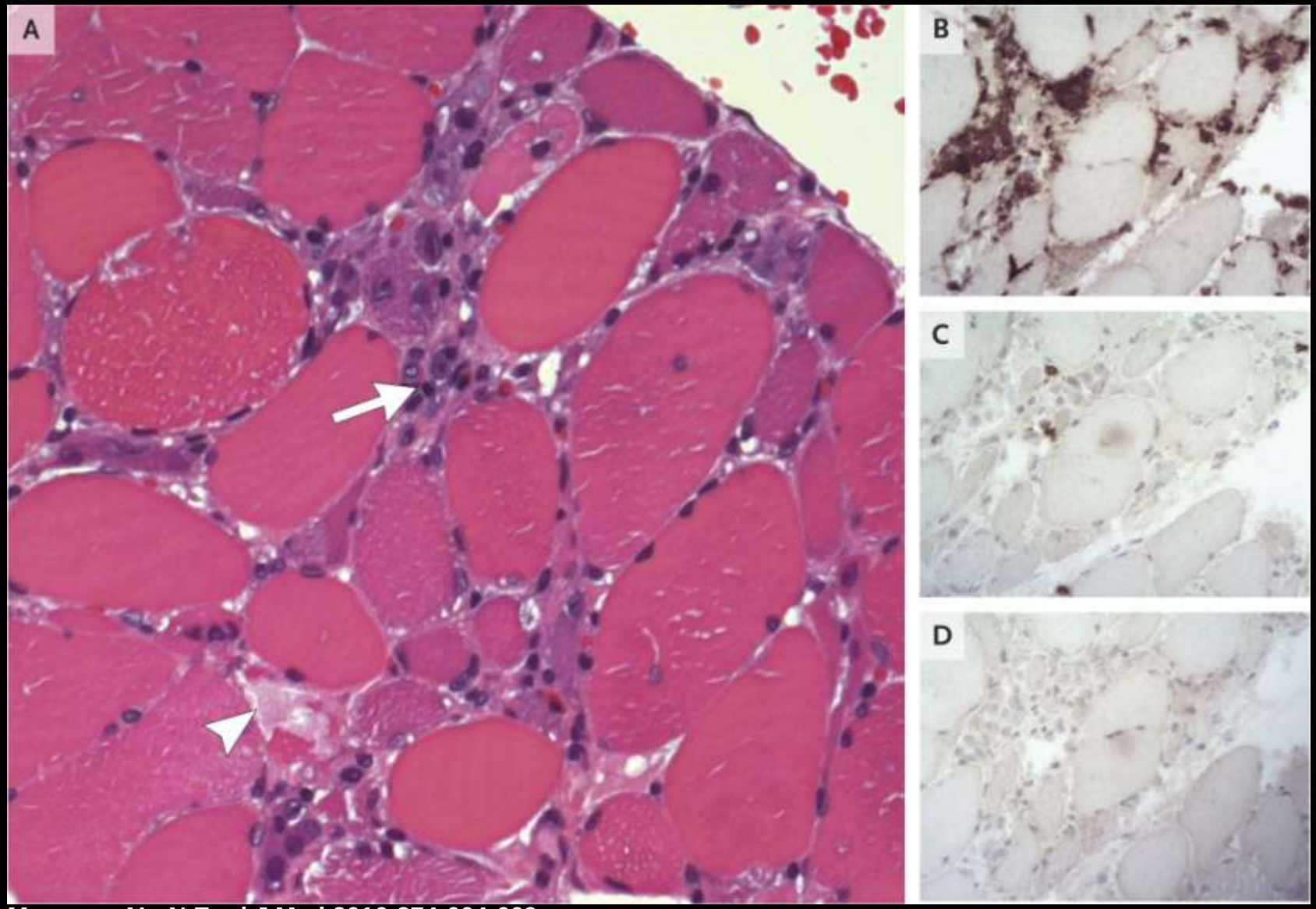
- Cellular infiltrates, found predominantly in endomysial and perivascular regions, are composed largely of macrophages, which probably play a role in tissue repair.
- Small numbers of CD4+ and CD8+ lymphocytes, as well as CD123+ plasmacytoid dendritic cells, may also be present
- Diffuse or multifocal up-regulation of major histocompatibility complex class I molecules is common
- Taken together, these histologic features are consistent with a diagnosis of immune-mediated necrotizing myopathy

- 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 ; these autoantibodies are associated with statin exposure.

- 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%.
- To avoid erroneous diagnoses, only patients with markedly elevated levels of muscle enzymes should be tested for these autoantibodies .

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



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Pathogenesis

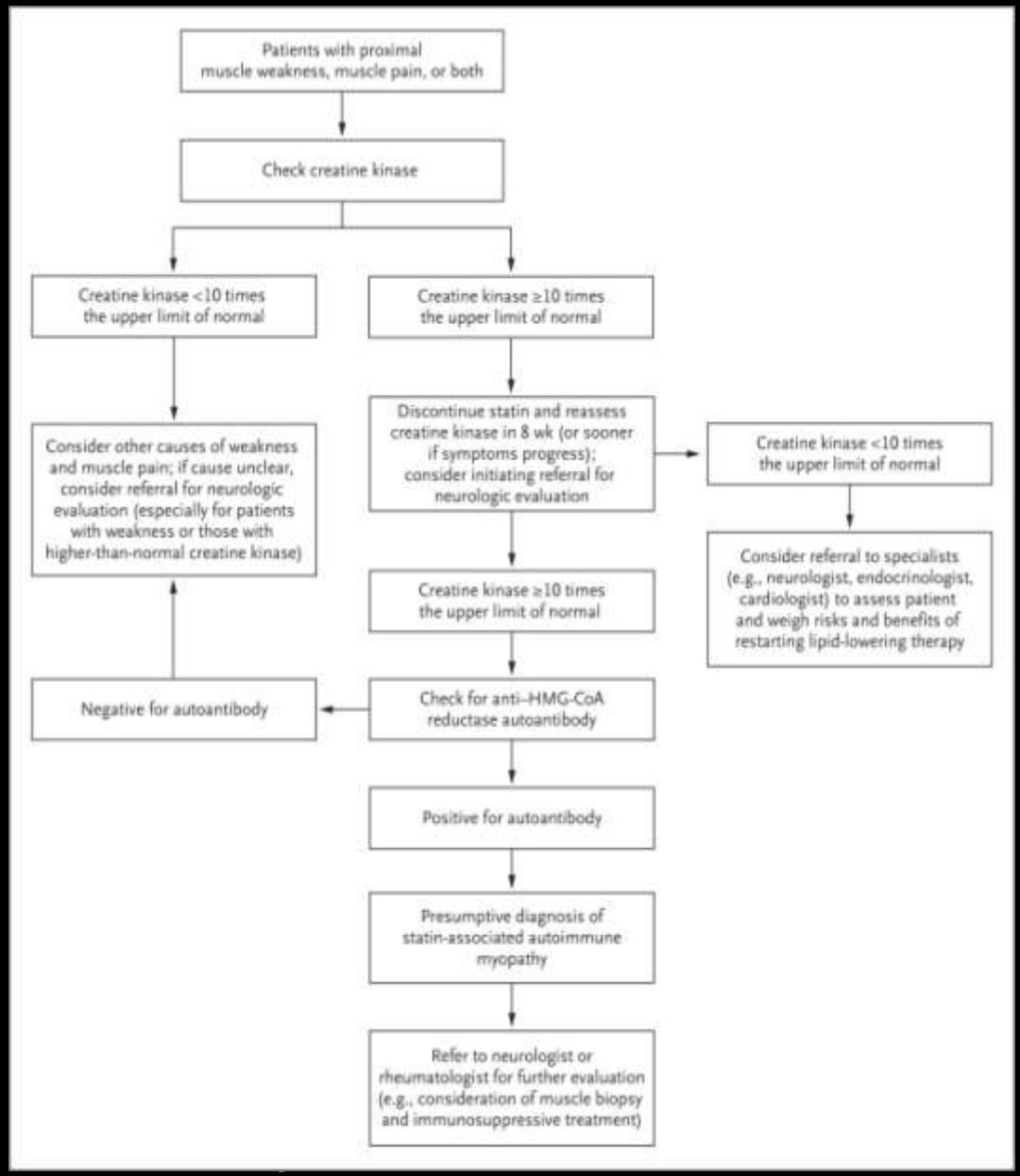
- The mechanisms underlying the development of HMG-CoA reductase autoimmunity remain unknown.
- However, several observations support a hypothetical mode
- First, the class II HLA allele DRB1*11:01 is strongly associated with the development of anti–HMG-CoA reductase autoantibodies, even in patients without known exposure to statins, with odds ratios of 25 and 57 in white patients and black patients, respectively

- 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.
- Third, regenerating muscle cells express high levels of HMG-CoA reductase protein, which is required for normal muscle-cell differentiation
- Taken together, these observations suggest that statin-induced over expression of HMG-CoA reductase in genetically susceptible patients may cause autoimmunity against HMG-CoA reductase

- 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.

- The cause of muscle damage in statin-triggered autoimmune myopathy is also not understood.

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



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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
- 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.

- Although no clinical trials of treatment 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
- Intravenous immune globulin has also been used successfully as monotherapy 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.
- Some treated patients recover full strength even though their creatine kinase levels remain markedly elevated, 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 under treatment 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

Summary

- Statins are widely used and lower the risk of death from cardiovascular causes.
- In a fraction of patients, an autoimmune myopathy may develop, characterized by the development of autoantibodies to the target enzyme, HMG-CoA reductase.

THANK YOU !