LEAP ROUNDS

Johns Hopkins University
School of Medicine
Division of Rheumatology
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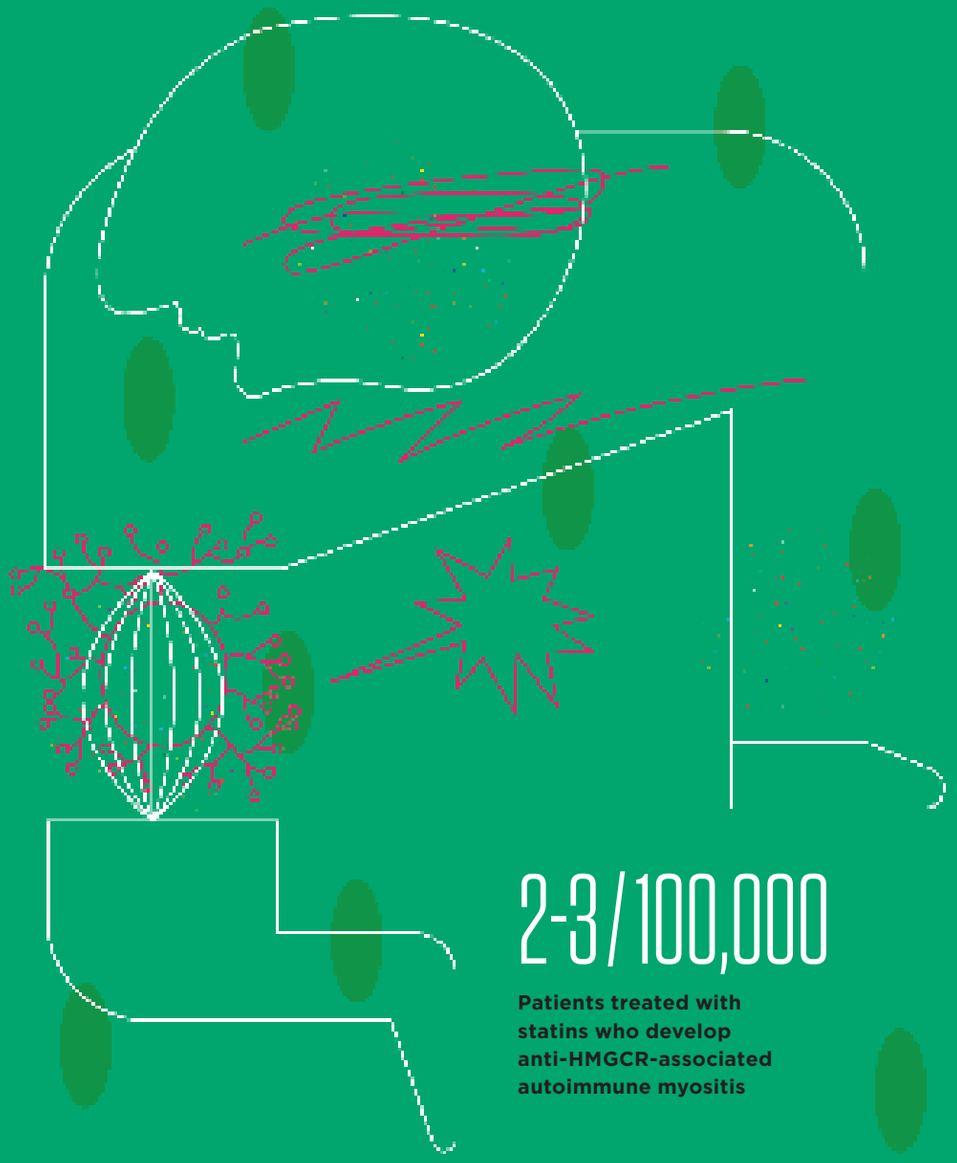
Statin-Triggered Autoimmune Myopathy

LISA CHRISTOPHER-STINE, M.D., M.P.H.

A Rare But Serious Complication of Cholesterol-Lowering Drugs

STATIN-TRIGGERED AUTOIMMUNE MYOPATHY



2-3/100,000

Patients treated with statins who develop anti-HMGCR-associated autoimmune myositis

INTERVIEW: LISA CHRISTOPHER-STINE, M.D., M.P.H.

The vast majority of the patients who take statins don't ever have to worry about the side effect of muscle symptoms. Even among those who do experience muscle damage, with weakness and elevated levels of muscle enzymes such as creatine kinase (CK), symptoms generally go away when the statin is stopped.

However, for a rare few — an estimated 2 to 3 out of every 100,000 patients — statins cause a progressive, autoimmune-mediated necrotizing myopathy that can persist or even begin *after* the statin is discontinued, and that may only resolve with immunosuppression.

Why HMGCR?

Statins work by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), a key enzyme in cholesterol synthesis. Johns Hopkins Myositis Center researchers discovered that the HMGCR antibody is highly specific for immune-mediated necrotizing myopathy, suggesting that statins are capable of triggering this myopathy that is perpetuated even if the drug is stopped, through persistently elevated HMGCR expression associated with muscle repair. Patients with other types of myopathy, including inflammatory myopathy, do not have this antibody.

Making the Diagnosis

Patients with statin-associated autoimmune myopathy usually have symmetric proximal weakness and significantly elevated CK levels, above 2000 IU/L in 90 percent of cases — more than 10 times the upper limit of the normal range. Muscle edema is evident on MRI, and electromyography shows small-amplitude motor-unit potentials, with increased spontaneous activity.

The most prominent histologic features in muscle-biopsy specimens are muscle-cell necrosis and regeneration. Cellular infiltrates, found mainly in endomysial and perivascular regions, show macrophages, which probably play a role in tissue repair. Also seen in smaller numbers may be CD4+ and CD8+ lymphocytes, and CD123+ plasmacytoid dendritic cells. Diffuse or multifocal up-regulation of major histocompatibility complex class I molecules is commonly observed, as well.

Note: Just because it's necrotizing, doesn't mean the muscle is irreparable! Patients can have minimal strength loss in the beginning. We have seen a patient with a CK of 5,000 still doing cardio kickboxing! How is that even possible? Because we suspect regeneration is outpacing degeneration — until it no longer can. There is a point of no return where the muscle cannot regenerate at the same pace it's degenerating. Necrosis takes over, and that's when the patient requires therapy.

Another point to consider: Most — but not all — of those who have anti-HMGCR antibodies, particularly those over age 50, have had exposure to statins. Anti-HMGCR antibodies have also been found in patients with autoimmune myopathy who have never taken a statin. These patients tend to be younger, and to have myopathy that is less responsive to therapy (see below).

We have also seen patients with a much milder phenotype; in some, the CK may not be significantly elevated at first, but all have MRI evidence of muscle edema. Irritable myopathy has been seen on EMG in the vast majority (88 percent). Interestingly, some patients have presented with myopathies that are quite painful. We tend to think that inflammatory myopathies are painless; in fact, many of these patients have had considerable myalgias, but they are also weak; 50 percent of them also complain of arthralgias. And remarkably, 63 percent of these patients have had considerable dysphagia — a very unique feature that you would not normally see with a typical statin myopathy. Only 2 patients have had Raynaud's phenomenon.

The duration of use of statins before the onset of muscle symptoms is highly variable, ranging from just a few weeks to as much as 7 years!

The duration of use of statins before the onset of muscle symptoms is highly variable, ranging from just a few weeks to as much as 7 years! The average duration of exposure to a statin was 31 months prior to reporting any muscle symptoms.

Patients should be tested for anti-HMGCR if they have:

- A persistently elevated or rising CK, particularly above 1,000 IU/L, especially if the patient has been taking a statin and/or when other myositis-associated antibodies are negative
- Muscle symptoms (proximal or distal weakness) that persist 12 weeks after statin cessation, regardless of CK level, especially if the patient has dysphagia
- Muscle irritability on EMG or diffuse muscle edema on MRI
- Muscle biopsy showing necrotizing myopathy, with little or no inflammation.

Also, because necrotizing myopathy may be associated with malignancy, an age-appropriate malignancy evaluation is also warranted.

LISA CHRISTOPHER-STINE, M.D., MPH

Associate Professor of Medicine and Neurology and Director of the Johns Hopkins Myositis Center

Her primary research focus is inflammatory myopathy, describing unique phenotypes, finding novel therapeutic approaches, and identifying disease subsets among patients with inflammatory myopathy who are part of a growing cohort of 2,669 patients evaluated clinically for muscle disease at the Johns Hopkins Myositis Center and who agree to be part of the Johns Hopkins Myositis Database.

Christopher-Stine and her colleagues made the discovery of anti-HMGCR-associated autoimmune myositis and its close link to statins. She continues to study statins and their effects on muscle, both as a direct muscle toxin and as a contributor to autoimmune muscle injury.

Treatment

First, statin therapy should be discontinued. For a few patients, this is sufficient to cause spontaneous improvement of their symptoms — suggesting that, for very mild weakness, the patients can be closely observed, with immunosuppressive therapy only initiated if the muscle disease fails to improve or gets worse. The majority of patients, however, require immunosuppressive therapies. Our clinical experience suggests beginning with oral prednisone at a dose of 1 mg/kg per day. If the patient has more than mild weakness, another agent, such as methotrexate, azathioprine, or mycophenolate mofetil, may also be started at this time.

After full strength has been recovered, immunosuppressive medications should be tapered. However, for some patients, long-term treatment is needed.

If severe weakness develops, or if the patient does not respond to this initial combination after 8 to 12 weeks, intravenous immune globulin (IVIG) or another agent, such as rituximab, may be added. IVIG has also been used successfully as monotherapy, and for some patients, such as those with diabetes, this may be considered as first-line therapy. We are still on the hunt for the best therapeutic approach. We prefer an immune modulator such as IVIG, rather than immunosuppression, although sometimes a combination of both approaches is warranted. We avoid long-term prednisone as much as we can.

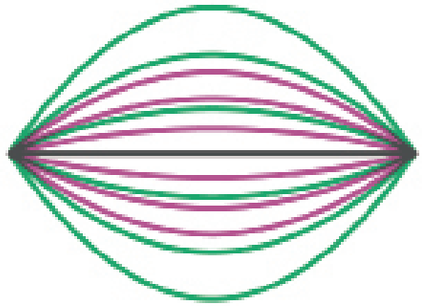
After full strength has been recovered, immunosuppressive medications should be tapered. However, for many patients, long-term treatment is necessary. Some patients who recover full strength still have markedly high CK levels, which suggests a still-active process of muscle regeneration outpacing degeneration. It is not clear whether therapy should be escalated in this situation. In some patients, muscle weakness persists even after CK levels return to normal. This may occur in patients who have received long-term undertreatment; these patients may have permanent damage, with fatty replacement of muscle tissue, which can be investigated with MRI of the muscles.

What about protecting patients at cardiovascular risk? Newly FDA-approved drugs (alirocumab and evolocumab) called PCSK9 inhibitors (given as injections) lower LDL cholesterol and do not seem to have myotoxicity. In some patients, these drugs may help treat the statin myopathy, as well; anecdotally, a few of our patients were able to stop immunosuppression after starting PCSK9 inhibitor therapy.

Older Patients Respond Better

The good news is that for most patients the prognosis is very good, with marked improvement in muscle strength. This is particularly likely in patients over age 50.

However, younger patients have more severe disease and a worse prognosis. In a recent study of 104 patients treated at the Myositis Center for anti-HMGCR



associated myositis, followed for an average of 3 years, we were surprised to find that younger patients had more severe weakness at the first visit compared with their older counterparts. Furthermore, older patients had a faster rate of strength improvement: 85% of patients over age 60 reached nearly normal muscle strength within 4 years after disease diagnosis, compared to only 45% of patients under age 50.

Among those patients who were treated with immunosuppression, a significant number regained normal strength. However, the majority continued to have elevated CK levels, indicating continued muscle damage, even in the setting of normal strength. All but 3 out of 105 patients were treated with immunosuppressive treatment, but only a handful could be weaned off therapy without having worsening of disease. Importantly, we found that nearly 1/3 of patients had disease that continued to worsen, despite aggressive treatment with immunosuppressive therapy, and these patients tended to be younger. These findings suggest that more aggressive treatment should be considered for younger patients.

FURTHER READING

A novel autoantibody recognizing 200- kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy.
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2010, PMID:20496415

Autoantibodies against 3-hydroxy-3- methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy.
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2017, PMID:28096458

Immune-mediated necrotizing myopathy associated with statins: history and recent developments.
Current Opinion in Rheumatology
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2019, PMID:31058470

2,669

Patients in the Johns Hopkins Myositis Center research cohort

JOHNS HOPKINS
MEDICINE

Division of Rheumatology
5200 Eastern Avenue
Mason F. Lord Building
Center Tower, Suite 4100
Baltimore, MD 21224

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14 SPECIALISTS

at the Johns Hopkins Myositis Center in rheumatology, neurology, pulmonology, genetics, physical medicine & rehabilitation

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PATIENTS: 410-550-5748