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A CASE REPORT ON STATIN ASSOCIATED AUTOIMMUNE MYOPATHY

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ABSTRACT

A 54 year old man presented with complaints of weakness of lower limbs and difficulty in walking. He was treated with atorvastatin 40 mg once daily for the past four months. The laboratory studies showed a significant elevation in the creatine kinase (CK) of 55449 U/L (normal range 38-174 U/L). The liver enzymes were also elevated. Tests for autoantibodies were negative including antinuclear antibody, rheumatoid factor, anti -Ro/SSA and anti- La/SSB. He was diagnosed with statin induced myopathy followed by rhabdomyolysis given his history of statin exposure. Initially he was treated with IV methylprednisolone 500 mg OD which then got tapered to tablet prednisolone 40 mg OD. Immunosuppressive therapy was started with mycophenolate mofetil 500 mg BD which resulted in a dramatic improvement in his muscle strength and CPK levels. The latter came down to a level of 383 U/L within 2 weeks. Statins have an acceptable side effect profile in which myotoxicity is the most common and well known. Appropriate counseling of the patient and possible strict criteria are suggested in conditions where statin use is inevitable.

KEYWORDS: Statins, Myopathy, Creatine kinase, Immunosuppressants.

INTRODUCTION

Statins are the most widely prescribed medications worldwide and has effectively reduced morbidity and mortality for both cardiovascular and cerebrovascular diseases.[1] Statins use is associated with a wide spectrum of muscular disorders. Statin associated autoimmune myopathy is a very rare side effect of statin use with a low incidence rate. It is estimated to occur in approximately 2 or 3 of every 100,000 patients treated with statins.[2] Statin associated autoimmune myopathy is usually characterized by a rapid onset of severe proximal

weakness and CK levels of typically over 6000 IU/L.[3] The average duration of statin treatment prior to onset of weakness was 3 years (range 2 months to 10 years). Risk factors for the development of statin associated myopathy include coexisting diseases associated with rhabdomyolysis (renal insufficiency, hepatic dysfunction, and hypothyroidism) and the use of concomitant medications that interfere with statin metabolism or independently cause myositis (gemfibrozil, cyclosporine, macrolide antibiotics, niacin, azole antifungals, protease inhibitors, and calcium channel blockers).[4] Herein, we describe a case of a 54 year old man with a history of statin use which developed autoimmune myopathy. We discuss the pathogenesis and therapeutic options for this condition.

CASE REPORT

A 54 year old man presented with complaints of weakness of lower limbs and difficulty in walking. At that point, he reported inability to walk upstairs or lift heavy objects. He had a medical history of diabetes mellitus, coronary artery disease and AWMI. He also underwent primary PCI to LAD two months back. His past medications included aspirin 75 mg once daily, clopidogrel 50 mg once daily and pantoprazole 40 mg once daily. He was on atorvastatin 40 mg once daily which got changed to rosuvastatin 40 mg OD one month back. The patient had no family history of autoimmune or neuromuscular disorders.

On physical examination, he had proximal muscle weakness and he was unable to walk without support. He had pain in the right upper jaws and gums. Deep tendon reflexes were intact. He had no skin rash or arthritis.

The laboratory studies showed a significant elevation in the creatine kinase (CK) of 55449 U/L (normal range 38-174 U/L). The liver enzymes were also elevated. Urine myogloblin was positive. Tests for autoantibodies were negative including antinuclear antibody, rheumatoid factor, anti -Ro/SSA and anti- La/SSB. The myositis panel was negative for Jo-1Ab, Pm Scl, Rib P, AMA, Ro 52 and nRNP. The patient was also seronegative for hepatitis A, B and C. Muscle biopsy could not be performed as he was on prasugrel 10 mg. USG abdomen showed mild fatty liver. The clinical diagnosis of statin induced myopathy followed by rhabdomyolysis was made given his history of statin exposure.

Initially, rosuvastatin was stopped and the patient was monitored for any clinical improvement. Since there was no change, he was treated with IV methylprednisolone 500 mg OD which then got tapered to tablet prednisolone 40 mg OD. However, the patient's

weakness was refractory to the treatment at 1 week with CPK level of 4808 U/L. Immunosuppressive therapy was started with mycophenolate mofetil 500 mg BD which resulted in a dramatic improvement in his muscle strength and CPK levels. The latter came down to a level of 383 U/L within 2 weeks (Figure 1).

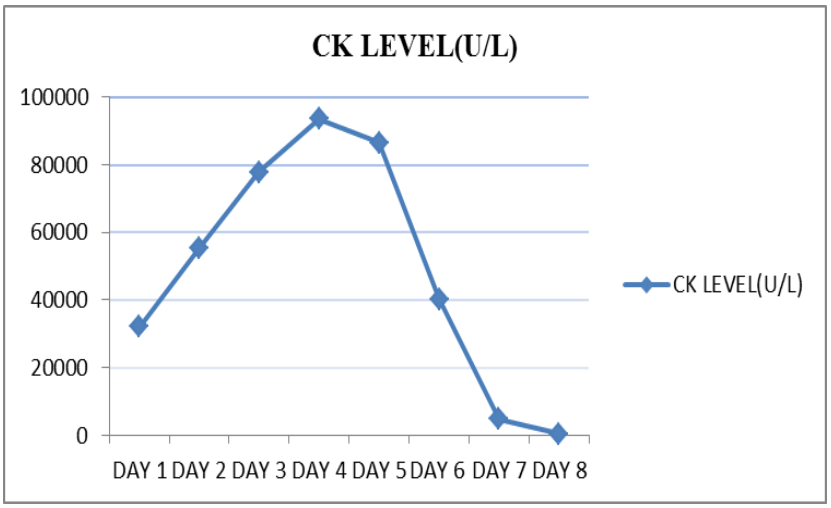

Figure 1: CK levels over the course of days.

Eventually, he maintained remission with prednisolone 20 mg and mycophenolate mofetil 500 mg.

RESULTS AND DISCUSSION

Statin has gained widespread support in use for cardiovascular and cerebrovascular risk reduction since their first commercial introduction in 1982.[5] It inhibits the function of 3-hydroxyl- 3- methyl glutaryl coenzyme A reductase (HMGCR), the rate limiting enzyme in cholesterol biosynthesis causing a reduction in the synthesis of cholesterol.[6] Statins have an acceptable side effect profile in which myotoxicity is the most common and well known. The statin myotoxicity has following clinical presentations:

a) A rise in CK levels asymptomatically which is usually mild and disappears after withdrawal of the statins.[7]
b) Myalgia, usually but not always associated with hyperCKaemia. The rate of this complaint is similar in patients who are on statins and those who are not.[8]
c) High CK levels with persistent muscle symptoms after the withdrawal of statin. This is less rare and may represent a residual statin induced myopathy or the presence of another neuromuscular condition revealed by statin.[9]

d) Immune mediated necrotizing myopathy is a condition in which patients have a progressive myopathy with hyperCKemia that responds only to aggressive immunotherapy.[10] In such patients, the signs appeared with statin therapy continues to progress even after withdrawal.
e) Rhabdomyolysis, which may be severe and even fatal. More than 3500 cases have been recorded with an estimated mortality rate of 78%.[11]

However, the mechanism underlying the development of HMG-CoA reductase autoimmunity remains unclear. Cristopher Stine etal discovered a novel HMGCR antibody directed against protein weighing 200 and 100 kDA in patients with autoimmunity. The antibody was found to target HMGCR. Statins cause an increased expression of HMGCR protein and an anomalous antigen recognizing process leading to production of this autoantibody. Blood testing for HMGCR antibodies is not available commercially. Therefore, it is limited to research purposes.[12]

Although there are no clinical trials available to provide evidence based guidelines for the diagnosis of statin associated myopathy, the following approach has been advised. Initial workup begins with obtaining CK levels. CK levels ≥10 times the upper limit of normal are suggestive of SAM, whereas levels below this threshold suggests other causes of weakness. Patients with significantly elevated CK levels are suggested to discontinue statins, allowing up to 8 weeks for observation of symptoms. If symptoms progress after statin discontinuation, the patient should be tested for anti-HMG-CoA reductase autoantibody.[13]

A few patients have had spontaneous improvement of their condition without treatment after the discontinuation of statin therapy. Andrew L Mammen et al suggested that initial therapy should usually include oral prednisone at a dose of 1 mg per kilogram of body weight per day.[2] Administration of IV methylprednisolone at a dose of 100 mg per day for 3-5 days before starting oral glucocorticoids is preferred in rapidly worsening diseases. After 3 to 4 weeks, prednisone can be tapered by a switch from a daily dose to doses on alternative days based on the response of the disease to therapy.

In patients who produced a response to glucocorticoids, azathioprine, methotrexate, mycophenolate mofetil or cyclosporine can be included for glucocorticoid sparing. When glucocorticoids fail to induce remission or patients does not respond to initial combination of

medications after 8 to 12 weeks, intravenous immune globulin therapy (2 g per kg in divided doses over a period of 2 to 5 consecutive days) is appropriate.[14]

If the patient has not responded to glucocorticoids and intravenous immunoglobulin, the patient should be reevaluated. If the diagnosis is reconfirmed, biological agents like rituximab (an anti CD20 antibody) seems effective at a dose of 2 g in some patients.

After patients recover, immunosuppressive medications can be tapered. Some treated patients recover full strength even though the creatine kinase levels remain elevated.[10]

CONCLUSION

Statin associated myopathy has a very unique clinical and therapeutic profile. If a strong indication for statin use exists, the patients with myopathies should not be denied this treatment. Appropriate counselling of the patient and possible strict criteria for statin use are suggested. Switch therapy to another category of cholesterol lowering agent such as ezetimibe, which inhibits the intestinal absorption of cholesterol is also recommended although it is not fully safe either.[15]

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