Statin-Induced Rhabdomyolysis

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Abstract

Rhabdomyolysis is syndrome characterized by muscle necrosis which causes the release of myoglobin into the bloodstream. The manifestations of this syndrome range from asymptomatic elevation of muscle enzymes to life-threatening cases associated with extremely high enzyme levels, electrolyte imbalance and acute renal failure. Symptoms of rhabdomyolysis include dark urine, muscle weakness and fatigue.

Statins are the most commonly used drugs for prevention and management of dyslipidemia. We present an interesting case report on statin induced rhabdomyolysis with renal failure.

Introduction

Statins have become the most widely prescribed drug worldwide since its introduction in 1987.¹ They are effective and generally safe. Rhabdomyolysis though rare is the most severe form of myotoxicity, which can occur with all statins, either in monotherapy or in combination therapy. The US Food and Drug Administration Adverse Event Reporting System database reports rates of statin-induced rhabdomyolysis of 0.3–13.5 cases per 1,000,000 statin prescriptions.¹ Here we report a case of Atorvastatin induced rhabdomyolysis with renal failure precipitated by underlying, undiagnosed hypothyroidism. We also discuss the pathogenesis, clinical features and management of such cases.

Case Report

A 74 years old male patient was admitted with complaints of progressive swelling all over the body associated with pain and stiffness in limbs since 2 weeks. He had history of oliguria and constipation for 4 days. His past medical history included hypertension, acid peptic disease and cholecystectomy. Ongoing medications were amiodarone, olmesartan, hydrochlorothiazide and pantoprazole. Atorvastatin 20mg was added 15 days prior to his symptom onset. No other significant history was given.

On examination the patient had tachypnoea, tachycardia and high blood pressure. Nonpitting subcutaneous edema with severe muscle tightness and rigidity was noted. Reflexes were depressed. Other systems were unremarkable. Investigations on admission revealed: Hemoglobin-14.3 gm/dl, hematocrit-42.5%, Total leukocyte count-22400/cumm (Neutrophil-90%, Lymphocyte-9%), Platelet-2.28 lacs/cumm, ESR-5 mm, Creatinine-1.13 mg/dl, BUN-12.5 mg/dl, Sodium-105.1mmol/L, Potassium-4.5 mmol/L, Bilirubin-1.1mg/dl, Total Protein-5.1g/dl, Albumin-2.94g/dl, SGOT/SGPT-2688/468U/L, Calcium-8.84 mg/dl, Creatinine phosphokinase (CPK)-1,92,000 U/L TSH-70.5 mIU/L, FT₃-1.32 nmol/L, FT₄-<0.88 nmol/L. Urine – high colored, positive for protein and RBC, Urine myoglobin-positive, Sr. ANA-negative, Anti-TPO Ab-high. Leptospirosis IgM & IgG were negative. Vitamin D-normal levels.

On the basis of history, clinical findings and laboratory reports – diagnosis of Atorvastatin induced rhabdomyolysis with underlying hypothyroidism was made. MRI was done which showed diffuse swelling and abnormal signal involving almost all muscles of both lower limbs with increased T2/STIR signal intensity and low T1 signal intensity. Areas of breakdown with liquefied necrosis were seen. All these features were consistent with diffuse myositis with muscle necrosis.

Atorvastatin was discontinued, intravenous hydration with alkalinization of urine was initiated with electrolyte correction. He was put on thyroxin supplements and symptomatic treatment. He gradually improved with symptoms resolving over next 2 weeks. His CPK levels were serially monitored which normalized to 3.95 which eventually normalized over a period of time. Deranged liver enzymes returned to normal limits within 2 weeks. He developed urosepsis which was successfully treated with appropriate antibiotics. His recovery course was uneventful except for bilateral foot drop.

Discussion

The clinical spectrum of statin induced myopathy range from myalgia, myositis, rhabdomyolysis to asymptomatic increase in the blood levels of creatine kinase. Symptoms include fatigue, muscle pain, muscle tenderness, muscle weakness, nocturnal cramping and tendon pain.² The muscle symptoms tend to be proximal, generalized and worsen with exercise. The mean duration of statin therapy before onset of symptoms ranges from 1 to 60 days.² The mean duration of myalgia after stopping statin therapy ranges from 1 week to 4 months. Risk factors for precipitating myopathy include advanced age, female sex, low body mass index, diminished hepatic and renal function, multiple comorbidities (untreated hypothyroidism, diabetes etc), medications, excess alcohol, intercurrent infections, surgery or trauma, drug interactions and dietary effect.²

The mechanism of statin induced myopathy is unknown. Several theories have been proposed. Impaired synthesis of cholesterol leading to changes in the cholesterol in myocyte membranes and behavior of the membrane. Secondly impaired synthesis of compounds in the cholesterol pathway—in
particular deficiency of coenzyme Q10 (ubiquinone) which could lead to impaired enzyme activity in mitochondria.3 A third mechanism is depletion of isoprenoids (lipids that are a product of the hydroxymethylglutaryl coenzyme A reductase pathway) which prevents myofibril apoptosis.3 Also pharmacodynamic factors, such as transporters affecting the bioavailability of statins are probably important in determining toxicity, although no direct evidence has been found in humans. Drug responses can also be affected by predisposing genetic factors. In vitro and in vivo experiments suggest that lipophilic statins (i.e. simvastatin, atorvastatin, lovastatin) are more likely to produce muscular effects than are relatively hydrophilic agents (such as pravastatin, rosuvastatin, and fluvastatin). Lipophilic compounds are more likely to penetrate into muscle tissue, enhancing the potential for myotoxic effects. Therefore, it is prudent to use a more hydrophilic agent in patients with pre-existing muscle disease.

For most patients, myopathy symptoms induced by statin therapy resolve relatively quickly; however, the results of the PRIMO study showed that it may take up to 2 months for resolution of symptoms. There is limited evidence regarding the treatment of statin-associated myopathy. While in most cases myopathy caused by statins is mild and can be reversed when the medication is discontinued, it may present as rhabdomyolysis or severe muscle damage as in the case mentioned. The mainstay of treatment consists of cessation of statins; however, it is prudent for clinicians to rule out other conditions that can cause myopathy and/or CK elevations, such as hypothyroidism (as in this case), overt physical activity, and alcohol abuse.2 Patients who present with clinically significant rhabdomyolysis require hospitalization and IV hydration to prevent renal damage.4

Once the patient’s muscle symptoms have resolved, clinicians have several options to treat patient’s dyslipidemia, including the use of a lower dose of the same statin, initiation of a different statin, and/or utilization of non-statin lipid-lowering agents.4 Failure to achieve the target LDL goal with statins can be augmented with drugs such as ezetimibe or bile-acid binding resins. The use of fibrates and niacin as monotherapy has been associated with myopathy. Clinical experience indicates that there may be an increased risk of myotoxicity associated with statin and fibrate combination therapy.5 Therefore, bile acid resins may be the optimal choice in those patients without triglyceride abnormalities who cannot tolerate statin therapy.6 There has also been interest in the use of CoQ10 Chinese red rice yeast, and vitamin D as prevention and/or management of statin-associated myopathy although there is no definite evidence.

In conclusion, statin-induced rhabdomyolysis although rare can sometimes present as life threatening condition. Thus clinicians should be vigilant about this complication and associated precipitating factors such as hypothyroidism.

References