Myopathy induced by statin-ezetimibe combination: Evaluation of potential risk factors

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ABSTRACT

Although both atorvastatin and ezetimibe may cause myopathy, statin-induced myopathy is less likely at low doses, and ezetimibe is only rarely reported to induce myopathy. Also, ezetimibe is not usually known to potentiate statin-induced myopathy. We report a case of myalgia with elevated serum creatinine phosphokinase in a patient after 2 months of therapy with fixed dose combination of atorvastatin and ezetimibe (10 mg each). At the time of the event, the patient was undertaking moderate physical exertion in the form of brisk walking for 30–40 min a day and was detected to have low serum Vitamin D levels. The adverse event resolved after stopping atorvastatin-ezetimibe combination therapy. Potential risk factors, such as physical exertion and Vitamin D deficiency, co-existent in dyslipidemic patients, may exacerbate myopathy potential of these drugs, and precipitate muscular symptoms even at a low-dose.

KEYWORDS: Atorvastatin-ezetimibe combination therapy, myopathy, physical exertion, Vitamin D deficiency

Introduction

Muscle-related complaints are the most frequent adverse effects associated with statin therapy and strongly correlates to the dose of statin. To minimize the risk of myopathy in patients who require aggressive lipid lowering, combination of a low-dose statin with another hypolipidemic agent is often used. Fibrates and niacin are known to potentiate statin-induced myopathy. However, the addition of ezetimibe to statins is generally considered safe and does not exacerbate the risk of myopathy.

We report a case of myalgia with elevated serum creatinine phosphokinase (CPK) in a patient receiving atorvastatin and ezetimibe combination and explore the risk factors which might have potentiated the occurrence of myopathy.

Case Report

A 35-year-old male was diagnosed with dyslipidemia (total serum cholesterol = 195 mg/dL, serum triglyceride = 171 mg/dL, serum low-density lipoprotein cholesterol = 152 mg/dL, and serum high-density lipoprotein cholesterol = 24 mg/dL). Patient, a nonsmoker, nonalcoholic, did not suffer from any other illness and was not taking any medication. He was prescribed a fixed dose combination of atorvastatin and ezetimibe (10 mg each), once a day along with the lifestyle modification in the form of brisk walking for 30–40 min a day.

Two months after initiation of therapy and exercise, the patient presented with moderate to severe pain in both legs. History revealed that he had fleeting pain in back, chest, shoulder, and arms 5 days preceding the leg pain. The patient initially attributed the pain to exercise and had stopped going for the walks. However, the pain worsened, causing episodes of nocturnal awakening. Clinical examination did not reveal any abnormality. Laboratory investigations revealed high serum CPK (1991 U/L, normal = 39–308 U/L) and low serum Vitamin D levels. Other laboratory parameters including blood count, erythrocyte sedimentation rate, blood urea nitrogen, serum lactate dehydrogenase, serum creatinine, serum electrolytes, serum Vitamin B₁₂, and
electrocardiogram were normal. Assessment for antinuclear antibody was negative.

Atorvastatin-ezetimibe combination was discontinued. Patient was treated with oral diclofenac (50 mg twice daily for 3 days), vitamin D (50,000 IU once a week for 8 weeks), and calcium carbonate (500 mg twice daily for 8 weeks). Myalgia subsided in 3–4 days. Two weeks later, serum CPK level was 342 U/L.

Upon resolution of symptoms, patient resumed physical activity of similar intensity. Atorvastatin-ezetimibe therapy was not re-introduced. Three months after resuming physical activity, the patient did not complain of myalgia and serum CPK level was normal (155 U/L).

The adverse event was “probably” related to atorvastatin-ezetimibe combination, as assessed by WHO-UMC scale and Naranjo’s score (7). The adverse event was moderately severe (i.e. level 3) as assessed by Modified Hartwig and Siegel Scale.[44]

Discussion

Statin-induced myopathy is less likely to occur at low (i.e. 10 mg) doses, and monotherapy of ezetimibe is rarely associated with myopathy.[1] Also, ezetimibe is not known to potentiate statin-induced myopathy except in rare cases.[1-3]

Simard and Poirier had reported a case of myalgia and elevated serum CPK in a patient receiving 10 mg ezetimibe and 40 mg atorvastatin.[5] In contrast, patient in this case experienced myopathy while receiving a combination of ezetimibe (10 mg) and low-dose atorvastatin (10 mg). Thus, we explored co-existing factors that might have a potentiated occurrence of myopathy at this low-dose.

Patient experienced myopathy during the period he was undergoing moderate physical exertion. Upon discontinuation of pharmacotherapy and resolution of myopathy, patient resumed physical exertion of similar intensity without recurrence of muscular symptoms or elevation in serum CPK. Statins have been reported to be less well tolerated in physically active individuals. Myopathy induced by low-dose (10 mg) simvastatin in an athlete has been reported.[59] The incidence of myalgia associated with statins increases from ~11% in patients engaging in leisure-type physical activity to ~15% in patients undertaking vigorous exercise.[53] In the present case, the unaccustomed physical exertion in a previously sedentary subject might have potentiated myopathy.[54] Statins are believed to up-regulate myocyte apoptosis, inflammation, and protein catabolism in response to exercise.[55]

At the time of the adverse event, the patient had a low level of serum Vitamin D which was corrected by supplementation. Correction of Vitamin D deficiency has been reported to improve statin tolerance and facilitate the resolution of statin-induced myopathy.[56] Vitamin D deficiency is believed to potentiate statin-induced muscular injury by interfering with the generation of proteins involved in the repair of the T-tubular system and subsarcolemmal damage associated with statin myopathy.[57]

Patient, in the present case, received a fixed dose combination of atorvastatin and ezetimibe at the time of occurrence of myopathy. Since both drugs carry myopathy potential, it was not possible to discern if myopathy was induced by atorvastatin or ezetimibe. Symptoms of statin-induced myopathy have an average onset time of about 6 months.[1,3] However, in the present case, symptoms appeared after 2 months of initiation of therapy. The combination of atorvastatin and ezetimibe might have accelerated the onset of myopathy, particularly in the presence of risk factors such as physical exertion and Vitamin D deficiency.

In patients with dyslipidemia, physical exercise is often co-advised with pharmacotherapy. Also, Vitamin D deficiency is frequently present in a sedentary patient with dyslipidemia who has inadequate exposure to sunlight.[58] The present case report highlights the need for clinicians to be aware of potential risk factors for myopathy. These factors may aggravate myopathy potentials of statins and ezetimibe, and precipitate muscular symptoms even at low doses.

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Conflicts of Interest

There are no conflicts of interest.

References
