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Case Report

Successful treatment of a patient with statin-induced myopathy and myotonic dystrophy type II with proprotein convertase subtilisin/kexin type 9 inhibitor, alirocumab (Praluent)

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Abstract: Presently there are limited treatment options for hypercholesterolemia in patients with statin intolerance and myotonic dystrophy. A 74 year-old male presented to endocrine clinic with hypercholesterolemia (serum LDL-C 210 mg/dL), hypogonadism, insulin-controlled type 2 diabetes mellitus, and minimally elevated serum creatine kinase (CK) levels (184 U/L, ref. range 38-174). Shortly after simvastatin treatment, patient developed severe myalgias in the proximal lower and upper extremities; and serum CK increased to 317 U/L. Subsequently patient was treated with various statins including rosuvastatin with similar outcomes. Patient was also treated with bile acid binding resin and ezetimibe without improvement. At this time, a diagnosis of myotonic dystrophy type 2 was confirmed. Patient was then treated with alirocumab, a PCSK9 inhibitor 75 mg subcutaneously every 2 weeks with significant improvement in LDL-C (90 mg/dL) and myalgias. In conclusion, PCSK9 inhibitors such as alirocumab may be an excellent lipid lowering agent in patients with statin intolerance and myotonic dystrophy.

Introduction

Statin-induced myopathy is a common cause of statin intolerance. Observational studies suggest that myalgias can occur in up to 10% of patients treated with statins.[1,2] Several options for managing statin-induced myopathy have been recommended although few of these strategies have high-quality studies to support them. The association between statin therapy and unmasking of previously unrecognized metabolic myopathy or inherited muscular dystrophy has been recognized.[3] Presently, there are limited treatment options for patients with myotonic dystrophy whose clinical history or risk factors indicate an increased risk for atherosclerotic disease. We describe a patient with myotonic dystrophy type II (DM2) that presented with statin-induced myopathy and was successfully treated with alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor recently introduced to treat hypercholesterolemia.[4–6]

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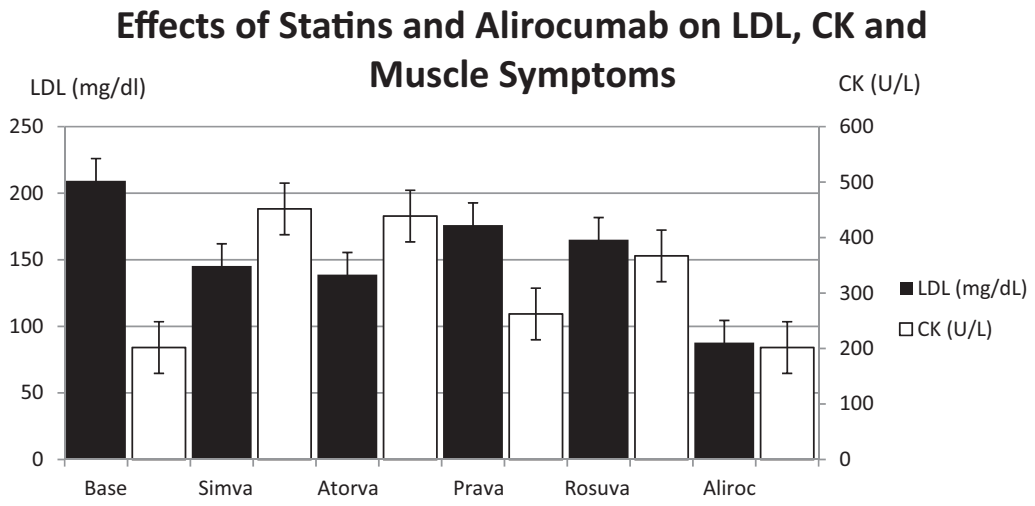

*Left Y Axis = LDL, Right Y Axis = CK

	Base	Simva	Atorva	Prava	Rosuva	Aliroc
Muscle Cramps*	±	+++	+++	++	++	±
Muscles Weakness*	±	+++	+++	+++	+++	++

*± Mild; ++ Moderate; +++ Moderately Severe

Figure 1 The effects of various statins and alirocumab on serum LDL cholesterol, creatine kinase, and muscle symptoms in a patient with myotonic dystrophy. LDL-C, low-density cholesterol; CK, creatine kinase; Base, baseline; Simva, simvastatin; Atorva, atorvastatin; Prava, pravastatin; Rosuva, rosuvastatin; Aliro, alirocumab.

Case

Seventy-four-year-old male with insulin-dependent type II diabetes mellitus and hypogonadism on testosterone replacement therapy was presented in 2004 with myalgias. Patient was initially treated with simvastatin for hyperlipidemia with a low-density lipoprotein cholesterol (LDL-C) 188 mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) 210 mg/dL, and HDL-C 72 mg/dL. Shortly after starting simvastatin, the patient developed severe myalgias in the proximal lower and upper extremities. The serum creatine kinase (CK) increased from a baseline of 184 to 317 U/L (ref. range 38–174; Fig. 1). Serum CK-MB was 7.5 ng/mL (ref. range 0–5.0). No specific etiology was identified to explain his myalgias other than statin therapy. Despite dose reduction, the myalgias persisted over the next several years. Other statins (atorvastatin and pravastatin) along with Coenzyme Q10 were also attempted with similar outcomes (Fig. 1). The patient was also trialed on bile acid–binding resins and ezetimibe without improvement. In 2012, the patient was diagnosed with coronary heart disease and underwent angioplasty. Rosuvastatin 5 mg was prescribed 3 times per week, but 6 months later, rosuvastatin was discontinued because of worsening myalgias (Fig. 1). In 2014, patient noted marked weakness of the proximal thigh and shoulder muscles despite discontinuation of all statins. Physical examination was notable for frontal baldness and muscle strength was 4/5 in both proximal thigh and shoulder muscles. A cardiac evaluation showed no conduction abnormalities. His history was notable for surgery of posterior subcapsular cataracts. An electromyography reported widespread myotonia and a subsequent genetic test confirmed repeat expansion mutation >15,420 binding-proteins consistent with myotonic dystrophy type 2 (DM2). In 2016, his serum LDL-C was 205 mg/dL, HDL-C 73 mg/dL, and non-HDL-C 216 mg/dL. The patient was started on alirocumab 75 mg SQ every 2 weeks, and 6 weeks later his serum LDL-C was 90 mg/dL with a non-HDL-C 94 mg/dL. His repeat serum lipids remained stable, and the patient did not have recurrence of myalgias on alirocumab. Although his muscle weakness persisted, his myalgias did not reoccur and his serum CK levels remained stable on alirocumab (Fig. 1).

Discussion

DM is an autosomal dominant inherited genetic disease with multisystemic effects, including muscle weakness, cataracts, cardiac conduction abnormality, hypogonadism, infertility, and insulin resistance. There are 2 major forms DM type I (DM1) seen in children and type II (DM2) in adults. DM2 is caused by an expanded cytosine-cytosine-

thymine-guanosine tetranucleotide repeat expansion located in intron 1 of the ZNF9 gene.[7] Patients may manifest primary hypogonadism, oligospermia, and infertility; however, the exact etiology of testicular hypofunction in these patients is not known. The muscle weakness seen in the adult type predominantly involves the proximal muscles, particularly the hip girdle. Atherosclerosis is frequently seen in patients with DM2.[7] There is also increased frequency of adverse reactions to statin treatment and this can be a therapeutic challenge because statin-related reaction can be masked in patient with DM2 and myalgia.[7] In these patients, CK of myocardial origin (CK-MB) levels may be mildly to moderately elevated[8]; however, in acute myocardial infarction, the CK-MB levels are acutely elevated, whereas in DM2 patients CK-MB elevation is sustained. The high CK-MB levels are thought to result from regenerative tissues and type I fibers, with regenerative type tissues being the main factor associated with an increasing proportion of CK-MB.[8] The diagnosis of DM2 was missed for more than 12 years in our patient and the combination of muscle cramps, hypogonadism, and diabetes mellitus should have alerted the possibility of DM2. Statin therapy may unmask asymptomatic patients with latent neuromuscular diseases by eliciting their neuromuscular symptoms.[3] Recent studies have reported similar presentations after statin therapy in polymyositis, dermatomyositis, and inclusion body myositis.[3] Statin therapy may also cause an immune myopathy, manifesting major histocompatibility complex-1 upregulation without inflammation, referred as necrotizing myopathy.[2,3] PCSK9 inhibitors prevent the LDL receptor from degradation mainly in the hepatic tissues and this mode of action appears to have less adverse effect on muscle tissue.[4–6] Although PCSK9 inhibitors such as alirocumab may induce myalgia in small percentage of patients,[6] this drug still may serve as an alternate lipid-lowering agent in patients with neuromuscular disorders and statin intolerance given its unique mechanism of action.

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