Ezetimibe-induced Relapsing Polymyositis

To the Editor:

The association of statins and myopathy is well established. Much less recognized, however, is the development of muscle involvement following the use of ezetimibe, another lipid-lowering agent introduced recently[1-5]. We describe a patient with polymyositis (PM) in remission who relapsed after starting therapy with this newer lipid-lowering medication.

A 59-year-old African American woman had biopsy-proven PM diagnosed in 2003; she was in complete remission following therapy with tapering doses of prednisone and methotrexate (MTX) for 5 years, and was maintained on weekly oral MTX 15 mg. She was seen on routine followup in September 2008. At that time, she was asymptomatic and performing activities of daily living without difficulties, and had normal muscle strength on examination, and also normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum levels of creatinine phosphokinase (CPK) and aldolase. Her history revealed a well controlled hypertension, type II diabetes mellitus, and hypercholesterolemia. She returned a month later because of increasing upper and lower extremity proximal muscle weakness, recurrence of neck drop, and diffuse myalgias, with normal ESR, CRP, and serum aldolase but with an elevated CPK (Table 1). Magnetic resonance imaging (MRI) of thigh muscles showed enhanced uptake of quadriceps on T2 scan. Further questioning revealed that just a few weeks earlier she had been started on ezetimibe 10 mg monotherapy for an abnormal lipid profile.

Prednisone 40 mg/day was started and MTX was increased to 20 mg/week without discontinuing ezetimibe. At her 4-week followup, she was doing better, with muscle strength 3+/5 bilaterally, but with persistent myalgias and CPK elevation. At that time, ezetimibe was suspected as the triggering agent for the relapse and was discontinued. This was followed by complete disappearance of myalgias and muscle weakness and normalization of CPK within the ensuing weeks, which allowed rapid tapering and discontinuation of prednisone. She was last seen in May 2009, when she was asymptomatic, without neck drop, and with muscle strength 4+/5 on upper and lower extremities, and maintained on MTX 20 mg/week.

The clinical presentation, laboratory evaluation, and outcome after withdrawal of ezetimibe in our case are very similar to reported cases of ezetimibe-associated myopathy. The severity of the clinical picture, however, with profound muscle weakness and a positive MRI of thigh muscles in spite of mild elevation of CPK led us to suspect that ezetimibe triggered a relapse of underlying PM rather than a myopathic process. Fux, *et al* first described elevation of CPK levels and myalgias following the addition of ezetimibe to statins, and normalization of both symptoms and CPK following discontinuation of ezetimibe[1]. Phillips had a similar experience: in a cohort of 300 patients with known intolerance to multiple lipid-lowering agents, ezetimibe was used as monotherapy in 30 patients and 18 of them developed myopathic symptoms, which characteristically occurred in the first 2 weeks of administration of the drug[2].

In 2005, the Australian Adverse Drug Reaction Bulletin[3] described that since ezetimibe registration in 2003, 144 reports had been received, of which 44 were related to muscle disorders, including myalgias, muscle cramps, weakness, and elevated CPK levels. Of interest, the reported rates of myalgias in premarketing clinical trials were less than 2% with ezetimibe as monotherapy, 2.4% with statins as monotherapy, and 3.2% with combination ezetimibe and statins. As reported, presentation of symptoms occurred from hours to 4 months following initiation of therapy with ezetimibe, with a median of 2 weeks. Almost half of patients with reported events have had muscle disorder or CPK elevation with statins[3]. An incidence of 24% of muscle-related side effects was seen in a group of patients treated with ezetimibe alone[4]. Rhabdomyolysis has not been described, however. More recent reports also emphasize the occurrence of myopathy following the use of ezetimibe in patients with preexistent muscle disease including McArdle myopathy[5,6].

Table 1. Muscle enzymes in ezetimibe-associated relapsing polymyositis.

Measure	October 2008	December 2008	January 2009
CPK, U/l (normal 29–143)	156	169	71
Aldolase, U/l (normal < 8.1)	NA	2	5.8

CPK: creatinine phosphokinase; NA: not available.

Several mechanisms of action have been proposed to explain this phenomenon, including the connection between metabolic and inflammatory disorders, but no clear pathogenic mechanism has been identified to date[7]. Evidence suggests that statin muscle toxicity including that with ezetimibe may be mediated by abnormalities in lipid metabolism. Phillips, *et al* described 11 patients with statin-induced myopathy and compared them with controls; their most significant finding was abnormal fatty acid oxidation in the myotubes in patients intolerant to statins[8].

The safety profile of ezetimibe in treatment of lipid disorders is very good. However, one needs to remain vigilant for the emergence of myopathy, especially in patients with underlying muscle diseases including PM and in those who have previously experienced side effects to lipid-lowering drugs.

IGNACIO GARCIA-VALLADARES, MD; LUIS R. ESPINOZA, MD,
Section of Rheumatology, Department of Medicine, Louisiana State University Health Sciences Center, 2020 Gravier Street, 7th Floor, Box E, New Orleans, Louisiana 70112-2822, USA. Address correspondence to Dr. L.R. Espinoza; E-mail: luisrolan@msn.com

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