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Monotherapy with Ezetimibe Causing Myopathy

To the Editor:

We report the first case of ezetimibe monotherapy causing reversible myalgia, muscle weakness, creatine kinase (CK) elevation, abnormal aerobic function, and myotoxicity as observed on muscle biopsy.

Ezetimibe monotherapy (10 mg/d), as used to block intestinal cholesterol absorption, has been touted as a safe alternative to statins in cases of statin-induced myopathy.

Ezetimibe is often prescribed as an adjuvant or as an alternative to HMG CoA-reductase inhibitors to lower cholesterol levels based on clinical trials that concluded there is no "excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control."[1] Our patient demonstrated measurable functional limitations, elevated CK, significantly decreased muscle strength as measured by the JAMAR dynamometer,[2] and abnormal muscle pathology while on ezetimibe.

A 59-year-old woman on ezetimibe monotherapy presented with severe leg pain and debilitating weakness. Three years before presentation the patient was placed on simvastatin for primary prevention, but after several months she began to have progressive exercise-induced leg pain with a normal CK of 165 IU/L (reference range 0-195 IU/L). Simvastatin was stopped and symptoms abated. Seven months later, ezetimibe 10 mg/d was alternatively started. The patient redeveloped debilitating leg pain and weakness that progressed rapidly over several months. Muscle strength, cardiopulmonary function tests (CPX), and biochemistry were abnormal, and ezetimibe was discontinued. Within a few weeks of discontinuing ezetimibe, her grip strength increased from 18 to 34 kg, CK decreased from 627 to 132 IU/L, anaerobic threshold increased from 12.2 to 13.7 mL · kg · min, and V02 max increased from 19 to 22.3 mL · kg · min as measured by CPX (Fig. 1). Muscle biopsy results demonstrated an unusually high number of cytochrome oxidase-negative fibers suggesting mitochondrial dysfunction (Fig. 1).

The definitive mechanism of myotoxicity induced by lipid-lowering therapy is unknown; however, our muscle biopsy results and cardiopulmonary function tests indicate

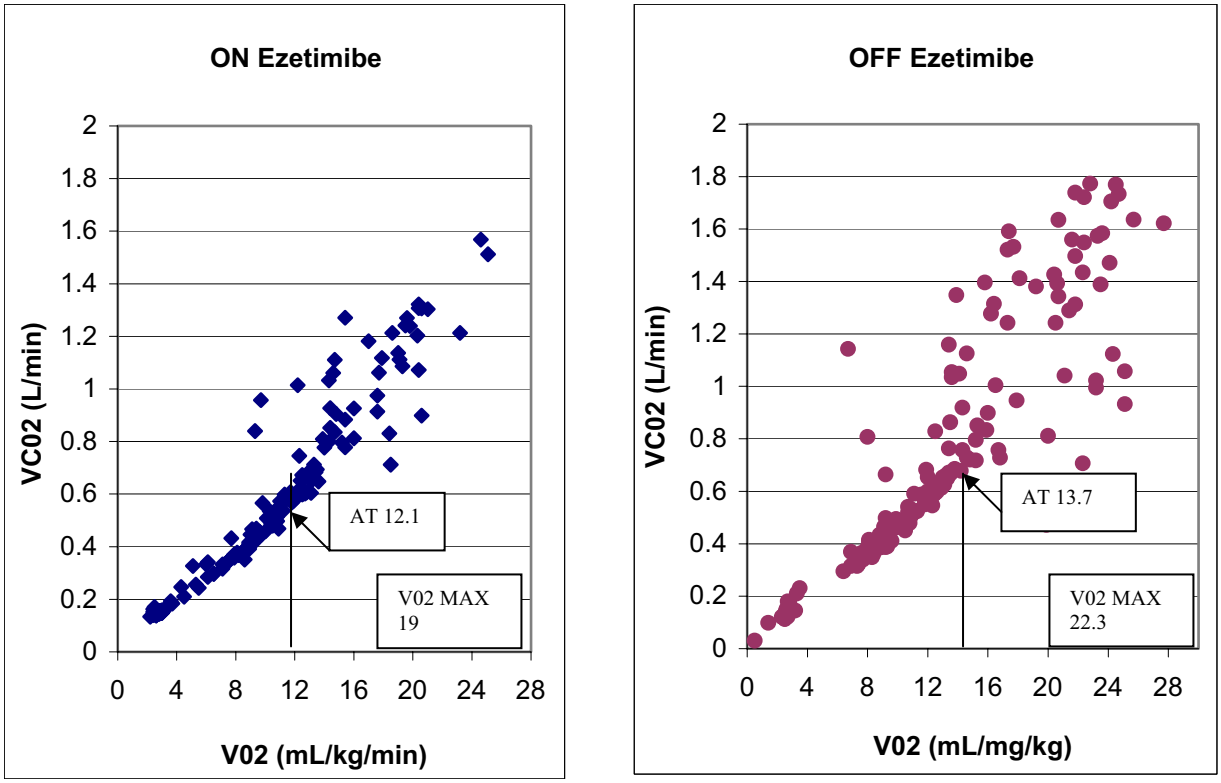

Figure 1 Anaerobic threshold (AT) and V02 max increased after discontinuing ezetimibe monotherapy.

impaired fatty acid oxidation (FAO). In fact, when our patient's myocytes were cultured, they demonstrated the same FAO abnormalities we previously described in statin-intolerant patients.[3] Muscle pathology in our patient and in statin-intolerant subjects suggests altered fat metabolism. In addition, the V02 max and the anaerobic threshold, the level at which the cells use glucose instead of fatty acids for energy, are decreased in vulnerable patients when exposed to statins[4] and in our patient when exposed to ezetimibe.

The abnormal CPX indices, muscle biopsy findings, and abnormal cell culture FAO responses suggest that the cause of statin and ezetimibe-induced myopathy is similar. Our patient, who had previously been intolerant to statin therapy, may have demonstrated recurrent myopathy when placed on ezetimibe because of an underlying FAO defect intrinsic to her and to others with statin intolerance. The cause of myotoxic reactions to lipid-lowering therapy must be better understood before making recommendations for one drug over another in patients who have demonstrated these adverse reactions.

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