Journal of Clinical Lipidology (2015) 9, 256–259

Journal of Clinical Lipidology

Case Studies

Use of lipid-lowering medications in myasthenia gravis: A case report and literature review

Sophie C. Ragbourne, BSc, Martin A. Crook, BSc, MBBS, MA, PhD, FRCPath, FRCPI, FRCP*

Department of Clinical Biochemistry, Lewisham Hospital NHS Trust, London, UK (Ms Ragbourne and Dr Crook); Department of Metabolic Medicine, University Hospital Lewishsam, London, UK (Dr Crook); Guy's Hospital, Southwark, London, UK (Ms Ragbourne and Dr Crook); St Thomas' Hospital, Lambeth, UK (Dr Crook); and University of Greenwich, London, UK (Dr Crook)

KEYWORDS:
Ezetimibe;
Hyperlipidemia;
Myasthenia gravis;
myopathy;
Statins

Abstract: We present a patient with myasthenia gravis (MG) who developed worsening of his condition after starting ezetimibe. We review the literature concerning lipid-modifying medications and MG.

The use of bile acid sequestrant agents may have a place in the lipid management of MG patients because they did not seem to cause muscle-related side effects or worsening of MG.

Case description

A 62-year-old male with myasthenia gravis (MG) was referred to our clinic with hyperlipidemia (see Table 1 for most recent clinical findings at the time of referral). MG is an autoimmune neuromuscular disease, involving the neuromuscular junction, causing muscle weakness and fatigue. After investigation for secondary causes of hyperlipidemia (hypothyroidism, liver and renal profile) and exclusion of familial hypercholesterolemia according to the Simon Broome diagnostic criteria, polygenic hypercholesterolemia was diagnosed, and he was commenced on the cholesterol absorption inhibitor, ezetimibe (10 mg/d).[1] Coincident with the initiation of ezetimibe, his MG again deteriorated, manifesting as a worsening of ptosis. To our knowledge, this is the first report in the medical literature of MG exacerbated by ezetimibe.

In 1995, our patient presented with a 6-week history of vertical diplopia and bilateral fatigable ptosis. He also reported generalized weakness of his body, with difficulty in undressing and performing daily tasks. Despite no evidence of thymic enlargement on a computerised tomography of the thorax and normal acetylcholine and smooth muscle antibodies, our patient had a positive Tensitron test, with improvement in ocular alignment, ptosis, and shoulder elevation. Electromyography confirmed the diagnosis of MG, with repetitive stimulation showing a detrimental response of the left trapezius of up to 29%, and single-fiber electromyography from the left biceps and left extensor digiti communis showing increased jitter and block. He was started on pyridostigmine 60 mg three times daily with improvement in limb weakness, but the ophthalmoplegia persisted and so prednisolone was

Competing interests: None.
Funding: None.
Ethical approval: An ethical approval was not required for this article. However, patient gave written consent for us to include his case history.
Guarantor: M.A.C.
* Corresponding author. Department of Clinical Biochemistry and Metabolic Medicine, University Hospital Lewisham, London SE13 6LH, UK.
E-mail address: m.crook@nhs.net
Submitted August 15, 2014. Accepted for publication December 8, 2014.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2014.12.005

commenced and gradually increased to 80 mg daily. It was found that on reducing steroids below 30 mg, his diplopia returned, implying that he was not truly in remission. Azathioprine 50 mg was added but was stopped after a severe episode of diarrhea and rash. Additionally, our patient was unable to tolerate methotrexate, which made him feel irritable, develop pruritus, and a macrocytosis, thought to be azathioprine related. Our patient was commenced elsewhere on simvastatin 20 mg daily (exact date unclear); he developed a worsening of his MG, with weakness and ptosis, and this drug was thus stopped. Our patient had previously been diagnosed in the 1970s with thyrotoxicosis, associated with a right proptosis but no ophthalmoplegia. Thyroid microsomal and thyroglobulin antibodies were found to be positive, and he received a diagnosis of Graves disease, which was treated with propylthiouracil.

On referral to our clinic, examination showed faint bilateral corneal arci. He was referred to a dietician for reinforcement of dietary and lifestyle changes, but his lipid levels failed to improve. Second-line treatment was therefore considered. As there have been reports in the literature associating statins and fibrates with rhabdomyolysis and other adverse muscular effects, these drugs were avoided, particularly given his side effects previously to simvastatin. An extensive literature search of ezetimibe in MG was undertaken and, with only reports of systemic side effects (eg, gastrointestinal disturbance) and in accordance with National Institute for Health and Clinical Excellence guidelines for the treatment of nonfamilial hypercholesterolemia, in 2005, ezetimibe was started.[2] His MG relapsed with the development of muscle weakness and diplopia. Subsequently, he was started on cholestyramine, with the idea that a drug that is not significantly systemically absorbed may be unlikely to cause muscle complications. Unfortunately, cholestyramine caused him to develop an unpleasant taste in his mouth, although no muscle-related side effects developed. Our patient is currently prescribed colesevelam, a new-generation bile acid sequestrant, which has better bile acid capacity, with only one quarter of the rate of adverse effects (AEs) of cholestyramine. He currently describes no muscle-related side effects to this agent.

He is currently on the following medications: prednisolone, pyridostigmine, pyridoxine, atenolol, and chlortalidone combination and calcium/vitamin D and has no known drug allergies. There is no family history for hyperlipidemia or muscle-related problems. He did not smoke nor drink alcohol.

Table 1 Most recent investigations of our patient (fasting samples)

Investigation	Level in patient
BMI (kg/m^2)	24.7
Sitting blood pressure (mm Hg)	108/70
Total cholesterol mmol/L	7.2
mg/dL	278
Fasting triglycerides mmol/L	1.61
mg/dL	142
HDL cholesterol mmol/L	1.89
mg/dL	73
LDL cholesterol mmol/L	4.59
mg/dL	177
Blood glucose mmol/L	4.9
mg/dL	88
Creatinine μmol/L	112
mg/dL	1.27
Creatine kinase (IU/L)	124
GFR (mL/min/1.73 m^2)	61
Alanine transaminase (IU/L)	26
TSH (mIU/L)	2.49

BMI, body mass index; GFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.

Discussion

It is of course possible that there may have been other explanations for the patient's apparent side effects to ezetimibe. However, the sequential worsening of our patient's MG on commencement of ezetimibe, together with the improvement on discontinuation of the drug, provides evidence toward an ezetimibe-induced exacerbation of myasthenia despite the fact that we did not recommence ezetimibe as a rechallenge. This is to our knowledge the first report of this drug's possible side effects in MG in the medical literature.

Ezetimibe functions as a potent inhibitor of intestinal cholesterol absorption through selective blocking of the internalization of the Niemann-Pick C1-like-1 (NPC1L1) transmembrane protein, situated in the brush border of jejunal enterocytes and the canalicular membrane of hepatocytes.[3,4] Compared with placebo, ezetimibe 10 mg monotherapy reduces low-density lipoprotein cholesterol by approximately 18.6% in hypercholesterolemic subjects and is generally well tolerated.[5] Additionally, ezetimibe is effective at reducing total cholesterol, apolipoprotein B cholesterol and triglycerides, while increasing HDL-C,[6] each of which lower cardiovascular disease risk. However, as with all lipid-lowering medications, AEs have been reported, and patients must be carefully selected before commencing either drug.

Muscle-related AEs, such as myalgia and myositis, are amid the most commonly reported AEs of statins. Indeed, statin myopathy has a prevalence of approximately 1.5% to 3.0% and up to 33% in clinical trials and community-based studies, respectively. This inconsistency may be because of the younger and healthier population included in trials compared with the general population, but also because of an underreporting of less severe statin myopathies in the former.[7,8] Rhabdomyolysis, associated with a 10-fold increase in serum creatine kinase, with subsequent renal failure and sometimes death, is a widely recognized rare