Statin Intolerance in a Patient with Gilberts Syndrome and Hypercholesterolemia

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Abstract

Background: Statin intolerance especially myalgias can be a serious problem. Whilst it is well known that drugs that compete for Cytochrome 450 system can result in myalgias there is sparse data on the role of glucuronidation of statins contributing to statin intolerance. We report on a 60 year old male with Hypercholesterolemia (HC) who was referred for management of his HC since he had statin intolerance manifesting as myalgias and was shown to have Gilbert’s Syndrome.

Case Report: Investigation of this patient revealed he had Familial Combined Hyperlipidemia with a LDL-cholesterol of 189 mg/dl. He was also diagnosed with Gilbert’s Syndrome since he had elevated unconjugated bilirubin with no evidence of liver disease or hemolysis. The combination of Niacin, Cholestyramine and ezetimibe resulted in a successful decrease in his LDL-cholesterol to 114 mg/dl.

Discussion: We believe that his Gilberts Syndrome resulted in an impairment in glucuronidation of statin drugs resulting in an increase in free drug levels and myalgias. We caution that clinicians should consider this possibility when confronted with a patient with both isolated elevations of unconjugated bilirubin and increase LDL-cholesterol levels before commencing statin therapy.

Introduction

The introduction of statin therapy in clinical medicine has resulted in a significant reduction in cardiovascular (CVD) morbidity and mortality. The safety of statin therapy in patients with Gilbert’s Syndrome (GS) has not been carefully documented in any series of patients. In this report, we describe a patient with GS who was statin intolerant and suggest that in such patients who cannot glucuronidate statin drugs adequately, the possibility of muscle symptoms and signs may be increased due to increase in active drug levels. Since data suggest an inverse relationship between unconjugated bilirubin levels and CVD we briefly review this topic.

Case Report

A 60 year old male was referred to the Metabolic Clinic at the VA Medical Center in 2008 with hyperlipidemia and statin intolerance manifest as myalgias and weakness. He had been tried on pravastatin, simvastatin and atorvastatin and could not tolerate any of these medications because of these symptoms. The referring physician did not assay statin levels in this patient. He had a positive family history of premature heart disease but none of his family members were available for evaluation. Physical examination and laboratory tests revealed a normal blood pressure (125/75 mmHg), a body mass index of 29.5 kg/m², no tendon xanthoma, a small multinodular goiter. Also all peripheral pulses were palpable with no bruits and cardiac examination was normal with no evidence of aortic stenosis. Relevant laboratory values since 2008 are shown in Table 1. There is evidence of hyperlipidemia with a total cholesterol (TC) of 258 mg/dl, LDL-cholesterol (LDL-C) of 189 mg/dl and an apolipoprotein B level of 147 mg/dl. There were no obvious secondary cause of hyperlipidemia as evidenced by the clinical examination, a normal TSH level of 2.4 mIU/ml (normal: 0.4–5.0), no albuminuria, and normal serum albumin and alkaline phosphatase levels. He had no evidence of liver dysfunction on repeated testing and normal hemoglobin, reticulocyte count, haptoglobin and lactate dehydrogenase levels. Screening for
viral hepatitis A, Band C were negative and both platelet and leucocyte counts were normal. All these tests did not change between 2008 and May, 2015. A diagnosis of GS was made based on the increased total and indirect bilirubin levels with no evidence of liver disease or hemolysis over this 7 year period. In 2008 he was started on cholestyramine, niacin, ezetimibe and low dose aspirin and he is currently taking cholestyramine 8 g/d, niacin 2 g/d, ezetimibe 5 mg/d and aspirin 81 mg on alternate days. His most favorable lipid profile reveals a TC of 191 mg/dl, LDL-C of 114 mg/dl and an apolipoprotein B level of 110 mg/dl. Over this 7-year period he has not experienced a cardiovascular event.

**Discussion**

This patient has both hypercholesterolemia and GS. The diagnosis of GS was made on the basis of an increase in both unconjugated and total bilirubin over this 7 year span without any evidence of liver disease or hemolysis. In a series of patients with GS (n = 22 and n = 59 matched controls), the investigators documented increased antioxidant defense and decreased biomarkers of inflammation, as well as significantly lower total and LDL-cholesterol levels in GS patients compared with controls [8, 9]. No plausible mechanism was provided for the decrease in LDL-cholesterol levels. Since most patients with GS will not have elevated LDL-cholesterol this problem will only surface if the patient has undesirable LDL-cholesterol requiring statin therapy. However, in patients with GS like our patient, who cannot tolerate statin therapy, other therapies including the recently ushered in PCSK9 Inhibitor therapy offer reasonable alternatives to achieve LDL-cholesterol goals.

The association of increased unconjugated bilirubin levels and lower risk of CVD is of interest. This topic was recently reviewed in depth [10]. There appears to be a significant reduction in CVD risk in patients with GS. This has been ascribed to the antioxidant action of unconjugated bilirubin, lower levels of LDL-cholesterol, potential anti-inflammatory effects of bilirubin, and improvement of endothelial function [10–12]. However a recent Mendelian randomization study coupled to a meta-analyses failed to confirm the decreased risk for CVD for patients with genetically elevated unconjugated bilirubin [13]. Much further work is required to confirm the hypothesis that unconjugated bilirubin is cardio-protective. Until then, patients with GS should have cholesterol-lowering therapy consistent with current guidelines but be aware that in certain patients with GS the issue of statin intolerance needs to be considered.

**Novelty Statement**

This is the first report of statin intolerance (myalgias) in a patient with both Gilbert’s Syndrome (UDPGT deficiency) and hypercholesterolemia due to impaired glucuronidation of statins.
Conflict of interest: None.

References
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