Atorvastatin and Cobicistat-Elvitegravir interaction causing Myopathy in the setting of Biliary Obstruction

B Edwards MD[1], A Stoltz MD[2], K Happel MD[3], Amita Krishnan MD[3]

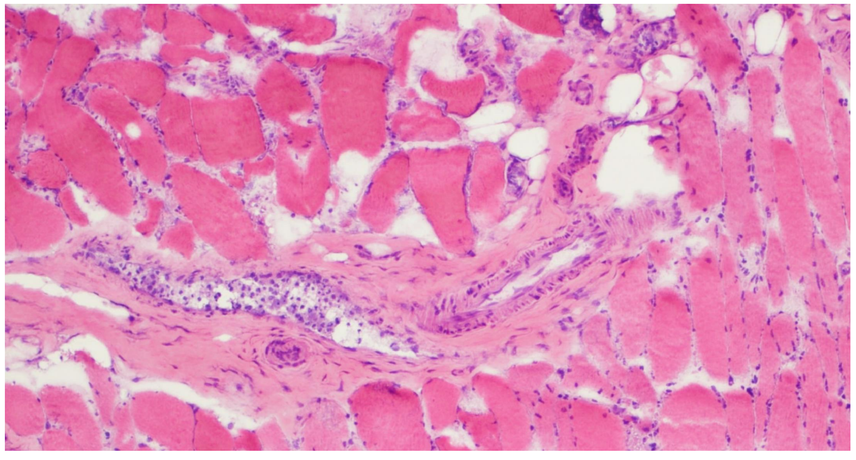
[1]Department of Medicine, LSU Health Sciences Center, New Orleans, LA
[2]Department of Neurology, LSU Health Sciences Center, New Orleans, LA
[3]Section of Pulmonary / Critical Care, LSU Health Sciences Center, New Orleans, LA

Introduction

Cobicistat is a potent CYP3A inhibitor that is combined with elvitegravir to boost its pharmacokinetics as part of antiretroviral therapy for HIV. Inhibition of CYP3A4 will cause elevated concentrations of substrates of that enzyme. Atorvastatin is a statin metabolized by cytochrome P450 3A, while rosuvastatin is metabolized by CYP2C9. Cobicistat inhibition of CYP3A significantly increases statin concentrations and thus enhances the risk of concentration-dependent adverse effects, including skeletal muscle damage.

Case Presentation

Patient is a 62 year-old male with a history of HIV on combination elvitegravir/cobicistat/emtricitabine/tenofovir (150-150-200-10), hyperlipidemia on rosuvastatin, alcohol use disorder, recurrent pancreatitis, a benign pancreatic head mass, and biliary stricture status post stent placement who presented for abdominal pain for 2 weeks. Patient was known to have a migrated biliary stent noted on ERCP over 1 year prior, at which time it was unable to be repositioned and an additional stent was placed. On admission, vitals were T 96.7, HR 109, BP 72/56, RR 32, O2 sat 100% on room air. Initial exam was notable only for mild abdominal tenderness in the lower quadrants. Laboratory studies revealed WBC 23.8, lactic acid 2.4, Cr 13.4 (baseline 1.3), AST 557, ALT 169, Tbili 2, and Alkaline phosphatase 2,141. HIV medication was held and the patient was started on atorvastatin 80 mg a day because the patient's home rosuvastatin 40 mg was not on formulary. Patient was treated with antibiotics, fluids, and later started on hemodialysis for his worsening renal function and volume overload. About 5 days into his hospitalization, the patient complained of myalgias and weakness. Atorvastatin was discontinued at that time. Patient was noted to have profound symmetric proximal muscle weakness with a CPK level over 36,000. EMG was consistent with fulminant myopathy. Patient developed worsening weakness, shortness of breath, and dysphagia, with NIF -25 which prompted intubation. Muscle biopsy was consistent with myositis. Patient's course was complicated by septic shock due to ascending cholangitis treated with ceftriaxone and metronidazole. He underwent an emergent percutaneous cholecystostomy tube placement as both intrahepatic biliary stents were found to be occluded on fluoroscopy. Blood cultures grew ESBL+ E. coli and patient was switched to meropenem. Patient was extubated after a total of 11 days on mechanical ventilation and improved with antibiotic treatment and biliary decompression.



Muscle biopsy. Per pathology report: necrotic fiber with mononuclear infiltrate, lack of lymphocytes, with intrafasciular fibrosis and fatty infiltration consistent with a necrotizing myositis.

Discussion

Statins are HMG-CoaA reductase inhibitors that are used to treat hypercholesterolemia. These drugs can cause adverse effects on skeletal muscle, ranging from myalgias to lethal rhabdomyolysis. Drug-drug interactions that increase serum levels of statins, often through CYP3A inhibition, increase the risk of these effects. Cobicistat is a CYP3A inhibitor that is part of ART therapy to boost elvitegravir concentration, but by consequence increases concentrations of other CYP3A substrates.

Atorvastatin is a statin metabolized by cytochrome P450 3A, while rosuvastatin is metabolized by CYP2C9. Simvastatin and lovastatin have the highest potential for drug-drug interaction with CYP3A inhibitors, and co-administration is contraindicated. Atorvastatin has less frequent interaction, however dosage should start low and close monitoring should be ensured.

Rosuvastatin does not interact with CYP3A, however interactions may occur through interactions with transporters. This case demonstrates the danger of co-administering high-dose atorvastatin with a cobicistat-containing ART regimen and the potential result of fulminant, life-threatening myositis.

References

Chauvin B, Drouot S, Barrail-Tran A, Taburet AM. Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. Clin Pharmacokinet. 2013 Oct;52(10):815-31. doi: 10.1007/s40262-013-0075-4. PMID: 23703578.