Letter to the Editor

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Rhabdomyolysis and Acute Renal Graft Impairment in a Patient Treated with Simvastatin, Tacrolimus, and Fusidic Acid

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Dear Sir,

Post-transplant hyperlipidemia (PTHL) is a frequent metabolic disease following renal grafting, and atherosclerotic vascular disease represents a major burden to transplant recipients. There is convincing evidence that long-term immunosuppression with steroids and calcineurin inhibitors such as cyclosporine A (CsA) and tacrolimus increase both cholesterol and triglyceride levels [1]. Since transplant recipients who have both PTHL and diabetes mellitus are particularly prone to atherosclerotic vascular disease, aggressive treatment of hyperlipidemia is mandatory [1].

Simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, is an efficient drug for the treatment of hyperlipidemia. In combination with the use of CsA simvastatin may increase the risk of rhabdomyolysis [2]. Tacrolimus is now more frequently used in solid organ transplantation. Rhabdomyolysis has not been described in patients treated concomitantly with simvastatin and tacrolimus.

We report a case of severe rhabdomyolysis complicated by acute renal transplant failure. In October 1998, a 51-year-old Caucasian female with insulin-dependent diabetes mellitus (IDDM) and dialysis-dependent renal failure due to diabetic nephropathy received a combined pancreas-kidney graft. Due to a hemorrhagic pancreatitis the pancreas graft was removed 4 weeks later. Apart from a cytomegalus infection 5 weeks post-transplant the following postoperative course was uneventful. In June 1999 the patient suffered from an ischemic stroke with left-sided hemianopia. Simvastatin was started at a daily dose of 10 mg. Immunosuppression consisted of tacrolimus (1–2 mg daily with blood trough levels between 6.4 and 13.9 ng/ml), aprednislone 5 mg and azathioprine 75 mg. The renal transplant function was stable with serum creatinine (SCr) concentrations between 0.9 and 1.4 mg/dl. Because of persistent hyperlipidemia in October 1999, the simvastatin dose was increased to 20 mg/day (table 1). Ten days later fusidic acid (500 mg TID) was started because of soft tissue infection and osteomyelitis of the second left toe. Five weeks later the patient was admitted to the hospital because of muscle pain which had started gradually 2 weeks earlier. On admission the medication was tacrolimus, azathioprine, aprednislone, felodipine 10 mg, citalopram 20 mg, aspirin 100 mg, simvastatin 20 mg, fusidic acid (500 mg TID), and insulin (intensified insulin therapy regimen). The SCr concentration was 3 mg/dl, the creatinine clearance was 12 ml/min, the serum creatine kinase (CK) concentration was 24,000 U/ml (normal range: 10–70 U/l). The tacrolimus trough level 4 days before admission was 9.1 ng/ml. The therapy with simvastatin and fusidic acid was immediately stopped and treatment was started with saline and mannitol. Renal transplant function improved and the patient was discharged on day 13 with a creatinine clearance of 45 ml/min and a CK level of 298 U/l. Simvastatin was replaced with fluvastatin (40 mg/day), aprednislone was tapered and withdrawn after 6 months. In January 2001 a soft tissue infection and osteomyelitis of the third left toe was treated with fusidic acid (500 mg TID); no side effects occurred. Fourteen months after the rhabdomyolysis the patient is well with good graft function (SCr 1.0–1.5 mg/dl).The immunosuppressive regimen is unchanged. Hyperlipidemia is currently treated with fluvastatin 40 mg/day.

To the best of our knowledge this is the first report of severe rhabdomyolysis in a transplant patient treated with simvastatin and tacrolimus. There is an intriguing temporal relationship between the increase of the simvastatin dose and the onset of signs and symptoms of rhabdomyolysis (table 1). Simvastatin is a substrate for cytochrome P 450 3A4 (CYP3A4). CsA and tacrolimus are inhibitors of CYP3A4 and can elevate the plasma concentration of HMG-CoA reductase inhibitory activity derived from simvastatin. The concomitant use of CsA and simvastatin has been shown to increase the risk for myopathy [2]. In contrast, to our knowledge no myopathy has been observed with CsA and fluvastatin, a statin metabolized by CYP2C9 [3].

Two previous reports [4, 5] describe patients who experienced rhabdomyolysis after

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Table 1. Clinical course and therapeutic regimen in a renal transplant patient suffering from rhabdomyolysis

Date	Tac mg/day	Statin mg/day	Fus g/day	SCr mg/dl	Event
Oct 25th, 1998					combined pancreas/kidney graft
Nov 11th, 1998	4			0.9	pancreas graft removed
Nov 1998–Dec 1998	3 to 4			1.1	CMV infection
Nov 1998–May 1999	3 to 4			1.2	uneventful course
June 1999	3 to 4			1.1	ischemic stroke
July 1999–Sep 1999	3	sim 10		1.1	uneventful course
Oct 4th, 1999	3	sim 20		1.2	simvastatin dose increased
Oct 13th, 1999	3	sim 20	1.5	1.2	osteomyelitis, fusidic acid started
Nov 19th, 1999	3	sim 20	1.5	3.0	rhabdomyolysis, CK 24,000
Dec 1999–Mar 2000	3	flu 40		1.5	uneventful course
Mar 2000–Dec 2000	2	flu 40		1.1	uneventful course
Jan 2001	2	flu 40	1.5	1.0	CK normal range

Tac = Tacrolimus; sim = simvastatin; flu = fluvastatin; fus = fusidic acid.

initiation of simvastatin and fusidic acid therapy. Fusidic acid has a time-dependent activating effect on the CYP450 system [6]. Whether or not this pharmacologic property is responsible for the observed rhabdomyolysis remains to be determined. One case of rhabdomyolysis associated with tacrolimus in a 17-month-old bone-marrow recipient was reported [7], but no details of concomitant drugs were given. A rise of plasma CK levels was observed in rats receiving a combined simvastatin-tacrolimus regimen [8].

Our observation suggests that the combined use of tacrolimus and simvastatin in a dose exceeding 10 mg/day may put a patient at an increased risk for rhabdomyolysis. Statins not metabolized by the CYP3A4 system may be the lipid-lowering drugs of choice in patients treated with tacrolimus. Whether or not in our patient the use of fusidic acid presented an additional risk factor for the development of rhabdomyolysis is unclear.

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