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ORIGINAL ARTICLE

Severe Rhabdomyolysis Due to Rosuvastatin in a Liver Transplant Subject With Human Immunodeficiency Virus and Immunosuppressive Therapy–Related Dyslipidemia

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Statins are relatively safe first-line agents to use in the setting of dyslipidemia associated with immunosuppressive therapy in subjects undergoing liver transplantation, and also in HIV-infected patients with dyslipidemia due to antiretroviral drugs, especially ritonavir-boosted protease inhibitors. Rosuvastatin, a new statin, has demonstrated higher potency than previously released statins and is not extensively metabolized by the liver P450 system; therefore, the probability of deleterious pharmacokinetic interactions with commonly used immunosuppressants and antiretroviral drugs is reduced. We present the first case of severe rhabdomyolysis in a liver transplant patient receiving rosuvastatin for the treatment of immunosuppressive therapy–related grade IV dyslipidemia, an HIV-infected subject on protease inhibitor-sparing HAART, that resolved after rosuvastatin withdrawal, probably related to interactions between calcineurin inhibitors and hepatic rosuvastatin uptake transporters such as Organic Anion Transporting Polypeptides (OATPs). ***Liver Transpl 17:331–333, 2011.*** © **2011 AASLD.**

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Dyslipidemia due to immunosuppressants (ISs) is common (45%-69%) after liver transplantation (LT)[1] and is also a frequent side effect of highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV)–infected patients receiving ritonavir-boosted protease inhibitors (r-PIs).[2] In the setting of dyslipidemia after LT, statins are appropriate and well-tolerated first-line agents.[1] Rosuvastatin (ROS) is not extensively metabolized by cytochrome P450 3A4 (CYP3A4) and is more effective than pravastatin for the treatment of both low-density lipoprotein cholesterol and triglyceride levels in HIV1-infected subjects who have dyslipidemia and are receiving r-PIs.[3] The most serious adverse effects of statins are related to muscle injury and increases in liver enzymes in a dose-dependent manner.[4,5] However, the rates of creatine kinase (CK) elevations and myopathy (CK elevations >10 times the upper limit of normal), whether or

Abbreviations: 3TC, lamivudine; ABC, abacavir; CK, creatine kinase; CYA, cyclosporine A; CYP3A4, cytochrome P450 3A4; FK, tacrolimus; GFR, glomerular filtration rate; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; HIV, human immunodeficiency virus; IS, immunosuppressants; LDH, lactate dehydrogenase; LDL, low-density lypoprotein; LT, liver transplantation; MF, mycophenolate; RAL, raltegravir; ROS, rosuvastatin; r-PI, ritonavir-boosted protease inhibitor; sCr, serum creatinine; ST, steroid.

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TABLE 1. Baseline and Evolutive Features

	LT Discharge (December 23, 2009)	Before Partial Splenic Embolization (April 16, 2010)	Baseline ROS (May 3, 2010)	Rhabdomyolysis (July 26, 2010)	Last Value (August 25, 2010)
IS therapy	STs and CYA	STs, FK, and MF	STs, FK, and MF	STs, FK, and MF	FK and MF
Calcineurin inhibitor drug level (ng/mL)	132	5.4	8.9	10.9	11
HAART*	RAL, 3TC, and ABC	RAL, 3TC, and ABC	RAL, 3TC, and ABC	RAL and Truvada	RAL, 3TC, and ABC
Total cholesterol (mg/dL)	—	455	422	411	468
High-density/low-density lipoprotein cholesterol (mg/dL)	—	11/390	—	15/343	—
Triglycerides (mg/dL)	—	267	359	263	228
Aspartate aminotransferase/ alanine aminotransferase (U/L)	177/294	97/118	74/69	1199/475	189/153
Gamma-glutamyl transpeptidase/alkaline phosphatase (U/L)	5059/1614	1195/798	934/1157	2266/2081	2144/1199
Bilirubin (mg/dL)	6.70	19	16.60	5.20	5.35
Creatinine (mg/dL)	2.15	1.22	2.81	2.22	1.28
Glomerular filtration rate (mL/minute)	36	59	27	29	54
CK/aldolase/lactate dehydrogenase (U/L)	—	—	<6/—/220	23,124/36/1370	65/2.5/270
CD4 [% (absolute)]	53% (222)	23% (326)	17% (658)	15% (595)	
HIV RNA (copies/mL)	<50	<50	<50	<50	<50
HCV RNA (IU/mL)	$>69 \times 10^6$	<15	Negative	Negative	Negative

*3TC and Truvada (a fixed combination of tenofovir and emtricitabine) were always adjusted to the renal function.

not accompanied by muscle symptoms, are rare (0–1.2% of patients receiving ROS doses between 5–80mg/day), with no cases of rhabdomyolysis among 12400 patients receiving ROS 5–40 mg/day.[6] We report for the first time the development of severe rhabdomyolysis in an HIV-coinfected subject on ROS with IS-related dyslipidemia after LT.

CASE REPORT

A 39-year-old Caucasian male with decompensated hepatitis C virus (HCV)/hepatitis B virus/hepatitis delta virus cirrhosis underwent LT on September 30, 2009; he received a graft from a female Japanese donor. Viral markers at the time of LT were as follows: $HBsAg^+$, HBV-DNA <20 IU/ml, negative HBeAg, positive HBeAb, HCV-RNA 1,474,098 IU/ml. His admission was prolonged (84 days), and he had many complications: severe preservation liver injury, cytomegalovirus viremia (day 5) resolved with ganciclovir, acute cellular rejection (day 16) treated with steroid (ST) boluses, acute renal failure requiring hemodialysis that evolved into chronic renal dysfunction, and spontaneous HCV RNA clearance after a peak $>69 \times 10^6$ IU/mL. Before LT, he was receiving r-PI–based HAART, but shortly after LT, he started to take raltegravir (RAL), abacavir (ABC), and lamivudine (3TC). On April 16, 2010, biopsy-proven ischemic liver damage related to persistent hypersplenism and splenic artery steal syndrome led to transarterial partial splenic embolization with progressive amelioration of cholestasis. On May 3, 2010, with his baseline CK and lactate dehydrogenase values normal but severe renal impairment (Table 1), ROS at the dose of 10 mg/day was started, and there were successive increases to 20 (May 24, 2010) and 40 mg/day (June 21, 2010). At the times of ROS increases sCr and GFR were 1.22 mg/dL and 70 ml/min, and 1.8 mg/dL and 39 ml/min, respectively, while CK levels remained below the lower limit of normal range. In addition, on May 24, 2010, ABC and 3TC were changed to tenofovir and emtricitabine, adjusted on June 21 2010 to one pill on alternate days, due to renal impairment (GFR 39ml/min), and non-previously developed proteinuria (150mg/dL) and glycosuria (10mg/dL), with therapeutic tacrolimus levels (10.8ng/mL). On June 8, 2010, liver biopsy demonstrated chronic rejection, and the doses of his triple regimen of immunosuppressive therapy [tacrolimus (FK), STs, and mycophenolate (MF)] were intensified. On July 26, 2010, the patient reported 10 days of malaise, muscle pain, weakness, and difficulty in walking. An analytical assessment (Table 1) showed severe rhabdomyolysis, worsening renal function, and

acidosis. He was hospitalized and received aggressive intravenous hydration plus oral bicarbonate. ROS was withdrawn, and ABC and 3TC were restarted. The IS drug levels were always within therapeutic ranges (Table 1). In addition, it should be noted that RAL was not stopped at any time during follow-up, including rhabdomyolysis-related admission.

This is the first reported case of severe rhabdomyolysis associated with ROS in an HIV subject after LT. It became clinically apparent after successive ROS dose increases and reverted after ROS withdrawal. Several factors might have increased ROS exposure and precipitated toxicity. First, because Asian subjects have lower oral clearance of ROS and higher plasma exposure than white subjects, donor race is probably related to differences in the expression or function of hepatic uptake transporters.[7] In addition, ischemic liver damage due to hypersplenism and chronic rejection led to maintained liver dysfunction, persistent cytolysis, and cholestasis. Hepatic clearance represents 70% of the total plasma clearance of ROS, and there is also active transport from the liver to bile.[8] Therefore, extensive hepatic impairment increases systemic exposure to ROS. In addition, drug interactions with ISs rather than HAART might have may have played a role in our patient. Rhabdomyolysis during HAART has been reported for statins other than ROS in subjects receiving r-PIs.[9,10] However, neither ROS[6] nor RAL[11] is metabolized by CYP3A4, and there has been only 1 anecdotal report of rhabdomyolysis in a patient on RAL with several risk factors.[12] Furthermore, to date, there have been no reports on rhabdomyolysis in HIV subjects receiving RAL-based therapy after LT[13,14] or in dyslipidemic, HIV-infected patients receiving ROS and r-PIs.[3] Furthermore, in our patient rhabdomyolysis resoved with ROS withdrawal, while RAL was not stopped at any time during follow-up. On the other hand, calcineurin inhibitors (especially cyclosporine) may increase ROS levels by inhibition of the organic anion transporter protein 1B1-mediated hepatic uptake of ROS and not by CYP3A4 interference,[6] and there are rare cases of severe myopathy.[15] Finally, although 90% of ROS is primarily eliminated unchanged in the feces, severe renal impairment (GFR <30 mL/minute), as observed in our patient at baseline of ROS use and also at the time of clinically evident rhabdomyolysis, produces substantial increases in the systemic exposure to ROS.[7]

In conclusion, in HIV subjects developing IS-related dyslipidemia after LT, clinicians should be alerted to the possibility of severe rhabdomyolysis when ROS is used, especially if dose increases are needed or there is renal insufficiency, even with r-PI–sparing HAART.

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