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Case Report

Rhabdomyolysis after ezetimibe/simvastatin therapy in an HIV-infected patient

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Case report

A 42-year-old white man was admitted to hospital with a 3-day history of progressive muscle weakness, myalgias and dark urines. He was HIV/hepatitis C virus (HCV) coinfected, with an absolute $CD4^+$ T lymphocyte count of 393 cells/mm^3, a serum HIV-1 RNA load of <40 copies/mm^3 and an HCV RNA load of 6 $\log_{10}$ before admission to the hospital. His antiretroviral treatment consisted of lamivudine (150 mg bd), abacavir (300 mg bd), indinavir (400 mg bd) and ritonavir (100 mg bd) at the time of admission. This regimen had not been changed in the past 2 years. The patient also had a history of hyperlipidaemia, coronary artery disease and a cerebral stroke in 2004. Because of severe hyperlipidaemia (LDL cholesterol, 175 mg/dL; triglyceride level, 191 mg/dL) that was refractory to dietary therapy and a 6-month trial of pravastatin (40 mg/day), a combination of ezetimibe (10 mg/day) and simvastatin (40 mg/day) was introduced 3 weeks prior to admission. The patient was also taking aspirin (75 mg/day), bisoprolol (5 mg/day) and perindopril (2 mg/day). He took no herbal or over-the-counter medications, and he did not use alcohol or illicit drugs. His basal serum creatinine level was 65 μmol/L (0.81 mg/dL). Calculated creatinine clearance using the modified diet in renal disease formula (MDRD) was 98 mL/min.

Ten days after the initiation of treatment with ezetimibe–simvastatin combination, the patient noted the development of new generalized and progressive muscle weakness and dark urines. He denied having recently exercised strenuously or having sustained a trauma, and he had no prior history of HIV myopathy. He was well nourished (weight 66 kg). Laboratory evaluation revealed findings that were consistent with rhabdomyolysis [creatine kinase (CK), 206 000 U/L with normal troponin-I level; alanine aminotransferase, 4200 U/L; aspartate aminotransferase, 1193 U/L; myoglobinuria, 26 700 μg/L and aldolase, 1990 U/L] without acute renal failure (serum creatinine, 0.68 mg/dL; BUN, 3.05 mmoL/L; MDRD GFR 100 mL/min). The urine was positive for myoglobin. Serum levels of amylase and lipase were within the normal range of 49 U/L (<100) and 22 U/L (7–60), respectively. Albumin level was 3.24 g/dL. Results of blood cultures, toxicology screening tests and serological testing for acute hepatitis and antinuclear antibodies, anti-smooth-muscle antibodies and rheumatoid factor were negative. Electromyography was not performed. No clinical or radiological evidence of active infections was documented.

The lipid-lowering agent was immediately discontinued while all antiretroviral drugs were maintained. The patient was treated with massive hydration and urine alkalinization. Clinical symptoms and laboratory abnormalities gradually improved, and within 10 days the patient fully recovered with normal muscle enzymes. He never developed acute kidney injury: serum creatinine was 43 μmoL/L (0.54 mg/dL), 37 μmoL/L (0.46 mg/dL) and 53 μmoL/L (0.66 mg/dL) 3 days, 7 days and 15 days after admission, respectively.

Methods

A literature search for published case reports involving lipid-lowering agents, rhabdomyolysis and HIV was performed using the Medline database (for articles published from 1990 through August 2007), with the following search terms: ‘ezetimibe’, ‘statin’, ‘rhabdomyolysis’ and ‘HIV’. Eight cases of statin-related rhabdomyolysis were identified [4–11]. Patient’s medical, medication histories and pertinent laboratory tests were obtained. Baseline data and clinical characteristics for all patients are shown in Table 1.

Results

We analysed the findings for our patient and for the eight patients described in the literature with statin-associated rhabdomyolysis in HIV-infected patients. The mean age of

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Table 1. Summary of published case reports describing LLA-associated with rhabdomyolysis in HIV-infected patients

	Case reports								
	Patient 1[4]	Patient 2[5]	Patient 3[6]	Patient 4[7]	Patient 5[8]	Patient 6[9]	Patient 7[10]	Patient 8[11]	This case
Age/Gender	74/M	57/M	51/F	63/M	70/M	34/M	49/M	72/M	42/M
Lipid-lowering agents									
Type, dose	Simvastatin, 20 mg/day	Gemfibrozil (600 mg/day) + Cerivastatin (0.6 mg/day)	Simvastatin 40 mg/day for 2 years	Atorvastatin 20 mg/day for 5 years	Simvastatin 80 mg/day	Atorvastatin 40 mg/day	Simvastatin 10 mg/day	Simvastatin 80 mg/day	Ezetimibe 10 mg + simvastatin 40 mg daily
Type, dose	Simvastatin, 20 mg/day	Gemfibrozil (600 mg/day) + Cerivastatin (0.6 mg/day)	Simvastatin 40 mg/day for 2 years	Atorvastatin 20 mg/day for 5 years	Simvastatin 80 mg/day	Atorvastatin 40 mg/day	Simvastatin 10 mg/day	Simvastatin 80 mg/day	Ezetimibe 10 mg + simvastatin 40 mg daily
HIV infection									
CD4 count (cells/mm^3)	>330	262	408	NA	216	110	150	NA	393
VL (log10 copies/mL)	Undetectable	6.1	<183	NA	<50	<40	29000	NA	<40
Infection duration (years)	10	NA	8	9	NA	NA	NA	NA	15
CYP3A4 inhibiting agents	Delavirdine	Indinavir	Indinavir, ritonavir	Indinavir, delavirdine	Nelfinavir	Ritonavir, lopinavir, clarithromycin	Fluconazole	Atazanavir, delavirdine, amiodarone	Indinavir, ritonavir
Other risk factors	CAD	None	T2DM	NA	NA	Cholangitis sclerosis	CRF (SCr, 1.7 mg/dL)	CAD, CPD, HT	CAD, HCV coinfection
Time to rhabdomyolysis	4 weeks after LLA started	4 weeks after LLA started	1 week after ritonavir started	4 weeks after delavirdine started	4 weeks after statin started	3 days after clarithromycin was added	3 months after statin started	19 days after amiodarone started	10 days after ezetimibe/ simvastatin started
Peak CK (U/L)	105 180	76 000	23 968	9600	78 000	11 332	25 340	70 000	206 000
Renal damage									
ARF, SCr (mg/dL)	Yes, 1.3	Yes, 2.73	NA	Yes, 7.6	Yes, 5.6	NA	Yes, 4.5	Yes, 4.1	No, 0.6
Haemodialysis	No	NA	NA	NA	Yes	NA	Yes	Yes	No
Outcome, time	Resolved, 3 months	Resolved, 2 weeks	Resolved, 10 days	Resolved, 1 month	No, died suddenly	Resolved, 1 week	Resolved, 18 days, remained dialysis-dependent	Resolved, 1 month	Resolved, 10 days

M, male; F, female; VL, viral load; NA, not available; CAD, coronary artery disease; T2DM, type 2 diabetes mellitus; CRF, chronic renal failure; CPD, chronic pulmonary disease; HCV, hepatitis C virus; LLA, lipid-lowering agents; CK, creatine kinase; ARF, acute renal failure; SCr, serum creatinine level.

the nine patients was 57 years (range, 34–74 years), with a ratio of male to female of 8:1. The mean duration of statin therapy was 90 days (range, 10 days to 5 years). The drugs most often administered were simvastatin (five of nine patients), atorvastatin (two of nine patients) and cerivastatin (one of nine patients). The CYP3A4-inhibiting drugs most often administered were indinavir (four of nine patients), ritonavir and/or ritonavir/lopinavir (three of nine patients) and delavirdine (three of nine patients). The increased mean serum CK level was 70 000 U/L. Statin treatment was discontinued for all patients, and abnormal laboratory findings dramatically resolved in the majority of patients by the time of follow-up (mean follow-up time = 16 days, range = 1 week to 3 months). Two-thirds of the patients experienced acute renal failure during rhabdomyolysis. Half of them required haemodialysis (temporary for two patients and definitive for one patient with previous chronic renal failure). After discontinuation of statin treatment and aggressive supportive care, renal failure resolved in those patients, and renal function returned to the baseline level in four out of the six patients.

Discussion

The concomitant use of antiretrovirals and statins has increased because of the hyperlipidaemia that often results from long-term antiretroviral combination therapy. Despite the excellent benefit/risk profile of statins, their use is limited by a dose-related risk of adverse events (AEs), particularly those related to muscle toxicity. Ezetimibe/simvastatin is a cholesterol-lowering therapy that inhibits the intestinal absorption (ezetimibe) and synthesis (simvastatin) of cholesterol. Ezetimibe has been effective in optimizing lipid levels when added to traditional therapy in non-HIV positive patients. McKenzy *et al.* reviewed muscle-related AE data from 17 randomized, blinded clinical trials (13 base and 4 extension studies), in which ezetimibe and simvastatin were either co-administered as separate entities or given as a combination tablet to 4558 patients. For all AE categories examined, the incidence of muscle-related clinical and laboratory AEs or discontinuations due to muscle-related AEs was no more common in patients taking ezetimibe/simvastatin than in those taking simvastatin alone. Thus, the clinical trial experience with ezetimibe/simvastatin suggests that ezetimibe does not enhance or aggravate the muscle effects of simvastatin [12].

Patients with HIV have an increased risk of coronary artery disease. Part of this risk may be due to the hyperlipidaemia associated with antiretrovirals. Often the lipid goals of patients in this group are not achieved by the therapy recommended in the current lipid-lowering guidelines. The efficacy of ezetimibe in HIV-positive patients has been assessed in three studies. Coll *et al.* showed that ezetimibe monotherapy decreases LDL as effectively as fluvastatin monotherapy in HIV-positive patients [13] and none of the participants experienced related side effects or interrupted the lipid-lowering therapies. Negredo *et al.* showed that LDL was also reduced when ezetimibe was added to pravastatin monotherapy [14]. No patients discontinued therapy due to intolerance or presented toxicity of grade 2 or more in this prospective, open-label, one-arm study of 24 weeks duration. Bennett *et al.* reported that adding ezetimibe 10 mg daily to maximally tolerated lipid-lowering therapy in 33 patients with HIV dyslipidaemia does not induce AEs [1]. However, five cases of suspected myopathy that occurred soon after the addition of ezetimibe have been reported. The statins administered were atorvastatin (three of five patients) and fluvastatin (one of five patients) [4,15]. One case involved ezetimibe monotherapy in a woman who had muscle pain on presentation and elevated CK levels on two occasions, first while taking ezetimibe 10 mg and then again while receiving a rechallenge of 5 mg after a washout period [15]. Our patient developed rhabdomyolysis while receiving ezetimibe with simvastatin combination therapy. The onset of this reaction was 10 days after the exposure to the combination. After discontinuation of ezetimibe and simvastatin, the patient's symptoms clearly resolved. No clear conclusions can be drawn about which molecule can be held responsible for the rhabdomyolysis observed. We preferred not to rechallenge the patient with ezetimibe reintroduction for the time being, leaving this to his infectious disease consultant to try perhaps later on.

Acute rhabdomyolysis may occur during HIV-1 infection and may be attributed to HIV-1 itself, opportunistic infections or drug toxicity. Drug-induced rhabdomyolysis has been reported in HIV-1-infected patients taking pentamidine, trimethoprim–sulfamethoxazole, sulfadiazine and antiretroviral agents such as didanosine, zidovudine, indinavir and ritonavir, and statins. Safe pharmacological treatment of hyperlipidaemia in HIV-infected patients requires an understanding of the drug–drug interactions between antiretroviral drugs and lipid-lowering agents (Figure 1). Rhabdomyolysis is an uncommon but well-recognized dose-related complication of therapy with statins, particularly in association with the concurrent use of drugs that inhibit the liver cytochrome P-450 isoenzyme 3A4 (CYP3A4), including mibefradil dihydrochloride, fibrates, cyclosporine, macrolide antibiotics, warfarin, digoxin and azole antifungals.

Pharmacokinetic patterns differ among individual protease inhibitor drugs and so do their results of interaction with statins. Simvastatin and lovastatin, and, to a lesser extent, atorvastatin and cerivastatin are metabolized by CYP3A4, whereas fluvastatin is metabolized by cytochrome P-450 isoenzyme 2C, and pravastatin is excreted mostly unchanged by the kidney. All currently available protease inhibitors are also metabolized by cytochrome P-450 enzymes; the most important of these enzymes *in vitro* is CYP3A4. Delavirdine can also inhibit CYP3A4 and has the potential to slow the metabolism of coadministered CYP3A substrates. Moreover, CYP2D6*4 allele is associated with broadly related muscle events caused by at least two structurally dissimilar 3-hydroxy-3-methylglutaryl coenzyme *A* reductase inhibitors and as such, may have implications for a better understanding of this statin-wide phenomena. In addition, all protease inhibitors are substrates for *P*-glycoprotein (*P*-gp), a bidirectional drug transporter present on the surfaces of many cells, including intestinal epithelial cells, lymphocytes and macrophages. Inhibition of *P*-gp by statins may lead to increased intracellular drug concentrations. Fichtenbaum *et al*. [16] reported that a

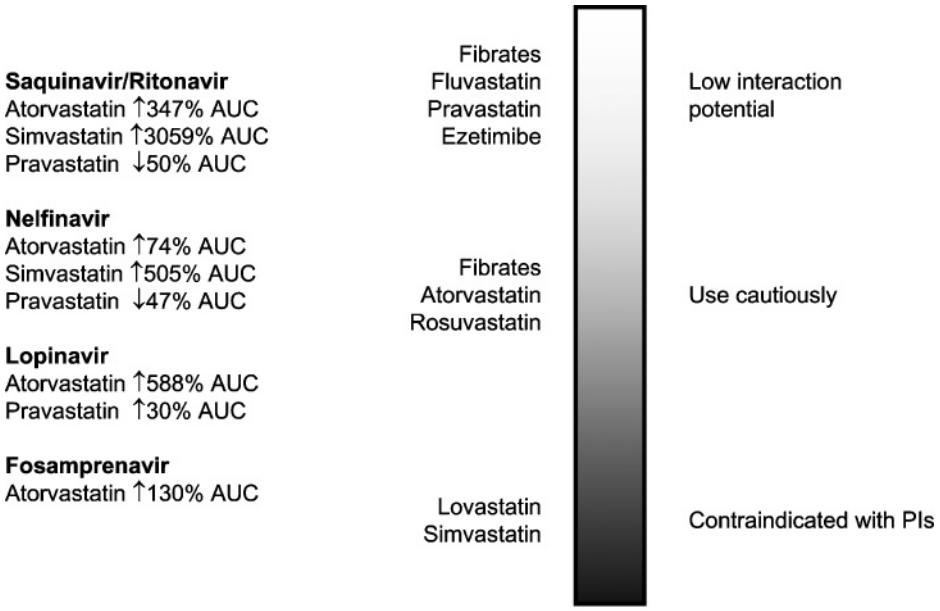

Fig. 1. Lipid-lowering agents and protease inhibitors: drug interactions. Made available through Clinical Care Options Informations.

Table 2. Summary of recommended statin in HIV-infected patients and their dosage in renal insufficiency

	Statin			
	Pravastatin (mg/day)	Fluvastatin (mg/day)	Rosuvastatin (mg/day)	Atorvastatin (mg/day)
Creatinine clearance (mL/min/1.73 m^2)				
>90	10–40	20–80	10–40	10–80
60–90	10–40	20–80	10–40	10–80
30–60	10 starting dose	20–80	10–40	10–80
15–30	10 starting dose	20–80	5–10	10–80
Haemodialysis[a]	10 starting dose	20–80	NA	10–80

Available from http://www.sitegpr.com/(accessed 22 October 2007).
NA, not available; 'starting dose' means the dosage may be further increased according to tolerance and efficacy.
[a]Drug administration may be performed before or after the haemodialysis session.

combination of ritonavir and saquinavir (each 400 mg po twice daily) increased simvastatin concentrations 25-fold and increased atorvastatin concentrations 74%. In contrast, pravastatin concentrations decreased 47%. In a retrospective study by Penzak *et al*. [17], 26 HIV-infected patients were identified who were receiving a protease inhibitor plus pravastatin, lovastatin, simvastatin or atorvastatin. Two patients, who had both received lovastatin, had diffuse myalgia. The serum CK concentration, measured in only one of the patients (who was also taking niacin), was 5.4 times higher than normal. In eight patients receiving indinavir-containing HAART, indinavir plasma levels were not significantly influenced by lipid-lowering therapy with fluvastatin and pravastatin [18]. There is no information regarding indinavir and other statin interaction, and abacavir and statin interaction.

Other risk factors for rhabdomyolysis among statin users were identified such as older age, high statin dosage and renal disease in a recent nested case-control study, conducted within a cohort of 252 460 new users of lipid-lowering medications [19].

Conclusion

Although neither ezetimibe nor simvastatin can be held responsible alone for the rhabdomyolysis observed in our case, we believe that clinicians should be cautious while choosing a lipid-lowering agent for HIV-infected patients. They should give special attention to potentially dangerous drug–drug interactions and renal insufficiency (Table 2).

Conflict of interest statement. None declared.

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