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CASE REPORT

Rapid onset of rhabdomyolysis after switching to a raltegravir-based antiretroviral regimen

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Raltegravir is the first integrase inhibitor antiretroviral agent that has been demonstrated to have antiviral efficacy and safety. However, the US Food and Drug Administration has recommended use with caution in patients with risk factors for rhabdomyolysis, based on four case reports of rhabdomyolysis in patients with identifiable risk factors. We present a 32-year-old Asian man with human immunodeficiency virus (HIV), but without other underlying diseases, who developed rapid-onset, raltegravir-associated rhabdomyolysis and hyperlactatemia. Our patient lacked predisposing factors for rhabdomyolysis, and the rapid onset time of 4 days was the shortest reported. Therefore, clinicians should exercise caution when using raltegravir and closely monitor all patients for the symptoms of muscle pain and weakness. This case has been reported to the National Adverse Drug Reactions Reporting System of the Department of Health in Taiwan.

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Introduction

The introduction of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) has resulted in prolonged life expectancy and improved quality of life. The choice of HAART depends not only on its efficacy, but also its side effects. New antiretroviral agents with less drug resistance and fewer side effects have been developed. Raltegravir is a first-in-class agent targeting the HIV integrase enzyme and has been demonstrated to have antiviral efficacy in both treatment-naïve and treatment-experienced patients. Raltegravir has been shown to have a good safety profile in randomized controlled trials, however, there have been reports of rhabdomyolysis in HIV-infected patients with chronic renal failure, hepatitis B or hepatitis C virus coinfection, or concomitant use of rhabdomyolysis-inducing agents. We report a case of raltegravir-associated rhabdomyolysis and hyperlactatemia, with rapid onset, in a young Asian male without underlying diseases, except for HIV infection.

Case report

A 32-year-old, Asian male (weight, 51 kg; height, 157 cm; body mass index, 20.7 kg/m^2) with HIV infection, diagnosed in 2005, presented to our emergency department with the chief complaints of palpitations, nausea, dizziness, and generalized numbness. He had received HAART since April 2007 with a nadir CD4 count of 232 cells/μL (10% CD4 cells) and HIV RNA of 85,600 copies/mL. His risk factor for HIV infection was man to man sex. He denied having a past history of dyslipidemia, diabetes mellitus, chronic renal disease, or chronic hepatitis B or C virus infection. He was neither an alcoholic nor a drug abuser, and denied taking any drugs other than HAART. His HAART medications included didanosine 400 mg once daily, lamivudine 150 mg twice daily, and lopinavir/ritonavir 400/100 mg twice daily for the past 4.5 years. His HIV viral load remained undetectable (<50 copies/mL) and his CD4 count was 758 cells/μL (23% CD4 cells) in September 2011. Due to persistent, chronic diarrhea despite long-term use of antidiarrheal agents, lopinavir/ritonavir was discontinued and switched to raltegravir 400 mg twice daily on November 15, 2011.

Four days later, he developed palpitations, nausea, dizziness, and generalized numbness, and presented to our emergency department. His vital signs were: body temperature, 36.8°C; heart rate, 70 beats/min; blood pressure, 145/79 mmHg; and respiration rate, 20 breaths/min. Physical examination was unremarkable. Laboratory evaluation revealed a serum lactate level of 4.3 mmol/L, creatine kinase (CK) of 830 U/L, alanine aminotransferase of 15 U/L, serum creatinine of 0.8 mg/dL, serum sodium of 140 mEq/L, serum potassium of 3.8 mEq/L, and a fasting serum glucose of 94 mg/dL. With a diagnosis of adverse drug effects, suspected to be related to HAART, he was discharged with antiemetic drugs, and referred to our infectious disease clinic for adjustment of his HAART regimen.

On November 22, 2011, he visited the clinic and complained of persistent symptoms. In addition, he developed generalized myalgia and exertional dyspnea. On physical examination, he had muscle tenderness, especially marked over his extremities. Laboratory evaluation revealed an elevated CK of 10,140 U/L, serum lactate of 2.37 mmol/L, lactate dehydrogenase of 352 U/L, total bilirubin of 2.8 mg/dL, aspartate aminotransferase of 117 U/L, alanine aminotransferase of 64 U/L, serum sodium of 139 mEq/L, serum potassium of 3.2 mEq/L, serum calcium of 8.8 mg/dL, blood urea nitrogen of 10 mg/dL, serum creatinine of 0.81 mg/dL, and a 24-hour creatinine clearance of 98 mL/min. An arterial blood gas analysis showed a pH of 7.447, pCO_2 of 28.5 mmHg, and serum bicarbonate of 19.2 mmol/L. His urine was yellow in color without hematuria on urinalysis. The diagnoses of rhabdomyolysis and hyperlactatemia were made and raltegravir-related adverse events were highly suspected. He was admitted and given intravenous fluid hydration with 0.9% normal saline. His antiretroviral therapy was switched to abacavir/lamivudine 600/300 mg and atazanavir 400 mg once daily. His clinical symptoms improved gradually. On November 29, 2011, after cessation of raltegravir for 7 days, his CK level declined to 214 U/L, serum lactate decreased to 1.23 mmol/L, and alanine aminotransferase decreased to 51 U/L (Fig. 1). His total bilirubin, aspartate aminotransferase, and lactate dehydrogenase levels normalized and he was discharged under stable conditions. The patient was well at follow-up at the outpatient clinic 1 year later.

Discussion

We report a case of raltegravir-associated rhabdomyolysis with several important features different from the four cases reported to date.[1–4] First, our patient lacked risk factors associated with rhabdomyolysis, including alcohol use, concomitant use of rhabdomyolysis-inducing agents (e.g., tenofovir, statins, amphetamines, antipsychotics, and diuretics), previous antiretroviral-related myopathy, severe underlying liver or renal diseases, or recent rigorous physical activity.[5,6] Previous case reports have had one or more of the above identifiable risk factors, although the mechanisms were not clear. Second, our case had a rapid onset of rhabdomyolysis in only 4 days; the shortest onset reported thus far. Previous cases have had a varying

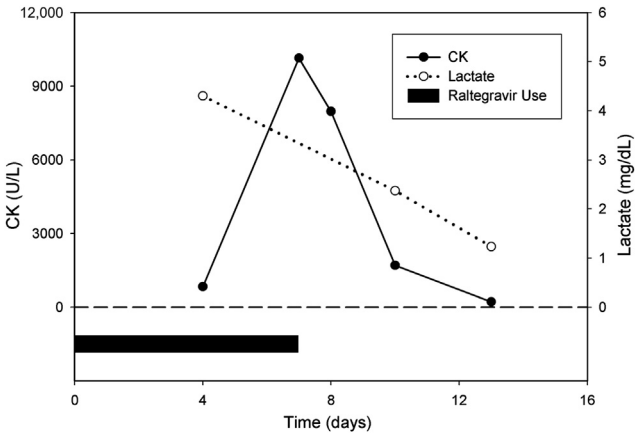

Figure 1. Dynamics of serum creatine kinase (CK) and lactate levels correlating with use of raltegravir.

duration of time to onset after drug exposure, ranging from 10 days to 23 months.

To date, only four cases have been reported with symptomatic rhabdomyolysis associated with raltegravir use, and presented with obvious symptoms including muscle pain and muscle weakness that were reversible after hydration. CK elevations may also occur in up to 8.9% of patients using raltegravir without clinical myopathy, myositis, or rhabdomyolysis, but do not lead to treatment interruption or discontinuation.[7] Therefore, it is recommended that baseline CK level should be checked prior to using raltegravir, and patients starting raltegravir should be monitored for symptoms of rhabdomyolysis.[5]

Several hypotheses have been postulated for the mechanism of raltegravir-induced rhabdomyolysis. One hypothesis suggests that liver function impairment may induce elevation of raltegravir concentration, because raltegravir is metabolized by hepatic glucuronidation via UDP-glucuronosyltransferases (UGT) 1A1. However, the clinical significance of UGT1A1*6/*6 or *28/*28 polymorphisms, associated with reduced UGT1A1 activity and subsequent increases in plasma raltegravir concentrations, remains unclear, and currently, dose adjustment of raltegravir is not required for individuals with the UGT1A1*28/*28 genotype.[8,9] Chronic renal failure is another possible cause reported previously.[1] However, about 50% of the dose of raltegravir is excreted by the feces and only 32% by urine. Hence, current recommendations do not require dose adjustments for age, sex, body mass index, and hepatic and renal function.[6] However, one study has revealed that Asians have a high raltegravir concentration when using a dose of 400 mg once daily,[10] indicating that dose adjustment may be needed for Asians. Measuring the concentration of raltegravir in patients developing rhabdomyolysis may aid further elucidation of the possible mechanisms involved.

The hyperlactatemia presented in this case was most probably associated with use of raltegravir, rather than didanosine, based on the temporality of events. Association of type B hyperlactatemia or lactic acidosis with nucleoside reverse transcriptase inhibitor (NRTI), especially stavudine, didanosine, and zidovudine, due to mitochondrial toxicity has been well documented.[11] However, major toxicity is not expected to occur in patients receiving NRTI therapy for longer than 20 months, and typical symptoms usually develop subacutely over 1—6 weeks. In addition, clinical recovery in patients with severe hyperlactatemia or lactic acidosis, ranged from 4 weeks to 28 weeks after stopping NRTI,[11] owing to the long half-life of the mitochondria (4.5—8 weeks). Our case had been taking didanosine for 4.5 years without any complications, making didanosine less likely to be the cause of hyperlactatemia. The rapid resolution of hyperlactatemia in our case made mitochondrial toxicity a less likely mechanism; this may be explained by either milder clinical severity or different pathophysiological mechanisms. Indeed, our case did not have known risk factors for NRTI-induced hyperlactatemia such as female sex, especially in pregnancy, advanced immunosuppression, chronic muscle or kidney disease, chronic hepatitis B or C virus infection, and combined use of stavudine and didanosine.

In conclusion, this case report demonstrates that raltegravir-associated rhabdomyolysis can have a rapid onset, and may occur in patients without risk factors, underlying diseases, or concomitant use of rhabdomyolysis-inducing agents. Patients starting raltegravir should have their CK levels checked prior to use, be educated about and monitored for symptoms of myositis and rhabdomyolysis, and advised to seek medical evaluation if such symptoms occur.

Conflicts of interest

All contributing authors declare that they have no conflicts of interest related to the material in this article.

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