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Case Report

Rhabdomyolysis in a HIV-infected Patient Following the Addition of Raltegravir, A Case Report with Review of the Literature

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Abstract

Antiretrovirals have traditionally been associated with much toxicity. Newer antiretrovirals are considered much less toxic relative to older antiretrovirals. Upon its FDA-approval in 2009, raltegravir's adverse drug reaction profile was found to be similar to placebo. However, recently there have been reports of increased creatine kinase and rhabdomyolysis following the initiation of raltegravir. We describe a 52-year-old, African-American man who developed rhabdomyolysis after starting raltegravir for HIV. Rhabdomyolysis resolved upon discontinuation of raltegravir. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 6). Although raltegravir is a well-tolerated antiretroviral, clinicians should be aware of the possibility of rhabdomyolysis when prescribing this medication.

Keywords:
raltegravir; rhabdomyolysis; HIV

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Introduction

The advent of highly-active antiretroviral therapy (HAART) has changed the disease course of HIV-infected patients. Mortality from HIV in the United States alone reached a peak in 1995, when 50,000 people died. Following HAART in 1995, mortality significantly decreased and has reached a plateau at approximately 10-15,000 deaths per year in the U.S. [1] With relatively extended patient life-expectancies, HIV is now being treated as a chronic disease, requiring therapy that is more tolerable with less adverse effects and fewer drug interactions. Raltegravir is a relatively newer medication considered to be well-tolerated. Since 2009, raltegravir has been recommended for use as a component of HAART regimens to treat patients with HIV. In the most recent update, The Department of Health and Human Services (DHHS) guidelines state that raltegravir, when used in combination with other antiretrovirals (tenofovir/emtricitabine), is a preferred regimen for treatment-naïve patients [2]. Raltegravir is preferred because drug interactions and adverse effects are limited compared to other antiretrovirals, making it an attractive treatment option for both treatment naïve and experienced patients. However, recent reports of patients developing rhabdomyolysis with kidney damage while taking raltegravir have surfaced, raising concern.

Rhabdomyolysis is characterized by the destruction of skeletal muscle cells. The classic presentation includes myalgias, elevated muscle enzymes, and tea-colored urine. A creatine kinase (CK) level at least 2-3x the upper limit of normal (ULN) is a hallmark feature of rhabdomyolysis. The serum CK may reach levels as high as 100,000 units/liter (L) (normal 44-196 units/L). The presence of myoglobin in the urine is also a factor that would raise suspicion of rhabdomyolysis. These features, in the presence of myalgias and risk factors suggest a diagnosis of rhabdomyolysis. This condition can lead to debilitating weakness and in some cases be life-threatening [3]. An important and dangerous complication of rhabdomyolysis is acute renal failure caused by precipitation of myoglobin in the kidney tubules. [4]

At this time there is limited data regarding the occurrence of CK elevations and rhabdomyolysis related to raltegravir use. The clinical trials conducted to gain Food and Drug Administration (FDA) approval of raltegravir did not report rhabdomyolysis as an adverse effect. There was no report of myopathy, myositis or rhabdomyolysis in these trials of both antiretroviral-naïve and experienced patients in which nearly 750 patients received raltegravir [5], [6]. More recently, a press release by the FDA August 4, 2010 included a warning to use “caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.”[7] This statement was also added to the raltegravir package insert. At this time, the package insert does not recommend routine CK monitoring for patients starting raltegravir. This case report follows a patient that experienced mildly-symptomatic muscle and kidney damage with no predisposing factors other than raltegravir use; evidenced by progressive increases in CK and findings consistent with renal damage upon urinalysis. This case report adds more evidence to the association between raltegravir and the risk of rhabdomyolysis along with a review of current literature. A search was conducted of MEDLINE and EMBASE for case reports detailing rhabdomyolysis or CK elevations suspected to be caused by raltegravir therapy. Search terms included: raltegravir, creatine phosphokinase, rhabdomyolysis, adverse effect.

Case

A 52 year old African American male with HIV, first diagnosed in 1990 experienced progressive CK elevations after beginning raltegravir as part of his HAART regimen. The patient's past medical history included hypothyroidism, psoriasis, schizophrenia, hypertension, history of latent tuberculosis, and history of thrombocytopenia. At the time of the incident, the patient denied any recent trauma or illness. The patient lived alone and worked at a fast food restaurant. His family history was non-contributory. The patient denied use of alcohol and recreational drugs.

The patient's HAART regimen prior to raltegravir initiation included Truvada® (tenofovir/emtricitabine) 300/200 mg daily and Lexiva® (fosamprenavir) 700 mg twice daily boosted with Norvir® (ritonavir) 100 mg twice daily. Other medications included rizatriptan 10 mg as needed for migraine, loratidine 10 mg daily, calcitriol 0.5 mg daily, magnesium oxide 400 mg daily, levothyroxine 225 mcg daily, lisinopril 10 mg daily, aripiprazole 10 mg daily and docusate sodium 100 mg every 12 hours as needed. The patient was also on various topical medications to manage psoriasis including Derma-Smoothe lotion, triamcinolone ointment, ketoconazole cream, fluocinolone solution, ketoconazole shampoo and hydrocortisone cream. There had been no recent changes in the patient's chronic medications. The patient denied the use any over-the-counter medications or dietary supplements.

Raltegravir 400 mg twice daily was added to the patient's initial HAART regimen in order to facilitate a CD4 count increase. At his 2 month office visit, the patient reported mild neuropathy, but stated that it was not bothersome to him and did not affect his quality of life. Neuropathy was not a patient complaint expressed at any other office visits around this time. Three months later, the patient complained of muscle pain and stiffness in his right bicep. This pain was elicited with extension of the arm at the elbow, and the patient stated that he had not been able to fully reach his arm above his head for approximately 1 month. The patient suggested that the muscle pain may have been attributed to lifting heavy objects at his workplace, but was unsure of the cause. A CK level was found to be 522 units/L. As a result of this elevation, the patient's CK was checked at each subsequent office visit. Two months later, the muscle pain had completely resolved, but the CK continued to increase from 205 to 665 to 2450 units/L at 2, 4, and 6 months, respectively. See Table 1.

The patient's baseline serum creatinine (SCr) was 1.37 mg/dL, but rose to 1.64 mg/dL at the time of the CK peak. Urinalysis (UA) revealed 1+ glucose, 2+ protein, and 2+ occult blood at this time. A baseline UA had revealed 2+ protein only. An aldolase level was drawn, and found to be elevated at 12.5 Units/L (normal < 8 Units/L). Other electrolytes and lab values were within normal limits. See Table 1 and Table 2

Table 1. Pertinent Laboratory Values

Month	0	2	3	5	6	8	11	13	14	19	20
CK (U/L)				522	205	665	2450	188			
Aldolase (U/L)							12.5	3.8			
CD4 (cells/uL)	211	205		269		215	261	232		315	253
VL (copies/ml)	<48	56		<48	75	<48	63	<48		<48	<48
AST	26	37	43	37	31	42	58		33	54	42
ALT	19	23	43	22	22	22	28		32	80	31
Alk. Phos.	93	84		101	86	97	80		71	73	87
S.Creatinine	1.37	1.53	1.53	1.66	1.4	1.54	1.64		1.46	1.51	1.52
BUN (mg/dL)		13	12	21	23	15	15		15	15	18

Table 2. Urinalyses (pertinent measurements)

Month	6	9	11	12
Color	Yellow	Yellow	Dark yellow	Yellow
Glucose	Trace	Trace	1+	Trace
Bilirubin	Negative	Negative	Negative	Negative
Ketones	Negative	Negative	Negative	Negative
Protein	2+	1+	2+	2+
Occult blood	Negative	Negative	3+	Negative
Nitrite	Negative	Negative	Negative	Negative
Leuk. Est.	Negative	Negative	Negative	Negative
WBC	Negative	0-5	0-5	0-5
Sq. Eph. Cells	Negative	Negative	Negative	Negative
Bacteria	Negative	Negative	Negative	Negative
Hyaline Cast	Negative	6-10	0-1	Negative

Following the blood draw with a peak CK of 2450 units/L, raltegravir was discontinued. The remaining antiretrovirals in the regimen were continued. Two months following discontinuation of raltegravir, the CK was 188 units/L. The UA returned to baseline and at 3 months following raltegravir discontinuation, the SCr was 1.46 mg/dL.

With the addition of raltegravir, the patient's CD4 count remained steady between 200 and 275, with a peak of 269 at 5 months after raltegravir initiation. The patient's viral load fluctuated throughout the course of raltegravir administration, in general remaining undetectable (<48 copies/ml) with 3 increases into the detectable range at 2, 4, and 11 months after raltegravir initiation. It is unclear what caused the viral load to become detectable at these times. The primarily undetectable level of virus for this patient demonstrates his adherence to his HAART therapy.

Discussion

After ruling out the presence of any other potential etiologies of rhabdomyolysis and the resolution of signs and symptoms following discontinuation of the medication, raltegravir appears to be the most likely cause of rhabdomyolysis in this patient supported by a Naranjo adverse drug reaction score of +6. [8]

To date, there are 5 additional case reports of rhabdomyolysis associated with raltegravir. Zembower et al reported the first case of severe rhabdomyolysis associated with raltegravir in 2008. [9] When this patient was initiated on raltegravir, he was critically ill and also taking multiple other medications. He was taking sulfamethoxazole/trimethoprim, which, based on case reports, has been associated with rhabdomyolysis alone. [10] The patient also suffered from chronic renal failure prior to raltegravir initiation which was worsened by rhabdomyolysis. The patient presented with rhabdomyolysis after being intermittently treated with raltegravir for 5 months, but had been off of raltegravir for 1 week prior. The patient was managed with intravenous hydration until his symptoms resolved. The patient's CK peaked at approximately 16,000 units/L and decreased after discontinuation of raltegravir, but remained above normal for more than 10 weeks.

The second case report of rhabdomyolysis is presented by Dori et al in 2009. The patient was an Italian man who experienced rhabdomyolysis after 2 months of raltegravir therapy. The patient started raltegravir shortly after the addition of pravastatin, another drug that has been associated with

rhabdomyolysis. In addition to pravastatin therapy, the patient was started on a regular exercise regimen at the same time raltegravir was started. This patient began to experience symptoms of rhabdomyolysis 2 months after initiation of raltegravir. The CK peaked at approximately 6,000 units/L. The patient was advised to discontinue raltegravir and received no other management. Two days after discontinuation the patient's CK level was declining. Within 1 month, CK, liver function tests and myoglobin returned to normal range. [11]

Masia et al reports the third case of severe renal failure and rhabdomyolysis associated with raltegravir use. The only predisposing factor the patient may have had for rhabdomyolysis was a history of intravenous drug use, but his drug test came back negative for cocaine, opiates, methadone, barbiturates, phencyclidine, cannabis, amphetamines and methamphetamine. This patient was taking raltegravir for almost 2 years before presenting with acute renal failure and rhabdomyolysis, including a CK which peaked at nearly 9,000 units/L. The patient's HAART was discontinued and the patient received hemodialysis. CK levels normalized within 1 week of raltegravir discontinuation and serum creatinine decreased to normal within 1 month. [12]

The fourth case of rhabdomyolysis associated with raltegravir was reported by Croce and colleagues. An antiretroviral-experienced patient co-infected with hepatitis C initiated a regimen containing raltegravir. Ten days later, the patient was admitted with muscle pain, weakness, and an elevated CK of 960 units/L. On day 3 of hospitalization, all medications were discontinued and aggressive hydration was initiated. On day 4, the CK peaked at 1300 units/L and the patient's severe muscle pain confined her to bed. Following this peak, the patient improved clinically and CK decreased. The patient was discharged on day 11 at which time CK was below 100 units/L. Of note, 1 month prior to admission, this patient experienced an asymptomatic elevation in CK of 4171 units/L after 2 years of taking a regimen of zidovudine and tenofovir/emtricitabine. The CK returned to normal following discontinuation of this regimen, but was slightly above normal at the time of the initiation of the raltegravir containing regimen. [13]

Recently, Tsai and colleagues published the fifth and most recent report of raltegravir-induced rhabdomyolysis. An antiretroviral-experienced patient presented to the emergency department with palpitations, nausea, dizziness, and generalized numbness 4 days after beginning a raltegravir-based regimen. The other medications of didanosine and lamivudine were continued from his past regimen. Laboratory data revealed a CK of 830 units/L and serum lactate of 4.3 mmol/L. The patient was continued on the same regimen, but the symptoms persisted in addition to generalized myalgia and exertional dyspnea, and muscle tenderness. His CK increased to 10,140 units/L and lactate decreased to 2.37 mmol/L on the eighth day. At this point, the patient received intravenous fluids and raltegravir was discontinued. Seven days following discontinuation, the CK was 214 units/L, serum lactate was 1.23 mmol/L, and his symptoms improved gradually. This patient had no predisposing factors to rhabdomyolysis. [14]

These previously published 5 case reports suggest an association between raltegravir and rhabdomyolysis, although none provided a Naranjo score. Three of these 5 patients had other risk factors associated with developing rhabdomyolysis. The third and fifth cases seemed to have no risk factors other than raltegravir use. The patient presented in the current case had no risk factors associated with rhabdomyolysis other than raltegravir use. He had mild renal impairment, which may have worsened his condition. Like the patient presented by Masia, this patient had been on raltegravir for over a year before experiencing symptoms that required raltegravir to be discontinued. [12]

To evaluate CK elevation (defined at least twice the upper limit of normal or symptomatic) alone in patients taking raltegravir, Monteiro and colleagues performed a retrospective cohort of 475 patients at Hospital Clinic Barcelona. Forty-eight patients (10.1%) developed grade 1/mild CK elevation defined as 2-2.9 times the upper limit of normal, while 45 patients (9.5%) developed grades 2 and 3/moderate CK elevations defined as 3-4.9 and 5-9.9 times the upper limit of normal, respectively. Five patients (1%) developed grade 4 or clinically significant CK elevation. There were no cases of rhabdomyolysis and no medication discontinuations secondary to elevated CK. The median time to increased CK was 5.9 months. Seven patients (1.5%) became symptomatic at a median of 7.8 months. Of these patients, 3 patients had grade 1 CK elevation, while the other 4 patients experienced grade 2 CK elevation [15]

In another recently published study, Lee and colleagues performed a cross sectional prospective prevalence study to determine the prevalence of the composite endpoint of skeletal muscle toxicity (isolated increase in CK, myalgias, proximal myopathy on exam, or rhabdomyolysis) associated with raltegravir. There were 159 patients each in the study and control arms. There were significantly more patients with skeletal muscle toxicity in the raltegravir arm compared to the control arm, 37% and 19%, respectively, ($p<0.001$). An evaluation of each of the 4 components of the composite endpoint showed no difference in the prevalence of rhabdomyolysis or CK elevation between groups, but did show a difference in the prevalence of myalgia and proximal myopathy. [16]

Although no cases of rhabdomyolysis were found in these studies, there remains case reports associated with the use of raltegravir. This is the sixth case of rhabdomyolysis and suspected renal damage associated with raltegravir. Unlike the previously presented cases, this patient did not have any predisposing factors and was not receiving any other medication that could have caused his condition. The time-course for the patient's CK elevation and renal damage suggest raltegravir as the cause. In addition, the patient's CK decreased significantly after just one week of raltegravir discontinuation. Based on this report and other published case reports, it may be prudent to add routine CK monitoring to quarterly labs for patients taking raltegravir, especially for patients with preexisting risk factors for rhabdomyolysis. Routine monitoring of CK will allow raltegravir to remain a preferred treatment of HIV by catching a potential adverse effect early, as was done in this patient.

Conclusion

Raltegravir has become a trusted treatment in the battle against HIV in the last few years. Its limited side effect profile makes it a treatment of first choice for many patients. However, the recent cases of rhabdomyolysis associated with raltegravir are alarming. The aggressive time course of CK elevation reported in 4 out of the 5 published cases suggests that baseline and routine CK monitoring should be considered for patients on raltegravir, regardless of whether or not concomitant risk factors for rhabdomyolysis are present. Patients beginning raltegravir should be educated to report any muscle pains to their physician at which time CK should be checked.

Competing Interests

The authors have no disclosures or conflicts of interest to report.

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