

Sustained Increase of Serum Creatine Phosphokinase Levels and Progressive Muscle Abnormalities Associated with Raltegravir Use during a 32-week Follow-up in an HIV-1 Experienced Patient on Simplified HAART Regimen, Intolerant to Protease Inhibitors and Abacavir: A Case Report

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ABSTRACT

Sustained increase of serum creatine phosphokinase (CPK) concentrations and muscle abnormalities have been reported in patients taking raltegravir (RAL). In this report, we describe a case of sustained and asymptomatic increase of serum CPK concentrations associated with raltegravir, zidovudine, and lamivudine in an HIV-1 experienced patient with intolerance to protease inhibitor, abacavir and penicillin during 32 weeks of continuous drug monitoring.

Keywords: Creatine phosphokinase, HIV-1, muscle abnormalities, raltegravir, side effects

Aumento Sostenido de los Niveles de Creatina Fosfoquinasa Sérica y las Anormalidades Musculares Progresivas Asociadas con el Uso de Raltegravir durante un Seguimiento de 32 Semanas en un Paciente de VIH-1 Experimentado en Régimen de Terapia TAAA Simplificada, con Intolerancia a los Inhibidores de Proteasa y Abacavir: Un Reporte de Caso

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RESUMEN

Un aumento sostenido de las concentraciones de creatina fosfoquinasa sérica (CPK) y las anormalidades musculares ha sido reportado en relación con pacientes que toman raltegravir (RAL). En este reporte, describimos un caso de aumento sostenido y asintomático de concentraciones séricas de CPK asociadas con raltegravir, zidovudina y lamivudina en un paciente experimentado de VIH-1 con intolerancia al inhibidor de la proteasa, al abacavir y la penicilina durante 32 semanas de monitoreo farmacológico continuo.

Palabras claves: Creatina fosfoquinasa, VIH-1, anormalidades musculares, raltegravir, efectos secundarios

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BACKGROUND

In the combined antiretroviral era, frequency and features of skeletal muscle abnormalities have been reported, related to mitochondrial damage probably associated with nucleoside

analogue use, and potentially also responsible for lactic acidosis, intracellular fat accumulation and phosphocreatine depletion.

Raltegravir, the first integrase inhibitor licensed in more than 70 countries for use in HIV-1 patients, represents an innovative choice in antiretroviral therapy (1). Despite the good tolerance and safety of raltegravir given at doses that effectively suppress HIV-1 replication, sustained increase of serum creatine phosphokinase (CPK) concentrations and muscle abnormalities have been incidentally reported (2).

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The mechanism and the causative role of raltegravir induced abnormal concentration of CPK, the correlation to the antiretroviral drugs associated and their duration of use, metabolic abnormalities, and all postulated pathogenetic pathways leading to muscle damage, are not known.

Here, we sought to describe the sustained and asymptomatic increase of serum CPK concentrations possibly related to the addition of raltegravir in a patient undergoing zidovudine and lamivudine antiretroviral therapy.

CASE REPORT

A 45-year old Caucasian male with a history of intravenous drug abuse was diagnosed with HIV-1 infection in October 1991. He had been hepatitis C virus (HCV) positive since 1990 (genotype 1A). There were no other sexually transmitted diseases (STDs). He was clinically asymptomatic and did not take any antiretroviral drug from February 1991 until February 2005. The patient had no history of past HIV-related symptoms and the CD4+ cell count nadir was 296/mm³ (January 2005 – CDC stage A2).

In 2003, before starting antiretroviral therapy, he was treated with peginterferon alfa 2β plus ribavirine for 48 weeks with a sustained virological response. Antiretroviral therapy was started in February 2005 [first regimen: tenofovir (TDF) + lamivudine (3TC) + efavirenz (EFV)]. The patient experienced numerous changes to antiviral therapy motivated by the low compliance, partial viro-immunological efficacy and side effects (nausea, headache, diarrhoea) probably due to protease inhibitors (PIs). He was intolerant to abacavir and many PIs (ritonavir, atazanavir, fosamprenavir, darunavir). Furthermore, at Trofile test, the patient did not show a preferential usage of CCR5. These latter limitations drove the therapeutic choice toward raltegravir.

In August 2008, a combination of highly active antiretroviral therapy (HAART) regimen based on zidovudine, lamivudine and raltegravir was started.

After 15 months of follow-up, the treatment was effective in raising CD4 count to 373/mm³ (baseline 219/mm³) and decreasing viral load to undetectable levels. Before starting this new regimen of HAART, creatine phosphokinase levels were in the upper normal range (442 IU/l, vn < 170 IU/l, ACTG grade 1 toxicity) and the patient had no signs and symptoms of hepatotoxicity and the clinical conditions were stable (no hepatomegaly, nausea, anorexia, asthenia). Subse-

quent samples demonstrated a rapid increase of CPK levels (October 2008, 699 IU/ml; January 2009, 705 IU/ml and April 2009, 846 IU/ml).

Blood samples (5 ml) for raltegravir plasma concentrations (C_{trough}) were collected before administering the morning drug dose. All samples were obtained between 8:00 and 10:00 am. Plasma samples were separated and submitted to heat treatment (56 °C for 45 minutes) to inactivate HIV, and then frozen at -20 °C until analysis. Raltegravir concentrations were determined using a modification of a validated high-performance liquid chromatography method with fluorescence detection. After eight months of therapy (April 2009), raltegravir concentration was as high as 450 ug/ml while CPK serum levels were greater than five times the normal range.

Further CPK increase was observed in July 2009 (CPK 1543 IU/l corresponding to ACTG grade 4 toxicity). To exclude a lactic acidosis due to HAART, a control of lactaemia was performed and it was normal. Despite the dramatic increase of CPK serum level, signs and symptoms of muscle abnormalities appeared only in July 2009 when the patient experienced muscle pain, weakness and difficulty walking.

Antiretroviral treatment was discontinued and a new regimen based on zidovudine, lamivudine and tenofovir was introduced. Discontinuation of raltegravir resulted in improvement of the clinical condition with regression of signs and symptoms of skeletal muscle abnormalities. Creatine phosphokinase values declined to 623 IU/l (February 2010) [Table].

DISCUSSION

Toxicity is a frequent drug-related complication in patients receiving antiretroviral treatment, and may commonly lead to interruption of treatment and hospital admission. Nucleoside reverse-transcriptase inhibitors (NRTIs) have been associated with functional and structural mitochondrial abnormalities, mild-to-moderate asymptomatic increase of serum levels of CPK and hyperlactaemia.

The risk of myopathy, rhabdomyolysis and muscle problems with muscle damage probably associated with integrase inhibitors has been incidentally reported. Recently, a case of severe rhabdomyolysis, associated with the new integrase inhibitor use, has been described (3). Skeletal muscle abnormalities (muscle pain, weakness and difficulty

Table: Virological, immunological and biochemical parameters of the patient considered during raltegravir treatment*

	May-08	Aug-08	Oct-08	Jan-09	Apr-09	Jul-09	Sept-09	Oct-09	Nov-09	Feb-10
CD4+/mmc	427	219	383	418	379	481	374	ND	373	393
VL (c/ml)	< 50	4613	< 50	93	96	298	83	ND	< 50	< 50
CPK (U/l)	596	442	699	705	846	1543	733	847	675	623

* HAART including raltegravir (plus AZT/3TC) was started on Aug-08 to Oct-09.

walking) under antiretroviral treatment are increased in the presence of raltegravir administration (4).

The clinical history of our patient clearly indicated the presence of hepatic intolerance to protease inhibitors, with episodes of severe toxicity that promptly reversed following discontinuation of treatment (5). Such episodes occurred during treatment with several protease inhibitors, such as indinavir and saquinavir, leaving no further therapeutic options in this class. In this patient, use of raltegravir led to an undetectable viral load and high CD4 levels, a good tolerance and optimal compliance with no subsequent flares of hepatic toxicity, and no other relevant side effects during the first months of therapy. The most significant adverse effect occurred during raltegravir therapy, when an increased serum level of CPK (grade 4 ACTG) was observed, without signs or symptoms of skeletal muscle damages. After the fifth month of therapy, laboratory examination revealed a dramatic increase of CPK to 1543 IU/l and muscle abnormalities were also reported (muscle pain and weakness). After interrupting raltegravir, the patient did not show any symptom of muscle damage.

Although CPK increase is mainly caused by NRTIs, the addition of raltegravir in our patient yielded a further increase of this enzyme. This finding would suggest that caution should be made in introducing this integrase inhibitor in patients already showing toxic antiretroviral effect. To our knowledge, the mechanism by which raltegravir induced myopathy, rhabdomyolysis and muscle damage is unknown.

Creatine phosphokinase levels should be determined in patients presenting with persistent myalgia during integrase inhibitor therapy. In our patient, the first signs of muscle damage occurred when the serum CPK levels and RAL plasma concentration had both reached high values, whereas

no symptom was observed during the 12 months of its gradual increase.

Medical providers should always be aware of the possible onset of muscle disorders in patients taking raltegravir and should accurately monitor CPK levels. When an increase in serum levels of CPK occurs in asymptomatic patients, a possible causal relationship with antiviral or concomitant drugs should be investigated (6). Nevertheless, the lack of guidelines for establishing specific intervention criteria in such circumstances may raise uncertainty on the most appropriate course of action, currently based on subjective assessment of the physician.

Further studies need to be carried out to detect adverse events associated with integrase inhibitors.

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