Creatine kinase elevation in HIV-1-infected patients receiving raltegravir-containing antiretroviral therapy: a cohort study

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Objectives: To evaluate the incidence and risk factors for significant creatine kinase elevation in HIV-1-infected patients who were prescribed a raltegravir-containing antiretroviral therapy.

Design: A retrospective analysis of a prospectively collected cohort involving all consecutive patients who were prescribed a raltegravir-containing antiretroviral regimen between June 2005 and December 2010.

Methods: Significant creatine kinase elevation was defined as an elevation of at least 3-fold from the upper limit of normal (ULN) (grade 2, WHO classification) while receiving raltegravir. Blood analysis at each visit included at least creatine kinase, as well as plasma HIV-1 RNA and CD4 cell count.

Results: There were 475 patients who had been exposed to raltegravir for a median of 11.5 (IQR 8.2–15.2) months. An increase of creatine kinase $\geq 3$-fold ULN was detected in 53 (11.2%) patients, representing an incidence of 3.8/100 person-years. Symptoms were reported by seven patients (1.5%), they showed either grade 1 ($n=3$) or 2 ($n=4$) creatine kinase increases. The median duration of raltegravir therapy before creatine kinase elevation was 5.9 (IQR 3.3–9.3) months. Evidence of creatine kinase elevation prior to raltegravir therapy [hazard ratio (HR) 3.30; 95% CI 1.59–6.86; $P=0.001$], abnormal baseline creatine kinase (HR 3.24; 95% CI 1.63–6.45; $P=0.001$) and male gender (HR 4.17; 95% CI 1.33–1.27; $P=0.001$) were identified as independent risk factors for creatine kinase elevation during raltegravir treatment.

Conclusions: Although $\approx 1$ in 10 patients on raltegravir therapy developed significant creatine kinase elevation as defined in this study, symptoms were uncommon, not severe and occurred in patients with easily identifiable risk factors.

Keywords: HIV, creatine kinase elevation, raltegravir, antiretroviral therapy, adverse effects

Introduction

Musculoskeletal manifestations are well-recognized complications of HIV itself (polymyositis) and also of treatment with some antiretroviral agents, such as zidovudine. Nowadays manifestations of AIDS are uncommon and zidovudine is no longer preferentially recommended, with polymyositis and zidovudine-induced creatine kinase (CK) elevations being now rarely reported.$^1$

The first drug of a new class of antiretrovirals that targets the integrase enzyme, raltegravir, has been involved in cases of myotoxicity. It was approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) in 2007. At that time, among the reported laboratory abnormalities were transient elevations in serum CK that did not require drug interruption.$^2$ During the post-marketing surveillance, at least four cases of rhabdomyolysis have been published.$^3$–$^6$

Currently, raltegravir is indicated in combination with other drugs for treatment-naïve and treatment-experienced patients in cases of virological or immunological failures, or in simplification of treatment.$^7$–$^9$ It has the advantage of being generally well tolerated and having few drug–drug interactions.$^{10}$–$^{12}$ Although a causal relationship with raltegravir has not been clearly established, the FDA, the EMA and the manufacturer recommend using raltegravir with caution in individuals at increased risk of myopathies [Isentress (raltegravir) package insert; Merck & Co., Inc., Whitehouse Station, New Jersey, 2007].

Grade 3/4 CK elevations have been reported in clinical trials, but there may be lower-grade CK elevations, whose incidence, clinical repercussions and risk factors are currently unclear.$^1$$^3$ To gain further insight into the potential for raltegravir-associated CK elevation in clinical practice, we evaluated the incidence and risk factors for CK elevation in HIV-1-infected patients...
patients who were prescribed a raltegravir-containing antiretroviral therapy (ART).

Methods

Study population

We conducted a retrospective analysis of the HIV cohort at Hospital Clinic Barcelona (Spain). This cohort has been previously described. All HIV-1-infected adults who initiated a raltegravir-containing antiretroviral regimen from June 2005 to December 2010 in the setting of routine clinical practice were eligible for the study. Data on clinical and analytical variables were prospectively collected in a database. Other risk factors for CK elevation, including evidence of CK elevation prior to raltegravir therapy or rhabdomyolysis, alcohol or illicit drug consumption, or use of any therapeutic drug potentially related with myotoxicity such as zidovudine and statins, were all assessed by review of medical records, as this information is actively collected in the clinical database. Blood analysis at each visit included CK, plasma HIV-1 RNA, CD4 cell count, as well as other chemistry and cell analyses.

Patients were followed from the initiation of the raltegravir-containing regimen until the censoring date (31 May 2011). Other censoring reasons were death, loss to follow-up and withdrawal of raltegravir for any reason. The HIV cohort database as well as this retrospective study were approved by the local research Ethics Committee.

Outcome

Considering that raltegravir Phase III studies (protocols 018 and 019) used high thresholds of CK to define abnormalities (greater than six times the upper limit of normal [ULN]), we set lower limits in order to increase the sensitivity and avoid individuals with milder abnormalities being excluded. For this purpose we relied on the WHO recommendations for the classification of acute and subacute toxic effects. CK elevations were graduated as grade 1 or mild (2.0–2.9 × ULN), grade 2 and 3 or moderate (3.0–4.9 × ULN and 5–9.9 × ULN, respectively) and grade 4 or clinically significant (≥10 × ULN). Significant CK elevation was defined whenever there was an increase of at least 3-fold in CK from the ULN during raltegravir therapy or when it was symptomatic. Nevertheless, CK elevation less than three times the ULN were further considered in order to characterize the incidence and the clinical impact of low-grade abnormalities. CK elevations of any grade in at least one consecutive visit were also analysed to characterize the incidence of persistent abnormalities. CK elevation was defined as symptomatic when it was accompanied by the presence of any unexplained muscular complaint (muscle pain, muscle tenderness, proximal muscle weakness, or muscle cramps) during raltegravir treatment.

Statistical analysis

Variables are expressed as mean and standard deviation, median and IQR, or proportions, as appropriate. CK elevation incidence analysis was performed considering the date of starting raltegravir and the incidence curve was estimated using the Kaplan–Meier product-limit method. The potential baseline factors associated with CK elevation were assessed using the generalized log-rank test (univariate Cox model analysis). Factors associated with a P value <0.10 in the univariate analysis were considered as candidate factors for the multivariate analysis (baseline CK, prior history of CK elevation, male gender). We used forward stepwise and backward elimination subset selection methods to identify variables that predicted survival. The hazard ratio (HR) and the associated 95% CI for each predictor were calculated. Statistical significance was defined as a bilateral P value <0.05. All statistical analyses were carried out using SPSS (release 15).

Results

Population characteristics

In this study 475 patients (75% males) had a raltegravir-containing ART initiated, with a mean (±SD) age of 46 (±9) years. Two subjects with missing information were excluded. Four-hundred-and-thirty-five (91.6%) patients had already received ART for a median period of 116 months (IQR 56.5–170.3 months) before starting raltegravir. The median duration of raltegravir-containing regimens was 11.5 months (IQR 8.1–15.2 months). The median CD4 cell count was 374 cells/mm³ (IQR 234–570 cells/mm³) and the median HIV RNA was 1.87 log₁₀ copies/mL (IQR 1.69–4.07 log₁₀ copies/mL). Blood analyses were scheduled as part of routine clinical care every 3–6 months.

Grade 1 CK elevations were seen in 48 patients (10.1%), and grade 2 or 3 CK elevations were seen in 45 patients (9.5%). Figure 1 shows the study population according to CK grade elevations. CK elevations as defined in this study developed in 53 patients (11.2%), representing an incidence of 3.8/100 person-years. The characteristics of participants are shown in Table 1. The median duration of therapy before CK elevations became apparent was 5.9 months (IQR 3.3–9.3 months). Of all cases of any CK elevations 123 (25.9%) persisted in at least one consecutive visit. Grade 4 toxicity was observed in only five patients (1.0%), and there were no cases of rhabdomyolysis. There was no need to discontinue raltegravir due to CK elevations in any patient. Kaplan–Meier estimates of the incidence of a 3-fold increase in CK are shown in Figure 2.

Symptoms were reported by seven patients—1.5% of the cohort representing 13% of patients with CK elevations. In these patients the CK increase was grade 1 in three and grade 2 in the remaining four. Clinical symptoms developed a median period of 7.8 months after starting raltegravir (IQR 6.5–22.5 months). The symptoms reported were muscle pain and/or contractures. None of the patients was taking statins concomitantly; one patient reported use of alcohol and two were on regimens with zidovudine, even though it had been prescribed for more than 1 year. None of these symptomatic patients had previously experienced similar symptoms or had muscle enzymes increased with ART prior to raltegravir initiation.

Risk factors for CK elevation

After adjustment in the multivariate model, abnormal baseline CK (CK ≥2 × ULN when starting raltegravir; HR 3.24; 95% CI 1.63–6.45; P = 0.001), evidence of CK elevation prior to raltegravir therapy (HR 3.30; 95% CI 1.59–6.86; P = 0.001) and male gender (HR 4.09; 95% CI 1.26–13.33) were associated with a higher risk of CK elevation.

Discussion

The frequency of CK elevations in clinical trials varies according to the definition of abnormality and the characteristics of the patients included in the study. In the Phase II trial protocol 005, with multiresistant virus-infected patients, the incidence of CK >10 × ULN was similar between raltegravir and placebo (6% versus 4%). On the other hand, in the BENCHMRK Phase III trial, also with treatment-experienced patients, CK
≥20×ULN was more common in the raltegravir group than in the placebo group (3% versus 0.8%). In the 96 week protocol 004, with treatment-naive patients, 6.3% in the raltegravir arm experienced CK ≥10×ULN versus 2.6% of patients in the efavirenz arm. Other prospective studies have described a frequency of grade 3/4 CK elevations between 5% and 13%, and most of the cases had no clinical repercussions.

The frequency of significant CK elevation with raltegravir-containing regimens as defined in this study was 11.2%, with an incidence of 3.8/100 person-years. This incidence is higher than that observed in Phase II and III trials, a finding already expected since we used lower limits for detecting laboratory abnormalities. A recent study by the Italian SCOLTA cohort analysed CK elevation in patients receiving raltegravir- or darunavir-based therapy. They reported CK elevations >200 U/L in 8.9% of patients treated with raltegravir, thus including what we consider grade 1 CK elevation; adding this to the incidence observed for grade 2–4 in this study the incidence is also higher (20.6%).

Among those who met the definition of CK elevations in our study, 64.2% had grade 2 CK elevations (3.0–4.9×ULN) and...
A potential limitation of our study is the lack of a control group. However, data from clinical trials have shown that the incidence of CK elevations was higher in patients receiving raltegravir-containing regimens. We also have to acknowledge that the physical activity of the patients was not routinely recorded in their clinical charts, so we cannot exclude a potential effect of strenuous physical exercise on muscular enzymes. What we aimed to do in our study was to analyse the impact and clinical repercussions of a CK increase in a cohort of patients receiving raltegravir-based ART in the setting of routine clinical practice. Although the risk of developing rhabdomyolysis in persons treated with raltegravir-containing antiretroviral regimens must be considered in prescribing therapy for HIV-1-infected patients, our data suggest that the risk of CK elevation in patients initiating raltegravir-containing regimens is low and not severe. As shown in this study, routine laboratory monitoring of CK might be of little value since the majority of subjects had mild CK elevations with no clinical complaints.

In summary, an increase of at least 3-fold in CK in a cohort of patients starting raltegravir-containing ART was not unusual, but clinical symptoms were uncommon and not severe. Evidence of CK elevation prior to raltegravir therapy and abnormal baseline CK might be helpful to identify those patients at higher risk. The results of this study do not support a monitoring approach different from that considered for other ART regimens to prevent severe adverse muscular reactions.

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### Transparency declarations
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### Author contributions
P. M. participated in the study design, in the acquisition of data and drafted the manuscript. I. P. performed the statistical analysis. E. M. conceived the study and its design, drafted the manuscript and revised the manuscript. P. M., I. P., J. P., J. M. G. and E. M. were involved in the interpretation of data. All authors read and approved the final manuscript.

### References

Figure 2. Kaplan–Meier time to 3-fold increase in CK levels from starting raltegravir.

30.2% grade 3/4 CK elevations (>5.0 × ULN) with no clinical repercussions at all. The cases of symptomatic CK elevations were very few and the intensity of symptoms was not related to CK increase. Moreover, there were other possible underlying factors (alcohol consumption and zidovudine use) that may have played a part in symptomatic patients. Madeddu et al. also found no relation between CK increase and muscle pain or weakness.26,27

We did not find any reports of rhabdomyolysis and only a minority (1.0%) of patients presented with a CK >10 × ULN. The Phase III STARTMRK trial reported only one case of severe CK elevation who recovered without discontinuing therapy.22 Since raltegravir was approved by the FDA in 2007, four cases of rhabdomyolysis have been reported to be associated with raltegravir-containing regimens. Causation could not be established in any of them since all the patients also had potential risk factors for CK elevations in addition of raltegravir: renal chronic dysfunction plus use of fosfocarnet, use of pravastatin and previous CK abnormality.23–26

Since raltegravir and statins share glucuronidation as a common metabolic pathway, there is a potential risk for drug–drug interaction.28 In this study, 17.3% of patients were receiving raltegravir concomitantly with statins, but this fact was not identified as an independent risk factor in multivariate analysis. In accordance with this, a cross-over study in 24 healthy subjects determined the effect of raltegravir on pravastatin pharmacokinetics, and vice versa; although participants were followed for a very short time, there were no CK elevations or any other types of myopathy.29

Because it occurs so rarely, especially clinically significant CK elevations, little is known about the pathogenic mechanisms of raltegravir-associated CK elevation. In this study, evidence of CK elevation prior to raltegravir therapy and baseline CK ≥2 × ULN were independent risk factors for CK elevation during raltegravir treatment. This finding raises the suspicion of a possible individual predisposition involved in the pathogenesis of muscular toxicity associated with raltegravir.

In the absence of a control group, we cannot deny a possible association between raltegravir and CK elevation. It is not clear if CK elevation is related to muscular toxicity associated with raltegravir, or some other reason. The cases of symptomatic CK elevations were very few and the intensity of symptoms was not related to CK increase. Moreover, there were other possible underlying factors (alcohol consumption and zidovudine use) that may have played a part in symptomatic patients. Madeddu et al. also found no relation between CK increase and muscle pain or weakness.26,27

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16 Martinez E, Milinkovic A, Biura E et al. Incidence and causes of death in HIV-infected persons receiving highly active antiretroviral therapy compared with estimates for the general population of similar age and from the same geographical area. HIV Med 2007; 8: 251–8.


