Hepatic safety profile of raltegravir in HIV-infected patients with chronic hepatitis C

Eugenia Vispo1, Alvaro Mena1, Ivana Maida1, Francisco Blanco1, Mateo Cordoba1, Pablo Labarga1, Sonia Rodriguez-Novoa2, Elena Álvarez2, Inmaculada Jimenez-Nacher2 and Vincent Soriano1*

1Infectious Diseases Department, Hospital Carlos III, Madrid, Spain; 2Pharmacy Department, Hospital Carlos III, Madrid, Spain

*Corresponding author. Tel: +34-91-4532500; Fax: +34-91-7336614; E-mail: vsoriano@dragonet.es

Received 25 August 2009; returned 2 November 2009; revised 2 November 2009; accepted 17 November 2009

Background: Patients with chronic hepatitis C virus (HCV) infection experience antiretroviral-associated liver toxicity more frequently than HIV mono-infected persons. Herein, we report the hepatic safety profile of raltegravir in a relatively large group of HIV/HCV co-infected patients, a population that was poorly represented in the registrational studies.

Methods: Prospective, observational study of all antiretroviral-experienced HIV-infected patients who initiated raltegravir from January 2006 to January 2009 at a reference HIV clinic. Clinical data, laboratory parameters and liver stiffness measured at baseline, week 4 and every 3 months thereafter were collected. Chronic hepatitis C was defined as positive serum HCV-RNA. Grade 1–4 hepatotoxicity was defined following the AIDS Clinical Trials Group definition for liver enzyme elevations (LEEs). A control group of patients who initiated protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) was examined similarly.

Results: Data from 218 HIV-infected patients on raltegravir were analysed, 126 HIV mono-infected and 92 HIV/HCV co-infected patients. Any degree of LEEs occurred in 10 (7.9%) HIV mono-infected and 23 (25%) co-infected patients (relative risk 3.1; 95% confidence interval 2.9–3.4; P = 0.002). Severe hepatotoxicity (grade 3–4), however, was only seen in 3 (1.4%) patients, all co-infected with HCV. It occurred at months 1, 15 and 15, respectively. In all three subjects other reasons than raltegravir exposure most likely explained LEEs. Multivariate analysis revealed HCV co-infection as the only independent variable associated with any degree of hepatotoxicity on raltegravir (P = 0.03). Finally, the rate of LEEs in patients on raltegravir was lower than in those who were treated with PIs or NNRTIs.

Conclusions: LEEs are less frequent in patients treated with raltegravir than with other antiretroviral drug classes. However, HIV/HCV co-infected patients treated with raltegravir experienced LEEs more frequently than HIV mono-infected persons. In this series, LEEs in patients treated with raltegravir were uniformly mild and no cases of grade 3–4 hepatotoxicity could be directly attributed to the drug. These results reinforce the overall hepatic safety profile of raltegravir.

Keywords: antiretroviral therapy, liver, hepatotoxicity

Introduction

Raltegravir is the first inhibitor of the HIV integrase approved for clinical use. The enzyme is responsible for the transfer of virally encoded DNA into the host chromosome. Raltegravir was initially approved for the treatment of HIV-infected patients failing other antiretroviral regimens and harbouring multidrug-resistant HIV variants. More recently, the drug has also been approved as first-line therapy. The registrational trials that supported the first approval of raltegravir are the BENCHMRK 1 and 2 studies.1,2 In these trials, the safety and efficacy of raltegravir versus placebo along with an optimized background regimen was assessed, and raltegravir outperformed the control arm. Interestingly, premature raltegravir discontinuations due to adverse events occurred in only 1.5% of patients while it was 2.5% in the placebo arm. The hepatic safety profile of raltegravir was good, with only 4.3% of treated patients experiencing grade 3–4 hepatotoxicity, compared with 3.4% in the placebo group. However, HIV+ patients with chronic hepatitis C were minimally represented in these studies and subjects with serum amino-transferases at >5-fold the upper limit of normality (ULN) were uniformly excluded.
Chronic hepatitis C virus (HCV) infection affects overall nearly one-quarter of the HIV-infected population worldwide. For almost all antiretroviral drugs, the rate of liver enzyme elevations (LEEs) is uniformly greater in HIV-infected patients with underlying chronic hepatitis C compared with the rest. Therefore, there is a need to evaluate the hepatic safety profile of raltegravir in HIV-infected patients with chronic hepatitis C.

Patients and methods
A prospective, observational study of the hepatic safety profile of raltegravir was initiated in January 2006 at a reference HIV clinic in Madrid, after the beginning of the expanded access programme for raltegravir in Spain. The study was extended following the approval of raltegravir, and enrolment of patients ended in January 2009. Clinical data and laboratory parameters were recorded at baseline, week 4 and every 3 months thereafter. The study received approval by the hospital Ethics Committee and written informed consent was obtained from all participants in the study. Chronic hepatitis C was defined based on the demonstration of positive serum HCV-RNA using a commercial real-time PCR assay (Taqman, Roche, Basel, Switzerland), which has a lower limit of detection of 10 IU/mL.

Estimates of liver fibrosis in chronic hepatitis C patients were measured at baseline and every 6 months using FibroScan® (Echosens, Paris, France). This method assesses hepatic stiffness and results are given as kilopascal units (kPa). There is a good correlation between liver fibrosis staging in liver biopsy and hepatic stiffness using FibroScan®. Since liver fibrosis is the major determinant of the severity of chronic hepatitis C, its longitudinal assessment may permit cofactors to be identified, including potentially hepatotoxic drugs, acting as accelerators of liver fibrosis progression.

Standard laboratory testing included complete blood cell count, serum biochemistry, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, CD4 count and plasma HIV-RNA. The change in serum ALT and AST from pre-treatment with raltegravir to the highest level during treatment was categorized using a standardized toxicity grade scale previously reported, which slightly modifies the AIDS Clinical Trials Group criteria. In more detail, patients with pre-treatment serum AST and ALT values within normal range (≤30 U/L) were classified as having hepatotoxicity based on changes relative to the UNL: grade 1, 1.25–2.5 UNL; grade 2, 2.6–5 UNL; grade 3, 5.1–10 UNL; and grade 4, >10 UNL. To avoid selection bias favouring inclusion of persons with chronic hepatitis C, patients with elevated raltegravir pre-treatment serum AST and/or ALT values (higher than the UNL) were classified based on changes relative to baseline values rather than UNL: grade 1, 1.25–2.5 baseline; grade 2, 2.6–3.5 baseline; grade 3, 3.6–5 baseline; and grade 4, >5 baseline. If AST and ALT grades were discordant, the higher of the two was used for classification. Hepatotoxicity of any degree was considered for LEE grades 1–4, and severe hepatotoxicity for LEE grades 3 and 4.

Statistical analyses
Descriptive values are expressed as absolute numbers and percentages, medians [interquartile range (IQR)] or means (±SD). Both groups of patients were first compared in a cross-sectional study using the χ² test for categorical data and parametric or non-parametric tests for continuous variables, as needed. Kaplan–Meier and log rank tests were used for survival analyses. Factors associated with hepatotoxicity were examined by univariate and multivariate logistic regression models. Variables with P < 0.2 in the univariate analysis were entered into the multivariate analysis. All data were recorded and analysed using the SPSS software package v15.0 (SPSS Inc., North Chicago, IL, USA).

Results
From a total of 311 HIV-infected patients who initiated raltegravir therapy during the study period, 218 (70.1%) entered this study. Irregular attendance of visits (n=43), complete loss to follow-up (n=17), poor drug adherence (n=16), lack of informed consent (n=16) and death (n=3) were the reasons for exclusion of the remaining patients. In addition, eight HIV/HCV co-infected patients were excluded from this analysis because they underwent hepatitis C therapy while on raltegravir treatment.

Of the study population, 126 (58%) were HIV mono-infected and 92 (42%) were HIV/HCV co-infected patients. Table 1 displays the main baseline characteristics of the study population, according to HCV status. HIV/HCV co-infected patients were younger and had lower CD4 counts than HIV mono-infected individuals, most likely reflecting that most were former intravenous drug users while many HCV-negative patients with HIV infection had been infected through homosexual contact. The two populations did not differ significantly in any other characteristic, including antiretroviral treatment modality.

All patients included in the study were antiretroviral experienced, given that raltegravir had been approved only for this subset of patients at the time the study was conducted. Besides being part of a rescue antiretroviral intervention in patients failing a prior regimen, in this study raltegravir was prescribed in 63% of patients because of poor tolerance or side effects with an otherwise virologically suppressive regimen. Raltegravir was accompanied in 87% of cases by two nucleoside reverse transcriptase inhibitors (NRTIs), mostly tenofovir/emtricitabine (Truvada®) or abacavir/lamivudine (Kivexa®). Besides, ritonavir-boosted protease inhibitors (PIs) were used by 39% of subjects and non-NRTIs (NNRTIs) by 8% of patients.

The mean length of follow-up of patients treated with raltegravir was 14.1 ± 6.1 months in HIV mono-infected subjects and 12.7 ± 4.8 months in HIV/HCV co-infected subjects. Any degree of hepatotoxicity (grade 1–4) occurred in 10 (7.9%) HIV mono-infected patients and 23 (25%) HIV/HCV co-infected patients [relative risk (RR) 3.1; 95% confidence interval (95% CI) 2.9–3.4; P=0.002]. The median time to any degree of hepatotoxicity was 6 months (IQR 3–16) and 3 months (IQR 1–6), respectively. Figure 1 shows the Kaplan–Meier curves for any degree of hepatotoxicity according to HIV co-infection status.

Only three patients developed severe hepatotoxicity (grade 3 or 4), all of which occurred in HIV/HCV co-infected individuals. In these subjects, LEEs occurred at months 1, 15 and 15, respectively. However, in all three cases reasons other than raltegravir exposure most likely explained LEEs. It was alcohol abuse (>50 g/day) in two patients and resumption of intravenous drug abuse in another. The first two subjects continued with raltegravir therapy and aminotransferases returned to normal values after stopping alcohol abuse. In the third patient, raltegravir was discontinued following virological failure as a result of poor adherence. Liver enzymes were persistently elevated during two subsequent visits 2 and 4 months later, while the patient admitted continuous intravenous drug use; he was lost to follow-up thereafter.

As a whole, in this observational study, raltegravir was discontinued in nine (4.1%) subjects; five (4%) HIV mono-infected patients and four (3.3%) HIV/HCV co-infected patients (P=0.6).
The main reasons for raltegravir withdrawal were poor adherence (n = 5), virological failure (n = 3) and headache (n = 1).

At baseline, median liver stiffness values were 5.6 and 8.0 in HIV mono-infected and HIV/HCV co-infected patients, respectively (P < 0.001). Overall, no significant changes in median values occurred at 6, 12 and 18 months (data not shown).

Progression of liver fibrosis from one Metavir staging estimate to the next over the 18 month study period occurred in three patients, all of them HIV/HCV co-infected. It was from F1 to F2 in two patients and from F3 to F4 in another. None of them experienced significant LEEs. Of note, only one out of six patients (all HIV/HCV co-infected) with liver cirrhosis at baseline experienced grade 2 LEEs.

In the univariate analysis, hepatotoxicity of any degree (grade 1–4) was significantly associated with HCV infection (P = 0.002), elevated baseline AST (P = 0.03), elevated baseline ALT (P = 0.04) and baseline advanced liver fibrosis (P = 0.02) (Table 2). The rate of LEEs did not differ according to baseline body mass index (BMI), CD4 count, plasma HIV-RNA, gender or age. The multivariate analysis (RR, 95% CI, P) revealed HCV co-infection as the only independent variable associated with any degree of hepatotoxicity (RR 2.9; 95% CI 2.3–3.3; P = 0.03).

In order to provide a proper view of the hepatic safety profile of raltegravir with respect to other antiretroviral agents, we carried out a similar analysis for patients that consecutively began regimens based on PIs or NNRTIs at our institution during the same period. The most common PIs used were atazanavir (53%), lopinavir (46%) and darunavir (1%), while the most common NNRTIs were efavirenz (67%) and nevirapine (33%). In all cases, except for half of the patients on atazanavir, PIs were used with low-dose ritonavir as a booster. All these drugs were taken in the majority of cases along with two NRTIs, Truvada and Kivexa being the most common. Figure 2 displays the rate of LLEs over the first 12 months of therapy using all these regimens.

**Discussion**

Hepatotoxicity is a potentially serious complication of HIV treatment and elevation of serum aminotransferases is often the first sign of antiretroviral-associated liver injury. Elevated AST and ALT and baseline advanced liver fibrosis were significantly associated with any degree of hepatotoxicity (RR 2.9; 95% CI 2.3–3.3; P = 0.03). In order to provide a proper view of the hepatic safety profile of raltegravir with respect to other antiretroviral agents, we carried out a similar analysis for patients that consecutively began regimens based on PIs or NNRTIs at our institution during the same period. The most common PIs used were atazanavir (53%), lopinavir (46%) and darunavir (1%), while the most common NNRTIs were efavirenz (67%) and nevirapine (33%). In all cases, except for half of the patients on atazanavir, PIs were used with low-dose ritonavir as a booster. All these drugs were taken in the majority of cases along with two NRTIs, Truvada and Kivexa being the most common. Figure 2 displays the rate of LLEs over the first 12 months of therapy using all these regimens.
following treatment of hepatitis C with pegylated interferon plus ribavirin.20,21

In our study the rate of any degree of LEEs and/or severe LEEs in patients treated with raltegravir was within the expected range for other antiretroviral agents that are considered as safe in terms of hepatic safety profile.4 As expected, LEEs occurred more frequently in patients with chronic hepatitis C than in the rest (3-fold on average). All episodes of LEEs were mild (grade 1–2) with no cases of severe hepatotoxicity attributed to raltegravir. Moreover, none of the patients discontinued raltegravir due to LEEs. Lastly, only one of the six baseline cirrhotic HIV/HCV co-infected patients treated with raltegravir experienced grade 2 LEEs. This observation is important given that the risk of drug-related liver toxicity is particularly increased in the subset of co-infected patients with liver cirrhosis.22

Figure 2. LEEs with distinct antiretroviral drug classes over 12 months.

Table 2. Predictors of LEEs (any grade) in HIV-infected patients treated with raltegravir

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>No. (%)</th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR 95% CI</td>
<td>P</td>
<td>RR 95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Hepatitis C co-infection</td>
<td>92 (42)</td>
<td>3.1 2.9–3.4</td>
<td>0.002</td>
<td>2.9 2.3–3.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>32 (15)</td>
<td>1.2 0.8–1.4</td>
<td>0.6</td>
<td></td>
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</tr>
<tr>
<td>Older age (&gt;55 years old)</td>
<td>58 (27)</td>
<td>1.1 0.8–1.5</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>174 (80)</td>
<td>1.2 0.8–1.6</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated BMI (&gt;25 kg/m²)</td>
<td>56 (26)</td>
<td>1.2 0.9–1.5</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated AST</td>
<td>63 (29)</td>
<td>1.6 1.2–2.1</td>
<td>0.03</td>
<td></td>
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</tr>
<tr>
<td>Elevated ALT</td>
<td>68 (31)</td>
<td>1.5 1.1–2.0</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced liver fibrosis (Metavir estimates F3–F4)</td>
<td>12 (6)</td>
<td>1.7 1.4–2.1</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low CD4 count (&lt;200 cells/mm³)</td>
<td>18 (8)</td>
<td>1.2 0.8–1.6</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detectable plasma HIV-RNA</td>
<td>81 (37)</td>
<td>1.3 0.8–1.8</td>
<td>0.8</td>
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</tr>
</tbody>
</table>

Hand, in both HIV mono-infected and HIV/HCV co-infected patients, antiretroviral agents prescribed along with raltegravir could account for some LEE episodes.6,14–19 Just for comparison purposes, studies that have assessed the incidence of hepatotoxicity in patients exposed to a well-known hepatotoxic agent, such as nevirapine, have reported rates of 12%–16% for grade 3–4 LEEs.5,6 In the control group examined in our study, LEEs over the first 12 months of therapy occurred more frequently with PIs and NNRTIs than with raltegravir, although the retrospective observational nature of the study and the heterogeneity of the patient populations precluded more definitive conclusions from being drawn.

Finally, the lack of recognition of any significant progression of liver fibrosis in HIV/HCV co-infected patients treated with raltegravir during the study period is reassuring in terms of the hepatic safety profile of the drug. It should be noted, however, that the mean follow-up was relatively short (~12 months), and hepatic fibrosis estimates were obtained using elastometry. Altogether our results demonstrate the hepatic safety profile of raltegravir in HIV-infected patients, including those with chronic hepatitis C.

Funding
This work was supported in part by grants from Fundación Investigación y Educación en SIDA (IES), Agencia Lain Entralgo, Red de Investigación en SIDA (RIS, RD06/0006) and the European NEAT project.

Transparency declarations
None to declare.

Author contributions
E. V., A. M., F. B. and V. S. designed the study. E. V., A. M., F. B., P. L., I. M., M. C. and V. S. were in charge of the follow-up of patients included in the study and of recording laboratory and clinical information. E. V. and I. M. performed the analysis of liver fibrosis estimates. S. R.-N., E. A. and I. J.-N. built and filled the database, recorded information from pharmacy registries and did the statistical analyses. E. V.
A. M. and V. S. wrote the manuscript. All authors checked the last version of this submission.

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