Raltegravir pharmacokinetics in HIV/HCV-coinfected patients with advanced liver cirrhosis (Child-Pugh C)

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Objectives: To describe raltegravir pharmacokinetics at steady-state in HIV/hepatitis C virus (HCV)-coinfected patients under antiretroviral (ARV) treatment with (n = 5) and without (n = 5) advanced liver cirrhosis (Child–Pugh C).

Methods: This was a non-randomized, Phase I, parallel-assignment, open-label pharmacokinetic study in HIV/HCV-coinfected patients with Child–Pugh grade C hepatic cirrhosis. We recruited clinically stable HIV/HCV-coinfected adult patients with controlled HIV viraemia (<50 copies/mL) for at least 6 months. Raltegravir (400 mg twice daily) was added under fasting conditions for 5 days to the successful ritonavir-boosted protease inhibitor-based ARV regimen. The trial was registered in the ClinicalTrials.gov database (NCT01289951) (LIVERAL).

Results: Raltegravir AUC0–12 and C12 were increased 1.72-fold (90% CI, 1.02 to 2.92) and 6.58-fold (90% CI, 2.92 to 14.85), respectively, in patients with advanced liver cirrhosis. No safety issues were identified and raltegravir was well tolerated by all patients.

Conclusions: Raltegravir plasma levels are increased in HIV/HCV-coinfected patients with advanced liver cirrhosis (Child–Pugh C). Despite the higher exposure, raltegravir was safe and well tolerated.

Keywords: integrase inhibitors, plasma concentration, end-stage liver disease

Introduction

Hepatitis C virus (HCV) coinfection in HIV-infected subjects is a major concern because of its high prevalence, accelerated progression of liver fibrosis, important associated morbidity and mortality and the added difficulty for the management of antiretrovirals (ARVs) due to the frequent hepatotoxicity of the drugs. In Spain, HCV coinfection is detected in up to 50%–60% of all HIV-infected patients, and up to 20% of coinfected patients have developed liver cirrhosis. The decrease in AIDS-related mortality has made end-stage liver disease (ESLD) a frequent condition among HIV-infected patients, one that has become the single most important cause of death in HIV-infected subjects in many Western countries.

Management of ARV treatment in patients with ESLD may be complex because of safety and pharmacokinetic concerns. First, up to 15% of coinfected patients, especially those with ESLD, who receive ARV treatment, have to discontinue the therapy due to drug-related liver toxicity, possibly as a consequence of altered drug metabolism and drug accumulation. Second, many ARV drugs are inducers or inhibitors of enzymes metabolizing other drugs frequently used in these patients, such as immunosuppressant agents in patients undergoing liver transplantation. These issues limit ARV treatment options for the management of HIV-infected patients with ESLD. Additionally, there is no recommendation on which ARV drug should be used in patients with advanced liver disease and for some drugs (efavirenz and protease inhibitors (PIs)) there is a correlation between drug plasma levels and liver fibrosis.

There is an urgent need for efficacious and safe ARV drugs for the management of HIV-infected patients with ESLD, ideally with a low potential for interactions with other drugs. Raltegravir is the first HIV integrase inhibitor to be used in humans. It has been shown to be highly efficacious and well tolerated in Phase III clinical trials in multi-drug-experienced HIV-infected patients, in naive HIV-infected patients as initial therapy and in HIV-infected subjects with hepatitis B and/or C. Raltegravir is cleared primarily by hepatic metabolism via glucuronidation through the UDP glucuronosyltransferase 1A1 (UGT1A1) isoenzyme, with a minor component of elimination occurring from renal excretion. In contrast...
to cytochrome P450 (CYP)-based metabolism, glucuronidation is relatively unaffected by liver disease. Moreover, chronic liver disease, including liver disease due to HCV, significantly decreases the amount and function of CYP enzymes in the liver.\textsuperscript{12–14} A study in healthy volunteers revealed that plasma levels of midazolam, a sensitive CYP3A4 probe substrate, were not substantially affected by raltegravir.\textsuperscript{15} These properties confer on raltegravir a low potential for drug interactions and thus make it a suitable option for the treatment of HIV-infected patients with advanced liver cirrhosis.

The administration of a single 400 mg dose of raltegravir in HIV-infected patients with moderate hepatic insufficiency showed that there was no clinically meaningful effect of moderate liver dysfunction on the pharmacokinetics of raltegravir,\textsuperscript{16} but data on raltegravir pharmacokinetics in patients with more advanced disease are still lacking. The objective of this study was therefore to describe the raltegravir steady-state pharmacokinetic profile and safety in HIV/HCV-coinfected patients with or without advanced liver cirrhosis.

**Patients and methods**

**Patients and clinical trial design**

A Phase I, open-label, clinical trial including HIV/HCV-coinfected patients with and without advanced cirrhosis was conducted. Eligible patients had to be HIV/HCV-coinfected patients aged ≥18 years who were receiving triple ARV therapy including an HIV PI (except ritonavir-boosted atazanavir, saquinavir or indinavir), and who had controlled viraemia (HIV-1 RNA load <50 copies/mL) for at least 6 months. Exclusion criteria included positive hepatitis B surface antigen, new decompensation events at screening, alcohol abuse, an ARV regimen including raltegravir, hypersensitivity to raltegravir, treatment with other UG11A1 inhibitors, current treatment with ribavirin or interferon or past treatment with these drugs if a sustained virological response was achieved, and pregnancy or contraceptive drug use in women.

Patients were classified into two groups according to measurements obtained in the 12 months prior to screening. Group A were HIV/HCV-coinfected patients with no or mild fibrosis shown by biopsy (Metavir score F0–F1) or transient elastography (FibraScan\textsuperscript{8} , Echosens, S.A., Paris, France) (values <6 kPa). Group B comprised patients with advanced liver cirrhosis, based on either biopsy (Metavir score F4) or a transient elastography >14 kPa performed within the previous 12 months, and previous episodes of decompensation (Child–Pugh score ≥10).\textsuperscript{17}

The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The study protocol (EudraCT registration number 2009-017791-14) was approved by the Spanish Regulatory Agency (Agencia Española del Medicamento y Productos Sanitarios-AEMPS) (reference MUH/CLIN N° 5076) and the Ethics Committee (Act No. 226, 22 March 2010) of Hospital Universitario Ramón y Cajal, Madrid, Spain. Written informed consent was obtained from all participants. The trial was registered in the ClinicalTrials.gov database (NCT01289951) (LIVERAL).

After inclusion, participants received 400 mg of raltegravir (developed and provided by Merck Sharp & Dohme, Whitehouse Station, NJ, USA) every 12 h under fasting conditions (30 min before or 2 h after a meal) from day 1 to day 5. The rest of the ritonavir-boosted PI-based ARV treatment remained unchanged. Serial blood samples to determine raltegravir concentrations in plasma were collected immediately before and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h after a witnessed morning dose of raltegravir on day 5. Safety was evaluated by clinical interview and physical examination and by laboratory assessment (creatinine, albumin, total protein, total bilirubin, aspartate aminotransferase (AST) [glutamic-oxaloacetic transaminase (GOT)], alanine

**Table 1.** Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Non-cirrhotic (Metavir score F0–F1) (n = 5)</th>
<th>Advanced cirrhosis (Metavir score F4) (n = 5)</th>
<th>Mann–Whitney U-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>1/4</td>
<td>4/1</td>
<td>P = 0.753</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>44 (43–55)</td>
<td>45 (39–60)</td>
<td></td>
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<tr>
<td>Risk practice for HIV infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intravenous drug use</td>
<td>4/5</td>
<td>4/5</td>
<td></td>
</tr>
<tr>
<td>heterosexual</td>
<td>0/5</td>
<td>1/5</td>
<td></td>
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<tr>
<td>blood transfusion</td>
<td>1/5</td>
<td>0/5</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)/BMI (kg/m(^2)), median</td>
<td>49.6/19.5</td>
<td>66.2/23.7</td>
<td>P = 0.047/P = 0.016</td>
</tr>
<tr>
<td>ARV regimens</td>
<td></td>
<td></td>
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<tr>
<td>DRV/r</td>
<td></td>
<td></td>
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<tr>
<td>TVD, LPV/r</td>
<td></td>
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<tr>
<td>KVX, FAPV/r</td>
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<tr>
<td>3TC, DRV/r</td>
<td></td>
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<tr>
<td>FAPV/r</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior unsuccessful treatment for HCV</td>
<td>3/5</td>
<td>1/5</td>
<td></td>
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<tr>
<td>Laboratory determinations</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>baseline CD4 count (cells/mm(^3)), median (range)</td>
<td>994 (354–1176)</td>
<td>245 (60–450)</td>
<td>P = 0.016</td>
</tr>
<tr>
<td>HCV RNA (IU/mL), median (range)</td>
<td>2852759 (454465–9122263)</td>
<td>91456 (50907–1080120)</td>
<td>P = 0.028</td>
</tr>
<tr>
<td>bilirubin (mg/dL), median (range)</td>
<td>0.54 (0.44–0.95)</td>
<td>2.33 (1.79–3.31)</td>
<td>P = 0.009</td>
</tr>
<tr>
<td>AST (GOT)/ALT (GPT) (IU/mL), median</td>
<td>40/50</td>
<td>56/36</td>
<td>P = 0.251/P = 0.175</td>
</tr>
</tbody>
</table>

BMI, body mass index; DRV/r, ritonavir-boosted darunavir; TVD, coformulated tenofovir plus emtricitabine; FAPV/r, ritonavir-boosted fosamprenavir; LPV/r, ritonavir-boosted lopinavir; KVX, coformulated abacavir plus lamivudine; 3TC, lamivudine.

P < 0.05 was considered statistically significant, and statistically significant \( P \) values are shown in bold.
aminotransferase (ALT) [glutamic-pyruvic transaminase (GPT)], γ-glutamyl transpeptidase (GGT), alkaline phosphatase, international normalized ratio (INR) and Model for ESLD (MELD) score) on days 5 and 15, 10 days after raltegravir withdrawal.

Pharmacokinetic analysis
Raltegravir concentrations in plasma were determined by HPLC with fluorescence detection (HPLC-Multifluorescence Detector 2475; Waters, Milford, MA, USA) according to a validated method18 at the Clinical Pharmacology Laboratory of the Institut de Recerca de la Sida IrsiCaixa, Hospital Universitari Germans Trias i Pujol (Badalona, Spain). The laboratory subscribes to the external quality assurance programme organized by the Association for Quality Assessment in Therapeutic Drug Monitoring and Clinical Toxicology of Radboud University Nijmegen Medical Centre, Nijmegen (The Netherlands).19

Raltegravir pharmacokinetic parameters were calculated for each individual using a non-compartmental approach by means of Winnonlin (Version 2.0, Pharsight, Mountain View, CA USA). AUC during the dose interval (AUC0–12) was calculated by means of the linear trapezoidal rule. Maximum concentrations (Cmax) and the concentrations at the end of the dosing interval (C12) were obtained by inspection of the concentration data.

Statistical analysis
Data analysis was carried out using SPSS version 15.0 statistical software (IBM Corporation, Armonk, NY, USA). Raltegravir pharmacokinetic parameters were described by the geometric mean and compared between groups by the geometric mean ratio (GMR) and its 90% CI. Baseline quantitative variables were compared by means of the Mann–Whitney U-test.

Results
A total of 10 patients were recruited, with 5 per group. Baseline characteristics of both groups were in agreement with the hepatic condition and the gender of the patients, and similar. Patients in the group with advanced liver disease had significantly higher weight, body mass index and bilirubin levels, and lower HCV RNA and baseline CD4 count (Table 1).

All the recruited patients in the advanced liver disease group had had previous episodes of decompensation. Two of these patients had a Child–Pugh score <10, but had ESLD as shown by prior decompensation events (ascites and several episodes of spontaneous bacterial peritonitis in both) and the fact that they were included in the liver transplantation waiting list. The remaining patients had Child–Pugh C scores (C10, C11 and C12). Four of the advanced cirrhosis patients had never received treatment for HCV and the fifth failed HCV treatment on two previous occasions. The ARV treatment in patients with advanced liver disease was based on ritonavir-boosted darunavir in four out of the five patients (administered as monotherapy in two of them) and on ritonavir-
boosted fosamprenavir in the remaining one. ARV regimens in the non-cirrhotic patients included ritonavir-boosted lopinavir, fosamprenavir or darunavir.

Mean raltegravir plasma concentration–time profiles in patients with and without advanced liver cirrhosis are shown in Figure 1. Raltegravir AUC₀₋₁ and C₁₂ were increased in patients with advanced liver cirrhosis (Table 2).

Treatment with raltegravir was safe and well tolerated as no clinically relevant adverse reactions related to the study drug were documented. HIV viral load remained suppressed throughout the study. No patients had to stop therapy and no significant changes were observed during follow-up in the registered hepatic and safety variables [creatinine, albumin, total protein, total bilirubin, AST (GOT), ALT (GPT), GGT, alkaline phosphatase, INR and MELD score] (Table S1, available as Supplementary data at JAC Online).

**Discussion**

Our study shows that raltegravir exposure is increased in patients with advanced cirrhosis without increased toxicity. Although limited by the short duration of therapy and the small number of patients, our study supports the administration of raltegravir to patients with advanced liver disease.

Barau et al. have recently reported results from another study also evaluating raltegravir pharmacokinetics in a group of 10 HIV-infected patients with ESLD. Even though the authors concluded that the pharmacokinetic parameters did not differ from those of patients without liver disorders from the literature, the strength of this conclusion is limited by the lack of a control group. In our study, raltegravir exposure in patients with advanced cirrhosis was in the same range as that observed by Barau et al., but it was significantly higher than in patients without liver cirrhosis in the control group. The safety of the increase in raltegravir exposure in patients with advanced liver disease is reinforced by the information provided by drug–drug interaction studies with raltegravir. The increase is of the same magnitude as that reported for raltegravir when combined with atazanavir (a known UGT1A1 inhibitor) in healthy volunteers, which, given the safety profile of raltegravir, was assumed not to be clinically meaningful. In fact, in raltegravir Phase II studies, where efficacy and safety was evaluated at 24 weeks and a subgroup of 52 patients received atazanavir in the optimized ARV background regimen, the safety profile was comparable to that of placebo.

There are few data on ARV therapy use in HIV-infected patients with advanced liver cirrhosis, and most of the data are from retrospective or single-dose pharmacokinetic studies with drugs metabolized through CYP. This is one of the few pharmacokinetic clinical trials of ARV drugs in HIV/HCV–coinfected patients with advanced liver cirrhosis. All of our cirrhotic patients had baseline high MELD scores (range 12–19), two of them being on the hepatic transplantation waiting list when recruited. In this population, the administration of multiple doses of raltegravir in combination with a ritonavir-boosted PI-based ARV regimen was safe and well tolerated at the standard dose, reinforcing previous reports on the safety and clinical benefits of raltegravir in patients with ESLD. Also, our group has previously described clinical experience of the safe co-administration of raltegravir with pegylated interferon and ribavirin and with HCV direct-acting antivirals, constituting an added clinical benefit.

In a Phase I multicentre clinical trial exploring the use of fosamprenavir in HIV-infected patients with different grades of hepatic impairment and a comparator group with no hepatic impairment, 10 Child–Pugh C cirrhotic patients were recruited but only 7 of them completed the study. The use of reduced ritonavir-boosted fosamprenavir doses and reduced dosing frequency did not lead to any significant safety issues, although the exposures to amprenavir and ritonavir were more variable in these patients, warranting close monitoring of their clinical status.

Our study had some limitations. The short duration of raltegravir therapy precludes definitive conclusions regarding long-term safety in advanced cirrhotic patients. Although not very likely due to the low toxicity of raltegravir, attention should be paid to unexpected adverse reactions in this population. Also, most of the subjects with advanced cirrhosis were men, so we do not know if these findings may be extrapolated to women. In addition, no firm conclusions can be drawn regarding the pharmacokinetics of raltegravir in patients with ascites, since only one patient had ascites at the time of the study. To our knowledge, there are no published data with respect to the influence of ascites on the pharmacokinetics of other ARVs. The presence of ascites could lead to changes in the volume of distribution, and hence in the plasma concentration, after a single dose, but such an effect would be negligible once the steady-state was achieved, as in our clinical trial.

In conclusion, despite higher raltegravir exposure, no dose adjustment of raltegravir seems to be necessary in HIV-infected patients with advanced liver insufficiency. These findings may be relevant for the management of HIV-infected patients with ESLD, an increasingly frequent scenario in our daily clinical practice.

**Table 2. Raltegravir pharmacokinetic parameters in patients with and without advanced liver cirrhosis**

<table>
<thead>
<tr>
<th></th>
<th>Non-cirrhotic (Metavir score F0–F1)⁴</th>
<th>Advanced cirrhosis (Metavir score F4)⁵</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>4.52 (2.59–7.19)</td>
<td>5.21 (3.17–8.57)</td>
<td>1.15 (0.55–2.43)</td>
</tr>
<tr>
<td>AUC₀₋₁ (mg·h/L)</td>
<td>11.38 (7.69–16.87)</td>
<td>19.64 (13.80–27.93)</td>
<td>1.72 (1.02–2.92)</td>
</tr>
<tr>
<td>C₁₂ (mg/L)</td>
<td>0.04 (0.02–0.07)</td>
<td>0.25 (0.14–0.43)</td>
<td>6.58 (2.92–14.85)</td>
</tr>
</tbody>
</table>

⁴Data are expressed as geometric mean (90% CI).

**Acknowledgements**

This work was presented at the Nineteenth Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA, 2012 (Abstract 609). We would like to thank Paloma Martí-Belda RN and Amaya Revilla Monaj RN for the pharmacokinetic sampling, Maria Angeles Galvez Mugica MD and Itziar de Pablo Lopez de Abechuco MD for support with the regulatory document preparation and filing, Marisa Serrano Olmeda PharmD for monitoring the clinical trial and our patients for their willingness to participate.
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Transparency declarations
E. F. is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and owns stock and/or stock options in the company. B. H.-N., A. M., M. J. P.-E., C. Q., F. D., and J. L. C. recruited and followed the patients. N. M.-E. processed the samples for HIV viral load in the Clinical Trial Unit. A. M., M. J. P.-E., C. Q., F. D. and J. L. C. recruited and followed the patients. N. M.-E. processed the samples for HIV viral load quantification. J. M. was the leader of the pharmacokinetic determinations and analysis. All authors contributed to writing the manuscript.

Author contributions
B. H.-N., M. A., E. F. and S. M. contributed to the clinical trial design. B. H.-N. and S. M. coordinated the study. M. A. was responsible for the stay of the patients in the Clinical Trial Unit. A. M., M. J. P.-E., C. Q., F. D. and J. L. C. recruited and followed the patients. N. M.-E. processed the samples for HIV viral load quantification. J. M. was the leader of the pharmacokinetic determinations and analysis. All authors contributed to writing the manuscript.

Supplementary data
Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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