Clinical experience of raltegravir-containing regimens in HIV-infected patients during rifampicin-containing treatment of tuberculosis

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Sir,

We read with great interest the leading article regarding integrase inhibitors in the treatment of HIV-1 infection recently published in JAC, where Powderly clearly analyses some clinical situations for these drugs. Tuberculosis (TB) remains a problem among HIV-infected patients, and the utilization of rifampicin as part of TB treatment limits the use of some antiretroviral treatments (ARTs). Traditionally this problem has been solved with the use of rifabutin [if protease inhibitors (PIs) were required as part of ART] or with ART regimens containing only reverse transcriptase inhibitors.

Rifampicin is a potent inducer of the UGT1A1 enzyme, the principal route of elimination of raltegravir. Pharmacokinetic studies in healthy volunteers and in HIV-infected patients with TB have been performed. In them, the AUC of rifampicin, with the usual dose (400 mg twice daily), was reduced by 40% due to UGT1A1 induction by rifampicin. Doubling the dose of raltegravir (800 mg twice daily) offset this effect, resulting in an increase in the AUC of 27%.

Recently Merck reported initial results from the MK-0518-071 study in which two doses of raltegravir were compared, 400 mg twice daily versus 800 mg once daily, in combination with tenofovir/emtricitabine in adult treatment-naive HIV-1-infected patients. After 48 weeks, raltegravir once daily did not demonstrate non-inferiority to the regimen with raltegravir twice daily. These results suggest that there could be a high risk of virological failure if levels of raltegravir are too low.

Herein we report our experience with eight HIV-positive patients diagnosed with TB and treated with rifampicin-containing tuberculosis regimens and raltegravir-containing ART. The median age was 47 years (range 33–49) and six of the patients were men (75%). Risk factors for HIV infection were as follows: six injection drugs users; and two men who have sex with men. The CDC categories, before the diagnosis of TB, were as follows: category A, 4; category B, 1; and category C, 3. Median follow-up of HIV was 15 years (range 1–21) and 6 patients had hepatitis C virus (HCV) co-infection. Four were receiving methadone maintenance treatment.

At the diagnosis of TB, four patients were undergoing ART, and all treatments included boosted PIs (three atazanavir/ritonavir and one darunavir/ritonavir); all of these patients had HIV-RNA <20 copies/mL and the median CD4 count was 332 cells/mm³ (range 236–589). They did not interrupt ART, but the boosted PI was changed for raltegravir (800 mg twice daily) and continued with the same backbone (three tenofovir/emtricitabine and one abacavir/lamivudine). For the four patients not on ART, the mean HIV-RNA was 5 ± 0.8 log₁₀ copies/mL and the median CD4 count was 118 cells/mm³ (range 9–224). This group started with ART 56 ± 22 days after beginning anti-TB drugs; the ART was tenofovir/emtricitabine and raltegravir (800 mg twice daily) in all cases.

The location of TB, treatment and outcome are shown in Table 1. During the follow-up, no cases of immune reconstitution inflammatory syndrome were found. All patients were monitored at the beginning of TB treatment in order to discard toxicity, mainly hepatic and myopathy, and every 2 or 3 months. The safety profile of TB treatment and ART was good; no adverse events due to TB treatment and ART were documented. It was not necessary to stop or change any of the drugs, and all the subjects finished the TB treatment with the same ART and continued it after.

At the end of TB treatment, all patients previously taking ART remained with HIV-RNA <20 copies/mL and the median CD4 count was 455 cells/mm³ (range 268–666). In those who were not under ART when TB was diagnosed, HIV-RNA was undetectable in all cases and the median CD4 count was 238 cells/mm³ (range 208–265). We did not find virological rebounds during the follow-up.

To our knowledge, these are the first clinical data reported on the use of raltegravir as part of ART in subjects taking rifampicin.

Table 1. Location of tuberculosis infection, tuberculostatic treatment, diagnosis and evolution of eight HIV patients treated with raltegravir-containing regimens

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Location</th>
<th>Treatment</th>
<th>Microbiological diagnosis</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>lung</td>
<td>2HRZE + 7HR</td>
<td>yes</td>
<td>yes</td>
</tr>
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<td>2</td>
<td>hepatosplenic</td>
<td>2HRZE + 7HR</td>
<td>no²</td>
<td>yes</td>
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<tr>
<td>3</td>
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<td>2HRZ + 7HR</td>
<td>yes</td>
<td>yes</td>
</tr>
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<td>4</td>
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<td>2HRZE + 10HR</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>lung</td>
<td>2HRZE + 7HR</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>6</td>
<td>disseminated</td>
<td>2HRZ + 10HR</td>
<td>yes</td>
<td>yes</td>
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<td>yes</td>
</tr>
<tr>
<td>8</td>
<td>lung</td>
<td>2HRZ + 7HR</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

⁵Numbers correspond to the durations of regimens in months (H = isoniazid, R = rifampicin, Z = pyrazinamide and E = ethambutol).
⁶Culture identification in Lowenstein–Jensen medium.
⁷Caseating granulomas in liver biopsy.
under real-life conditions. Raltegravir has been shown to be a safe drug in many clinical studies, with low rates of hepatotoxicity, even in patients co-infected with viral hepatitis; we had six subjects (75%) with HCV, and TB treatment was completed in all cases without liver damage. In spite of treatment with rifampicin, raltegravir maintained its virological and immunological efficacy.

Based on pharmacokinetic data and on the good tolerability of raltegravir, the FDA and the EMEA recommend that the dose of raltegravir be increased to 800 mg twice daily when it is used with rifampicin. Our data support these recommendations with real-life clinical experience, pending the arrival of results from ongoing clinical trials (e.g. NCT00822315), where two doses of raltegravir (400 mg twice daily and 800 mg twice daily) and efavirenz are being compared as part of ART in HIV patients with TB receiving rifampicin.

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**Transparency declarations**

None to declare.

**References**


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Extreme alkaline phosphatase elevation associated with tigecycline

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*Tigecycline is a treatment option for patients with infections due to multidrug-resistant (MDR) organisms. Clinical experience with this antimicrobial is evolving. In randomized trials, gastrointestinal adverse events, including nausea, vomiting, diarrhea, dyspepsia and abdominal pain, were all higher in frequency among tigecycline-treated patients as compared with comparator-treated patients. In addition, haematological side effects (hypofibrinogenemia and prolongation of partial thromboplastin time and/or prothrombin time) as well as several cases of tigecycline-induced pancreatitis have been reported. We observed several cases of extreme elevation of alkaline phosphatase (AP) among patients on tigecycline. Here, we describe the incidence of AP abnormalities associated with tigecycline use in a large retrospective cohort.

The institutional review board approved a retrospective review of patients receiving tigecycline at a single large tertiary care centre. Demographics, infections, medications, liver function tests and related interventions were retrieved from electronic medical records and the pharmacy database.

Between August 2006 and October 2009, 528 patients received tigecycline. Their mean age was 59 years (range 16–94), 52% were male and the median duration of therapy was 6 days (range 1–102). Twenty-eight patients developed extreme elevation of AP [EEAP; defined as AP >5 times the upper limit of normal (ULN) or >750 U/L] while on tigecycline or in the 2 weeks following cessation. In 12 patients EEAP could be explained by another process (underlying medical condition or medications).

Ten of 528 patients (2%) met criteria for probable adverse drug reactions (ADRs) (mean score 5.8) and 6 had possible ADRs (mean score 2), using the Naranjo causality scale. The trend for AP in 10 patients with probable ADRs is shown in Figure 1.

Among the 10 patients with probable ADRs, 3 were treated for pneumonia, 2 for bacteremia and 1 each for post-surgical meningitis, prosthetic joint infection, wound infection, intra-abdominal abscess and osteomyelitis. Pathogens included Acinetobacter baumannii (4/5 carbapenem resistant), Klebsiella pneumoniae (2/2 carbapenem resistant), Staphylococcus aureus (3/3 methicillin resistant), Burkholderia cepacia (1) and Stenotrophomonas maltophilia (1). Three patients had undergone solid organ transplantation (lung (2) and liver (1)).

Baseline AP values ranged from 79 to 437 U/L; peaks ranged from 779 to 1869 U/L. Six patients had peak levels >1200 U/L. Peak AP elevation occurred, on average, on day 23 (range 2–44) after starting tigecycline. Other baseline liver function tests were normal or near normal [median alanine aminotransferase (ALT) 17 U/L and aspartate aminotransferase (AST) 30 U/L], with only modest elevations during tigecycline therapy (median peak ALT and AST 63 U/L and 120 U/L, respectively).

Eight of the 10 patients with probable ADRs underwent diagnostic imaging (right upper quadrant ultrasound alone (6), CT of the abdomen (1) and both ultrasound and endoscopic retrograde cholangiopancreatography (ERCP) (1)); no abnormalities were found.

Tigecycline was discontinued in one patient as a result of the EEAP. The remaining patients completed their course (n=8) or