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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*,[1] 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[2] and in HIV-infected patients with TB[3] have been performed. In them, the AUC of raltegravir, 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 tuberculostatic 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/mm^3 (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 $\log_{10}$ copies/mL and the median CD4 count was 118 cells/mm^3 (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.

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

Patient no.	Location	Treatment[a]	Microbiological diagnosis[b]	Cure
1	lung	2HRZE+7HR	yes	yes
2	hepatosplenic	2HRZE+7HR	no[c]	yes
3	lung	2HRZ+7HR	yes	yes
4	lung	2HRZE+10HR	yes	yes
5	lung	2HRZE+7HR	yes	yes
6	disseminated	2HRZ+10HR	yes	yes
7	adenitis	2HRZ+7HR	yes	yes
8	lung	2HRZ+7HR	yes	yes

[a] Numbers correspond to the durations of regimens in months (H=isoniazid, R=rifampicin, Z=pyrazinamide and E=ethambutol).
[b] Culture identification in Lowenstein–Jensen medium.
[c] Caseating granulomas in liver biopsy.

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/mm^3 (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/mm^3 (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 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;[4] 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[5] and the EMEA[6] 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.

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