Lack of interaction between raltegravir and cyclosporin in an HIV-infected liver transplant recipient

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Sir,

Highly active antiretroviral therapy (HAART) has improved life expectancy in HIV-infected patients, allowing orthotopic liver transplantation as a reasonable treatment option for selected patients with end-stage liver disease. Both non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have been reported to have problematical interactions with immunosuppressive drugs such as tacrolimus and cyclosporin. In particular, cyclosporin undergoes oxidative metabolism by CYP3A4, with a consequent high potential for interactions with CYP3A4 inhibitors and inducers.1,2 Raltegravir is the first-in-class inhibitor of HIV integrase, and showed sustained virological efficacy in both experienced and naive HIV-infected patients without cross-resistance with other existing classes.3 Raltegravir is primarily metabolized by the liver via UDP-glucuronosyltransferase 1A1 (UGT1A1), and it is neither an inducer nor an inhibitor of CYP3A4.4,5

We present a case of co-administration of raltegravir and cyclosporin in an HIV-infected subject. A middle-aged Caucasian male haemophiliac with HIV-1 suffered from hepatitis C virus (HCV)-related end-stage liver disease, HCV genotype 1A. He had no history of HIV-related opportunistic diseases. He had started HAART in 1996 and was subsequently changed to different regimens, including nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs and PIs, mainly due to poor tolerability. The nadir CD4+ T cell count was 219 cells/mm3. When the criteria for transplantation were met, the patient was included in the programme of the National Protocol for liver transplantation in patients with stable HIV disease and end-stage liver failure.6 Liver transplantation from a cadaveric donor was successfully performed in June 2007. At the time of surgery he had a CD4+ T cell count of 130 cells/mm3 (21%) and an HIV RNA level of 490 copies/mL. Genotype resistance testing showed mutations

![Graph showing cyclosporin and raltegravir levels](image)

Figure 1. Cyclosporin C\text{trough} values and raltegravir C\text{trough} values in the course of pre- and post-raltegravir-based HAART. CSA, cyclosporin; FTC/TDF, emtricitabine + tenofovir; FDC, fixed dose combination; ENF, enfuvirtide; PEG-IFN, pegylated interferon; RAL, raltegravir; QD, once daily; BID, twice daily.

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V75I, K103N, V108I, Y115F, F116Y, Q151M, M184V and G109A in the reverse transcriptase region, and I13V, L33I, L63P and V77I in the protease region. The last HAART regimen before transplantation, discontinued pre-operatively, was lamivudine 150 mg twice a day, tenofovir 300 mg once daily and fosamprenavir 1400 mg twice a day. Immunosuppression was initially achieved with cyclosporin (300 mg twice a day) and steroids, and then maintained with cyclosporin only. On the third post-operative day, HAART was resumed with emtricitabine 200 mg, tenofovir 300 mg once daily and a subcutaneous (sc) injection of enfuvirtide 90 mg twice a day. At 3 months after transplantation, the CD4+ T cell count and HIV RNA level were 263 cells/mm³ (20%) and <50 copies/mL, respectively, while HCV RNA was 4.09 log10 copies/mL (Cobas Ampliprep/Cobas TaqMan HCV Test Roche Diagnostics). After 9 months, because of a further increase in HCV RNA levels (6.09 log10 copies/mL) and of macro- and micronodular cirrhosis revealed by transjugular liver biopsy, the patient started anti-HCV treatment with pegylated interferon (PEG-IFN) alfa 2b (180 µg sc once a week) and ribavirin (1200 mg twice a day). Cyclosporin was administered twice daily and its dosage was adjusted individually to match target trough levels of 75–125 µg/L. Four weeks later, because he had ongoing injection site reactions and complained of injection fatigue due to enfuvirtide and PEG-IFN, the patient switched from enfuvirtide to raltegravir (400 mg twice a day). Four weeks later, HIV RNA was still <50 copies/mL, while the CD4+ T cell count had increased from 162 (18%) to 336 (23%). Self-reported therapeutic adherence was apparently optimal. No other potentially interacting drugs were administered. Cyclosporin levels were monitored at regular intervals during outpatient visits (Figure 1). Moreover, at week 4 and week 8 raltegravir concentrations were also measured by a validated HPLC method before the morning dose and 3 h later and showed drug levels to be 60 and 5165 ng/mL at week 4, and 119 and 3386 ng/mL at week 8, respectively. No specific toxicity related to antiretroviral and immunosuppressive therapies was recorded. No administration of factor VIII for treatment of haemophilia A was requested. After 18 months of follow-up post-transplantation, the patient is alive and HIV RNA levels are undetectable.

In our patient, a raltegravir-based regimen was chosen in order to avoid the potential deleterious effect of PIs on cyclosporin. A new NNRTI-based regimen was excluded because etravirine is a substrate for, and inhibitor of, several CYP enzymes.

Because of the concomitant administration of ribavirin, zidovudine, didanosine and stavudine were not feasible, in order to avoid risks of toxicities.

In clinical trials raltegravir was shown to be well tolerated with no risk of additive haematological toxicities. Raltegravir might be considered as a suitable option in HIV-infected patients undergoing liver transplantation. The switch from an injectable to an oral medication is highly acceptable to patients and may facilitate long-term adherence. Plasma concentrations of raltegravir were shown to be comparable with published data, suggesting no significant impact on its plasma exposure by concomitant use of cyclosporin. Raltegravir and cyclosporin may be co-administered without dose adjustments.

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**Transparency declarations**

None to declare.

**References**


**Early hepatitis B virological rebound on entecavir through selection of lamivudine-associated mutations**

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