Case report

Drop in trough blood concentrations of tacrolimus after switching from nelfinavir to fosamprenavir in four HIV-infected liver transplant patients

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Solid organ transplantation in HIV-infected individuals requires concomitant use of immunosuppressants and antiretrovirals that may cause significant drug interactions. Here we report on a peculiar pharmacokinetic interaction between tacrolimus and protease inhibitors (PIs) which occurred in four HIV-infected liver transplant patients who had to shift PI therapy from nelfinavir to fosamprenavir as a consequence of regulatory restrictions. After the switch, tacrolimus trough blood concentrations significantly dropped in all patients (mean ± SD 6.9 ± 2.6 versus 3.2 ± 2.0 ng/ml before and after the switch, respectively; P=0.01), so that a marked dosage increase was needed (0.29 ± 0.14 versus 0.88 ±0.48 mg/day, 1–3 days before and 3 weeks after the switch, respectively; P=0.046) to attain the desired target (8.7 ± 2.3 ng/ml). Consistently, marked changes of the concentration/dose ratio of tacrolimus were observed in all cases (27.2 ± 9.7 ng/ml per mg/kg/day versus 9.7 ±4.0 ng/ml per mg/kg/day before and after the switch, respectively; P<0.001). Our findings suggest that fosamprenavir may be less potent than nelfinavir in inhibiting tacrolimus clearance and support the need for higher tacrolimus dosage to avoid insufficient immunosuppression in HIV-infected liver transplant patients when switching from nelfinavir to fosamprenavir or even when directly starting antiretroviral therapy with fosamprenavir.

Introduction

The current use of highly active antiretroviral therapy (HAART) has enhanced the overall life expectancy for patients with HIV [1]. Accordingly, orthotopic liver transplantation (OLTx) has become a therapeutic option for selected HIV-infected patients concomitantly affected by end-stage liver disease [2,3].

Solid organ transplantation in HIV-infected individuals requires concomitant use of immunosuppressants, like cyclosporin, sirolimus or tacrolimus, and antiretrovirals, including protease inhibitors (PIs) and/or non-nucleoside reverse transcriptase inhibitors, and may therefore be complicated by significant drug interactions [4]. In HIV transplant patients, different PIs were shown to cause marked increases of blood concentrations of either cyclosporin [5] or tacrolimus [6–8], so that major dosage reductions coupled with intensive therapeutic drug monitoring (TDM) have been advocated for appropriately handling immunosuppressant therapy under these circumstances [4,9].

Here we report on a peculiar pharmacokinetic interaction between PIs and tacrolimus, which occurred in four HIV-infected OLTx patients who had to change their HAART as a consequence of regulatory restrictions concerning nelfinavir.

On 5 June 2007, the European Medicines Agency was warned by Roche Registration Limited of a harmful contamination affecting the production of nelfinavir due to unacceptably high levels of an impurity known as ethyl methanesulfonate. As a result, the drug was recalled from the European Union market with immediate effect [10]. At that time, four HIV-infected OLTx patients (3 male, 1 female; age range 41–59 years; weight range 53–64 kg; range of time from OLTx 4–26 months) followed at Udine University Hospital (Udine, Italy)
were receiving nelfinavir (1,250 mg every 12 h) in their HAART regimen. For all patients, nelfinavir represented the major moiety potentially interfering with tacrolimus elimination, because the other co-administered antiretrovirals were almost equal in all cases (tenofovir [n=4], lamivudine [n=3] and emtricitabine [n=1]) and were not expected to cause significant drug interactions.

At last TDM while on nelfinavir cotreatment, all of the patients were receiving low tacrolimus doses (mean ±0.29 ±0.14 mg/day) for the maintenance of tacrolimus trough blood concentrations (Cmin) (determined by means of microparticulate enzyme immunoassay using an IMx Analyzer [Abbott Laboratories, Abbott Rome, Italy]) within the desired therapeutic range (6.9 ±2.6 ng/ml) (Table 1).

As a consequence of the regulatory restriction, a switch from nelfinavir to fosamprenavir (1,400 mg every 12 h without a ritonavir booster in order to avoid an exaggerated toxicity risk) [5] was promptly decided. Fosamprenavir was preferred for two reasons: it has a favourable tolerability profile and can be safely administered without a ritonavir booster, providing comparable efficacy in terms of virological response [11].

Interestingly, when shifting PI therapy, tacrolimus Cmin significantly dropped in all of the patients (3.2 ±2.0 ng/ml, P=0.01) (Table 1), so that a two- to fourfold increase of tacrolimus dosage was needed (1.00 ±0.71 mg/day at 2 weeks after switching, P=0.089; 0.88 ±0.48 mg/day at 3 weeks after switching, P=0.046) for maintenance of the desired target (8.6 ±2.1 ng/ml at 2 weeks after switching [non significant, P=0.124]; 8.7 ±2.3 ng/ml at 3 weeks after switching [non-significant, P=0.153]). Consistently, marked changes of the concentration/dose ratio (C/D) of tacrolimus (that is, blood Cmin normalized for each mg/kg/day dose [ng/ml per mg/kg/day]) were observed in all of the cases after the switch (C/D pre-switch 27.2 ±7.6 ng/ml per mg/kg/day; C/D post-switch 9.7 ±4.0 ng/ml per mg/kg/day; P<0.001) (Figure 1).

No episodes of acute or chronic rejection had previously been noted in any of the patients during both the study period and the follow-up.

To the best of our knowledge, this is the first report showing the pharmacokinetic drug–drug interaction occurring between fosamprenavir and tacrolimus and addressing the different relevance that nelfinavir and fosamprenavir may have in impairing tacrolimus clearance in HIV-infected liver transplant patients.

Our findings seem to suggest that fosamprenavir may be less potent than nelfinavir in inhibiting tacrolimus clearance. We recognize that a 12 h pharmacokinetic study before and after the PI switch would have been more informative. However, this was simply an observational study that reports occurrences of daily clinical practice, taking into consideration the wide acceptance of drug Cmin as a valuable tool for optimal management of immunosuppressant therapy in OLTx patients.

Fosamprenavir is a phosphate ester prodrug of amprenavir with improved solubility over the parent drug, which is rapidly and almost completely hydrolyzed to amprenavir and inorganic phosphate in the gut epithelium during absorption; thus, amprenavir represents the active moiety reaching the systemic circulation [12].

Tacrolimus is primarily metabolized in the liver and in the gut by the cytochrome P450 enzyme CYP3A4 [13], and it is well known that PIs, being potent inhibitors of CYP3A4 activity, can reduce tacrolimus clearance [13,14] even if differential inhibition among the

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Table 1. Changes of dosage and blood concentrations of tacrolimus after switching from nelfinavir to fosamprenavir in four HIV-infected liver transplant patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>FK dosage during NFV*</th>
<th>Last FK Cmin during NFV, ng/ml</th>
<th>First FK Cmin after PI switch, ng/ml</th>
<th>FK dosage during FAMP, 2 weeks after switching, ng/ml</th>
<th>FK Cmin during FAMP, 3 weeks after switching*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.5 mg q24h</td>
<td>10.8</td>
<td>5.7</td>
<td>11.1</td>
<td>10.9</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.5 mg q48h</td>
<td>6.2</td>
<td>3.3</td>
<td>8.8</td>
<td>10.3</td>
</tr>
<tr>
<td>Patient 3</td>
<td>0.5 mg q72h</td>
<td>5.5</td>
<td>0.9</td>
<td>5.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Patient 4</td>
<td>0.5 mg q48h</td>
<td>5.2</td>
<td>2.8</td>
<td>8.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>0.29 ±0.14</td>
<td>6.0 ±2.6</td>
<td>3.2 ±0.1</td>
<td>8.6 ±2.1</td>
<td>8.7 ±2.3</td>
</tr>
</tbody>
</table>

Values are expressed as means (±SD) because the Kolmogorov–Smirnov test showed normal distribution. Statistical significance was tested by paired t-test. The desired ranges of tacrolimus (FK) Cmin were 8–15 ng/ml for patients with less than 6 months from orthotopic liver transplantation (OLTx; patients 1 and 2) and 5–10 ng/ml in those beyond 6 months from OLTx (patients 3 and 4). Average dosage, mg/day. *Significant (P=0.01) versus last tacrolimus Cmin, during nelfinavir (NFV). †Not significant (P=0.089) versus last FK dosage during NFV; §Not significant (P=0.124) versus last FK Cmin during NFV; ¶Significant (P=0.046) versus last FK dosage during NFV; ‡Not significant (P=0.153) versus last FK Cmin during NFV. Cmin, trough blood concentration; fAMP, fosamprenavir; q12h, every 12 h; q24h, every 24 h; q48h, every 48 h; q72h, every 72 h; TDM, therapeutic drug monitoring.
various compounds was observed according to their physicochemical properties [15]. Indeed, nelfinavir and amprenavir were shown to be almost equipotent inhibitors of CYP3A4 activity in various in vitro studies assessing the inhibitory potency of different PIs [15,16]. It seems unlikely, therefore, that the differential impairment of tacrolimus elimination induced by these two PIs could be attributable to this mechanism.

Tacrolimus is also a substrate of P-glycoprotein (P-gp) [17], the efflux pump highly represented in the gut and in the emunctory organs, which is devoted to the extrusion of xenobiotics from the body [18]. It should not be overlooked that the PIs may be potent P-gp inhibitors [17]. Interestingly, in a recent comprehensive in vitro study comparatively assessing the P-gp inhibitory potency of the vast majority of the PIs, a wide range of inhibition rates was observed, with nelfinavir being one of the strongest inhibitors [19].

Figure 1. Concentration/dose ratio of tacrolimus over time shows the effect of switching nelfinavir to fosamprenavir on trough blood concentration of tacrolimus.
antiretrovirals currently used to treat HIV infection, nelfinavir was shown to be the most potent whereas amnprevir was found to be among the least potent [19]. Consistently, it is our contention that the different modulation of P-gp-mediated excretion of tacrolimus induced by nelfinavir and fosamprenavir could explain our findings. 

Whatever the mechanism responsible for this effect, our findings support the need for higher tacrolimus dosage to avoid insufficient immunosuppression in HIV-infected liver transplant patients when switching PI therapy from nelfinavir to fosamprenavir. Moreover, these results suggest that increases might also be necessary even when starting antiretroviral therapy directly with fosamprenavir. Our observations reinforce the helpful role that intensive TDM may play in appropriately handling immunosuppressant therapy with tacrolimus under these circumstances.

Disclosure statement

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References


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