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LETTER TO THE EDITOR

Extended release tacrolimus and antiretroviral therapy in a renal transplant recipient: so extended!

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HIV-infected patients are at risk of developing end-stage renal disease. In selected patients with controlled disease, kidney transplantation (KT) has been recognized during last years as a safe and effective treatment [1]. Highly active antiretroviral therapy (HAART) drugs can interfere with immunosuppressive agents, and this has to be taken into account when adjusting immunosuppression regimen. We report the case of an HIV1-infected patient who developed a severe interaction between extended-release (ER) tacrolimus and lopinavir boosted by ritonavir (lopinavir/r) shortly after KT. This resulted in sustained tacrolimus overdosage, surprisingly well tolerated by the renal graft. Careful therapeutic drug monitoring and pharmacokinetics follow-up, led to a drastic reduction of ER tacrolimus dosage administered on a once weekly basis.

A 45-year-old man with end-stage renal disease secondary to cidofovir toxicity, given for CMV retinitis, underwent KT from a heart-beating deceased-donor after 5 years on haemodialysis. His past medical history included HIV-1 infection diagnosed 22 years earlier, without hepatitis B or C virus coinfection. CD_4 cell count and viral load were 516/μl and below 50 copies/μl, respectively, 3 months before KT. Recovery of diuresis was immediate following KT and serum creatinine rapidly decreased from 9.97 mg/dl at admission to 1.06 mg/dl at day 7. Immunosuppressive regimen included ER tacrolimus 0.2 mg/kg o.d (Advagraf®, Astellas Pharma Europe, Staines, UK), mycophenolate mofetil 500 mg b.i.d. (Cellcept®, Roche, Basel, Switzerland) and prednisolone. At the time of KT, HAART included lopinavir/r 600/150 mg b.i.d., lamivudine 300 mg o.d., raltegravir 400 mg b.i.d. and nevirapine 200 mg b.i.d. Acetylsalicylic acid and prophylactic trimethoprime–sulfamethoxazole 800–160 mg three times a week were added in the early post-operative period. At day 3 post-KT, tacrolimus dosage, performed with Chemiluminescent Microparticle Immuno-Assay on the Architect® analyser (Abbott Diagn., Chicago, IL, USA), had to be reduced because of trough levels >30 ng/ml and completely withdrawn at day 7 (Fig. 1). On day 15, the patient developed fungal and herpetic oesophagitis treated with oral fluconazole 50 mg o.d. (for 10 days), aciclovir 800 mg b.i.d. and pantoprazole 40 mg o.d. Despite tacrolimus discontinuation, whole blood levels remained >30 ng/ml until day 30, with a value of 47.4 ng/ml obtained by dilution on day 24. On day 47, 40 days after drug discontinuation, trough level was

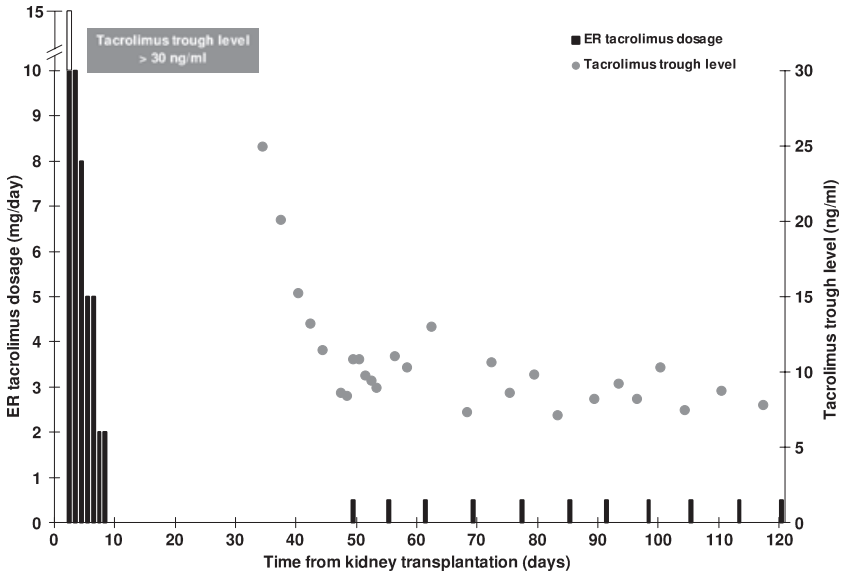

Figure 1 Evolution of tacrolimus trough levels, dosages and intervals of ER tacrolimus administration.

8.6 ng/ml and a single dose of 0.5 mg of ER tacrolimus was given. Peak concentration and whole-blood half-life after a single 0.5 mg dose of ER tacrolimus under lopinavir/r were 13.3 ng/ml and 330 h, respectively. Further ER tacrolimus maintenance dose of 0.5 mg every 7 days until day 90, every 8 days subsequently, allowed achieving tacrolimus trough levels between 8 and 10 ng/ml, and between 6 and 8 ng/ml, respectively (Fig. 1). During the whole follow-up, graft function remained stable despite sustained tacrolimus overdosage, with a creatinine ranging between 1.1 and 1.6 mg/dl. The patient underwent only slight and transient tremor. Currently, six months after KT, serum creatinine is 1.1 mg/dl.

Tacrolimus drug disposition depends on the metabolic enzymes cytochrome P450 3A4 and 3A5 (CYP3A4-A5) and on the efflux transporter P-glycoprotein [2]. Protease inhibitors, especially ritonavir, are amongst the most potent inhibitors of both CYP3A4 activity [3] and P-glycoprotein [4]. Marked increases in tacrolimus trough levels have been reported in transplant recipients co-treated by protease inhibitors boosted or not by ritonavir [5–9]. A recent pharmacokinetic study has shown that the average tacrolimus daily dose had to be reduced to 0.7 ± 0.5 mg while the dosing interval underwent a sevenfold increase reaching 80 ± 54 h in patients under protease inhibitors [10].

Other medications of the HAART regimen of our patient – including raltegravir [11], but also aciclovir [12], pantoprazole [13] and trimethoprim-sulfamethoxazole [14] do not affect CYP3A4 activity. On the contrary, fluconazole is a well-known inhibitor of CYP3A4 [15] and is likely to have further increased tacrolimus levels in our patient. These complex drug-drug interactions account for the severe and sustained drug overdosage (40 days without tacrolimus) in our patient. These are to our knowledge the first pharmacokinetics data of ER tacrolimus in a patient under concomitant lopinavir/r. Further adaptation in drug dosage and interval allowed achieving efficient tacrolimus trough levels. Physicians taking care of HIV-infected patients undergoing KT should be aware of these interactions. The present case highlights the importance of a dramatic and early reduction in dose and/or increase of dosing interval of tacrolimus in patients under concomitant lopinavir/r; and the interest of repeated tacrolimus dosage – with drug dilution if required – in patients at risk of such intoxications.

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