and S. Reigadas (Bordeaux), S. Vallet (Brest), J. D. Poveda (Cerba), A. Mirand (Clermont-Ferrand), A. Krivine (Cochin, Paris), C. Auvray and A. de Rougemont (Dijon), S. Verly (Genève), A. Signori-Schnurck (Geneva), L. Bocket (Lille), S. Rogez (Lirmogens), C. Tamalet (Marseille), V. Schneider and C. Amiel (Tenon), M. Bouvier-Alias (Mondor), B. Montes (Montpellier), E. Schoerger (Nancy), V. Ferré (Nantes), M. L. Chaux (Necker, Paris), J. Guinard (Orleans), S. Haim-Boukobza (Paul Brousse), C. Soulé, A. G. Marcelin, P. Flandre, L. Assoumoun and V. Calvez (Pitié-Salpêtrière, Paris), A. Maillaud (Rennes), L. Morand-Joubert (St Antoine, Paris), C. Chaplain (St Denis), C. Delaugerre (St Louis, Paris), T. Bourlet (St Etienne), S. Bertsch (Strasbourg), J. C. Plantier (Rouen), S. Raymond (Toulouse) and S. Marque-Juillet (Versailles).

**Funding**

The research leading to these results received funding from the European Community’s Seventh Framework Program (FP7/2007-2013) under the project ‘Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN)’—grant agreement no. 223131 and the Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS, France).

**References**


Advance Access publication 18 December 2012

**Pharmacokinetic interaction of maraviroc with tacrolimus in a patient coinfected with HIV and hepatitis B virus following hepatic transplant due to hepatocellular carcinoma**

Ngozi E. Dufty1,2*, Gerry Gilleran1, Daniel Hawkins1, Laura J. Else3 and Stephen Taylor1,4

1Birmingham Heartlands HIV Service, Directorate of Infection, Birmingham Heartlands Hospital, Birmingham, UK; 2Department of Military Medicine, Royal Centre for Defence Medicine, Birmingham, UK; 3Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK; 4Division of Immunity and Infection, University of Birmingham, Birmingham, UK

*Corresponding author. Birmingham Heartlands HIV Service, Directorate of Infection, Birmingham Heartlands Hospital, Birmingham, UK. Tel: +44-121-424-3361; Fax: +44-121-424-3211; E-mail: ngozi.dufty@nhs.net

**Keywords:** HIV antiviral pharmacology, hepatic transplantation, immunosuppression, HBV

Sir,

Limited data are available regarding interactions between tacrolimus and commonly used highly active antiretroviral therapies, such as first-line nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and some protease inhibitors (PIs). When first-line combinations are contraindicated and newer antiretroviral agents are required, there are even less data on the interactions between newer agents such as maraviroc (a CCR5 inhibitor) with immunosuppressants such as tacrolimus (a calcineurin inhibitor). There are some animal model data of the beneficial effects on cardiac allograft survival when using maraviroc alongside immunosuppressants, with the potential that CCR5 inhibition could improve long-term outcomes after transplantation.1,2 In our patient undergoing hepatic transplant, with limited antiretroviral therapy options such as maraviroc (a CCR5 inhibitor) with immunosuppressants, we set out to observe concentrations of the immunosuppressant tacrolimus before and after administration of maraviroc to ensure that effective and non-toxic concentrations of both drugs were achieved.

We describe a 49-year-old man from Sierra Leone, recently diagnosed with fully sensitive HIV clade C and chronic hepatitis B virus (HBV). After routine blood tests revealed abnormal liver

---

**Transparency declarations**

None to declare.
function tests (LFTs) and rising α-fetoprotein, ultrasound scan and then further imaging (CT and magnetic resonance imaging) demonstrated a focal 26 mm × 20 mm hypodense lesion with a central nodular focus in the right lobe of the liver consistent with a hepatocellular carcinoma. Biopsy of the unaffected part of the liver revealed cirrhosis. Following a staging laparoscopy, the lesion was deemed not amenable to resection. The patient was put on the liver transplant waiting list and tenofovir/emtricitabine/efavirenz was started. He became undetectable for both HIV and HBV within 12 weeks, but suffered severe efavirenz-related CNS side effects. When called for liver transplantation 5 months later, he had an unplanned stop of his antiretrovirals. Post-transplant, in the intensive care unit, he went into acute renal failure, had grossly deranged LFTs and was also anaemic. He received hepatitis B immunoglobulin (10 000 units when the liver was removed, followed by 5000 units on days 1–3 post-transplant) with regular 12-weekly hepatitis B surface antibody checks to maintain concentrations >100 IU/mL. He was also established on the immunosuppressants tacrolimus (10 mg twice daily reduced to 2 mg twice daily), 500 mg of mycophenolate twice daily and 10 mg of prednisolone once daily. His CD4 count remained between 200 and 300 cells/mm³ and the decision to restart antiretrovirals was made.

Tacrolimus is a substrate of cytochrome P450 3A4 (CYP3A4) and therefore concentrations can be dangerously elevated when co-administered with ritonavir-boosted PIs. This can cause fatal tacrolimus toxicity with a small dose of tacrolimus. Conversely, tacrolimus concentrations may be decreased with NNRTIs, and the concern regarding NNRTI resistance after his unplanned stop, previous severe side effects with efavirenz and continued mild derangement of LFTs precluded the use of efavirenz, nevirapine and etravirine. There are limited data on the use of maraviroc and raltegravir with these immunosuppressants, therefore possible interactions were predicted according to their metabolic pathways. Maraviroc and tacrolimus are both

![Figure 1. Trough tacrolimus concentrations pre- and post-maraviroc show no difference. Maraviroc concentrations remain therapeutic with coadministration of tacrolimus. The horizontal broken line indicates the required trough tacrolimus concentration used in routine practice. MVC, maraviroc.](image-url)
The concentration of 25 ng/mL 5 (see Figure 1). HIV virological concentrations were above the recommended trough range after co-administration of maraviroc and maraviroc. Tacrolimus trough concentrations remained within the therapeutic range. After achieving steady state concentrations, we observed tacrolimus concentrations (on 2 mg twice daily) without maraviroc and then subsequently after the addition of maraviroc. The patient then had blood drawn over 12 h at 0, 0 h 30 min, 1 h, 2 h, 3 h, 4 h, 6 h and 12 h. Trough tacrolimus concentrations were in keeping with recommendations. After achieving steady state (2 weeks after commencing maraviroc), tacrolimus and maraviroc concentrations were taken at the same timepoints. Tacrolimus trough concentrations remained within the therapeutic range after co-administration of maraviroc and maraviroc concentrations were above the recommended trough concentration of 25 ng/mL 5 (see Figure 1). HIV virological suppression was achieved within 12 weeks (42984 copies/mL to <40 copies/mL), HBV DNA remained undetectable throughout and the patient remained negative for HBV surface antigen. The CD4 count rose to 483 cells/mm 3 with no side effects reported and no changes in laboratory parameters.

In conclusion, this clinical report provides the first clinical and pharmacological data to support the use of maraviroc in combination with tacrolimus in the setting of post-hepatic transplantation. Although there was a 21% increase in exposure to tacrolimus when in combination with maraviroc, both tacrolimus and maraviroc remained in the therapeutic range when co-administered. Unfortunately our patient had a hepatic artery thrombosis and is awaiting re-transplant, but there are emerging data of the potential use of maraviroc for prolonging graft survival. These initial observations need to be substantiated by formal pharmacokinetic interaction studies.

**Funding**

No funding was received. Data were generated as part of the patient’s workup in a unique clinical scenario where no prior data were available.

**Transparency declarations**

S. T. has received educational and/or travel grants from Pfizer, VIV and Janssen Pharmaceuticals. All other authors: none to declare.

**References**

4. Clinical Biochemistry Department, Queen Elizabeth Hospital, Birmingham. Tacrolimus Assay Performed Employing Tandem Mass Spectrometry, Waters-liquid chromatography with MS-MS detection (Acquity/premier XE MS and Alliance 2795/Micro MS).

**J Antimicrob Chemother 2013**

doi:10.1093/jac/dks485

Advance Access publication 5 December 2012

**Twelve week post-treatment undetectable hepatitis C virus (HCV)-RNA by PCR assay predicts a sustained virological response to anti-HCV therapy independently from immunological status of the infected patients**

Maria Francesca Donato*, Anan Judina Bastiampillai, Matteo Manini and Sara Monica

First Division of Gastroenterology, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

*Corresponding author. Tel: +39-0255035432; Fax: +39-0250320410; E-mail: francesca.donato@policlinico.mi.it

**Keywords:** HIV/HCV co-infection, pegylated interferon, ribavirin, liver transplant recipients

SIR, The approval of first-generation directly antiviral agents (DAAs), the NS3 protease inhibitors boceprevir and telaprevir, opens a new era in the field of treatment against hepatitis C virus (HCV) genotype 1. Indeed, registration trials have shown a substantial improvement in rates of sustained virological response (SVR) compared with standard therapy based on pegylated interferon alfa and ribavirin (PEG-IFN/RBV).1 Unfortunately the increased healthcare costs associated with the addition of a DAA will preclude triple therapy in many countries. Moreover, PEG-IFN/RBV will remain the standard-of-care therapy in several subgroups of patients, including those with non-1 HCV genotype and liver transplant recipients. Early assessment of SVR to PEG-IFN/RBV in these subgroups of patients will therefore still carry important clinical implications, while also being relevant in drug development programmes.

SVR at week 12 (SVR12), defined as unquantifiable/undetected HCV-RNA at 12 weeks after the completion of treatment,1 was first assessed in a French study2 published in 2010...