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LETTER TO THE EDITORS

Management of rifamycins–everolimus drug–drug interactions in a liver-transplant patient with pulmonary tuberculosis

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Dear Sirs,

The inhibitors of the mammalian target of rapamycin (mTOR), sirolimus, and everolimus have emerged in Europe as a new class of immunosuppressive drugs in solid-organ transplantation (SOT). After liver transplantation, switching from calcineurin inhibitors (CNI) to mTOR inhibitors is associated with improved outcomes and renal function preservation. Their antiproliferative capabilities suggest a role in preventing malignancies, which is important to liver-transplant patients at risk of recurring hepatocellular carcinoma [1]. Because of their narrow therapeutic index, mTOR inhibitors require therapeutic drug monitoring (TDM). The therapeutic range of everolimus trough blood level (C0) is 3–8 ng/ml when associated with cyclosporine, but was increased to 8–13 ng/ml as a monotherapy use [2].

Post-transplantation tuberculosis is a rare infection with an incidence of 0.4–2.4%. Therefore, the optimal antituberculous regimen is not established [3]. In standard therapeutic regimens, the most potent sterilizing drugs rifampin and rifabutin (rifamycin) are essential in short-courses treatment (6 months) for pulmonary tuberculosis. However, rifamycins are potent inducers of both the cytochrome 3A4 (CYP3A4) and P-glycoprotein efflux transport systems and exhibit significant drug–drug interactions (DDI) with most immunosuppressants [4]. Interactions between rifampin and CNI, or the mTOR inhibitor – sirolimus – have been reported, but have not been studied with everolimus in transplant patients [5,6]. As rifabutin is a weaker CYP3A4 inducer than rifampin, its use over rifampin to treat tuberculosis could be favored as in HIV-infected patients receiving antiretroviral agents [7]. The interactions between rifabutin and CNI were reported in a kidney-transplant recipient, but are largely unknown with mTOR inhibitors [8].

We describe the case of a liver-transplant patient with pulmonary tuberculosis who experienced a complex DDI between rifampin and everolimus, which resolved after switching from rifampin to rifabutin.

A 63-year-old man was referred to our institution in December 2009 for sputum-positive pulmonary tuberculosis. He received an orthotopic liver transplant in October 2008 for HCV-induced cirrhosis associated with hepatocellular carcinoma. The initial immunosuppressive regimen consisted of corticosteroids, mycophenolate mofetil, and everolimus combination. Everolimus was favored because of its expected antiproliferative effects on the underlying malignant disease. The starting dose was 0.5 mg BID (1 mg/day), resulting in a C0 of 12 ng/ml, established by LCMS/MS assay.

In February 2009, pulmonary localizations of hepatocarcinoma were treated with radiofrequency ablation and sorafenib. In November, the patient presented with cough, high-grade fever, and chills. Chest radiographs showed bilateral infiltrates. Influenza A (H1N1) virus was detected using PCR amplification. Oseltamivir was administrated, but a low-grade fever persisted. Sorafenib and mycophenolate mofetil were withdrawn as a result of drug-induced pancytopenia. In December, chest X-rays showed cavitary-lung lesions. Acid-fast examination of sputum was diagnosed of >100 acid-fast bacilli/microscopic field. Cultures grew fully susceptible *Mycobacterium tuberculosis*. Antituberculous therapy was started (Day 1): rifampin (600 mg/day), isoniazid (250 mg/day), pyrazinamide (1500 mg/day), and ethambutol (1200 mg/day); without other interferential medications.

Despite increases in everolimus dosages up to 8 mg TID (24-fold increase compared with the period without rifamycin), C0 remained <5 ng/ml (Fig. 1). Mycophenolate mofetil was resumed on day 13 to prevent acute liver rejection. On day 45, because everolimus C0 were still low, rifampin was switched to rifabutin (450 mg/day). Within few days, everolimus concentrations increased (Fig. 1); everolimus doses were gradually decreased to 5.25 mg/day over a period of 30 days, resulting in therapeutic steady-state C0 (10.3 ± 1.8 ng/ml). After 10 weeks of antituberculosis treatment; sputum cultures became sterile while microscopic examination was still positive. Pyrazinamide and ethambutol were stopped, while rifabutin and isoniazid were continued. At 12 weeks, mycophenolate mofetil was withdrawn for nosocomial pneumonia. After 4 months, sputum smears became negative.

At 5 months, liver-enzyme levels increased to 20 times above the reference value. Rifabutin and isoniazid were

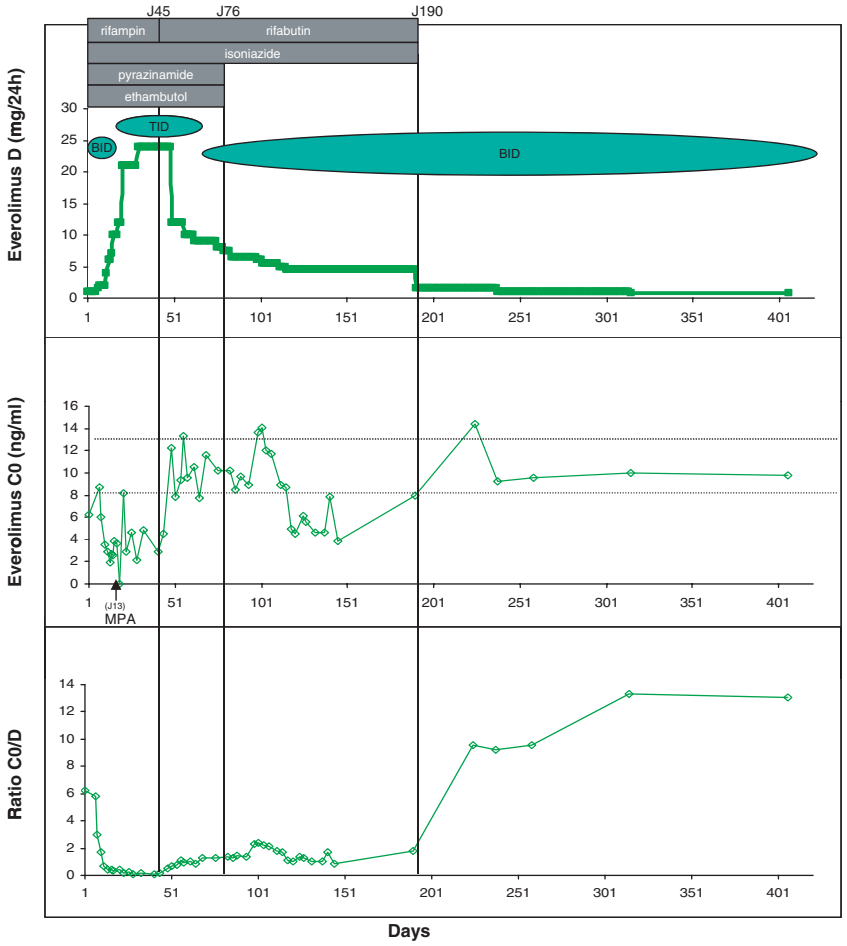

Figure 1 Evolution of everolimus trough concentration (C0), dose (D), and concentration to dose ratio (C0/D) during rifampin, rifabutin, and no antituberculous treatment successive periods (MPA, mycophenolic acid).

definitely stopped. Liver enzymes decreased gradually during the 2 months and no liver biopsy was performed. Follow-up showed that everolimus metabolism induction reversed within 4 weeks after discontinuing rifabutin. Tuberculosis did not relapse within 24 months.

To quantitatively compare the induction potency of each rifamycin on everolimus, we computed the normalized C0 to dose ratio (C0/D) of everolimus during successive periods of treatment (Fig. 1). This ratio was significantly lower during rifampin (0.3 ± 0.2) than during rifabutin (1.4 ± 0.5) periods or without rifamycin (10.4 ± 1.9) ($P < 0.0001$, one-way ANOVA). The use of rifampin and rifabutin were associated with a C0/D ratio decrease in a respective magnitude of 34-fold and sevenfold. Thus, the induction potency of rifabutin on everolimus metabolism was four to fivefold less than rifampin.

Our report provides a thorough description and quantification of the induction in both rifampin and rifabutin on everolimus metabolism. It is noteworthy that our patient did not receive any cyclosporin or steroids, which also interfere with the CYP3A4. CYP3A4 induction began soon after rifampin initiation, and despite the short half-lives of both rifamycins, an average of 4 weeks was necessary to achieve steady-state induction after each change in antituberculous therapy.

Very few data are available on the co-administration of rifampin and mTOR inhibitors. In healthy subjects, rifampin decreases everolimus exposure by a factor 1.7, and its half-life is reduced from 32 to 24 h [9]. In post-transplantation tuberculosis, there is no published report of rifampin–everolimus DDI. A rifampin–sirolimus DDI was studied in two kidney-transplant recipients in which sirolimus daily doses were increased by a factor 5 to maintain therapeutic concentrations [7].Compared with sirolimus, everolimus is more hydrophilic and exhibits pharmacokinetic properties (shorter half-life and linearity) likely to improve DDIs management [3]. The induction potency of rifampin on CNI is not well known, but few reports indicate that daily dose of cyclosporin and tacrolimus have to be, respectively, multiplied by a factor 3 and 10 to maintain effective concentrations [5].

As rifabutin is a less potent CYP3A4 inducer than rifampin, DDI with agents metabolized through CYP3A4 are expected to be less difficult to manage.

Our case is the first report describing rifabutin-mTOR inhibitors DDI in liver-transplant patient. It shows that

the association of rifabutin and everolimus is safe, effective, and easy to manage under close therapeutic drug monitoring. We believe that rifabutin should be the first line drug in rifamycin regimen for post-transplant tuberculosis in patients receiving m-TOR inhibitors.

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Conflicts of interest

The authors of this manuscript have no conflicts of interest.

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