Received: 17 December 2018 | Revised: 18 March 2019 | Accepted: 22 March 2019

DOI: 10.1111/bcp.13958

LETTER TO THE EDITOR

Differences in CYP3A genotypes of a liver transplant recipient and the donor liver graft and adjustment of tacrolimus dose

Tacrolimus (Tac) is well established as main immunosuppressant in most immunosuppressive regimens in solid organ transplantation. Due to the narrow therapeutic window, pre dose Tac levels (C0) are monitored in all patients receiving Tac to reach optimal therapeutic levels. Tac is metabolized in the liver and intestine by the cytochrome P450 3A (CYP3A) isoforms CYP3A4 and CYP3A5. We present a case of an African American woman who underwent a liver transplantation in which adequate Tac levels were difficult to accomplish due to differences in cytochrome P450 3A4/5 (CYP3A4/5) polymorphisms of the transplant recipient and the donor liver graft. This case report highlights that genotyping the liver transplant recipient and the donor liver graft might provide data which could be used to predict the tacrolimus metabolism post transplantation.

After solid organ transplantation, **tacrolimus** is used to prevent allograft rejection in the long term. Tac is known for its narrow therapeutic window with large interpatient pharmacokinetic variability where underexposure poses a risk to allograft rejection and overexposure might increase the incidence of infections and toxicity.[1] Tac is metabolized in the liver and intestine by the **cytochrome P450 3A (CYP3A) isoforms** CYP3A4 and CYP3A5. Patients carrying at least one CYP3A5*1 variant allele are considered to be CYP3A5 expressers; these patients have low Tac exposure due to rapid metabolism of Tac. Patients carrying a CYP3A5*3, CYP3A5*6, or CYP3A5*7 variant allele have nonfunctional CYP3A5 protein and are considered to be CYP3A5 non-expressers. Approximately 55% of African Americans are carriers of the CYP3A5*1 variant allele.[2] CYP3A5 expressers require a Tac dose that is approximately 1.5- to 2-fold higher than non-expressers to reach equivalent Tac exposure.[3] Also, the effect of the drug-drug interactions between Tac and CYP3A4/CYP3A5 inducers/inhibitors will be enhanced in CYP3A5 expressers. Monostory et al found an association between Tac blood levels in liver transplant recipients and donors' CYP3A5 genotype as well as CYP3A4 expression.

We present a case in which the genotype of the donor liver graft had a significantly less important effect on Tac pharmacokinetics than the genotype of the liver transplant recipient during the first month post transplantation. A 33-year-old African American woman, known to have sickle cell disease, G6PD deficiency, osteoporosis, and colitis ulcerosa, received an uncomplicated donation after brain death (DBD) liver transplantation (LTx) because of a cirrhosis and recurrent cholangitis due to primary sclerosing cholangitis (PSC). Tac was initially started at day 5 at a lower dose (2 mg twice daily; 62 kg) because of a postoperative pulmonary infection.

Target Tac whole blood levels were set at 6-10 μg/L in the first month after LTx followed by target Tac whole blood levels of 4-8 μg/L from the second month onwards.[4] Tac levels were measured by ultra-high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UHPL-MS/MS Xevo TQ, Water Chromatography, BV, USA). After several dose adjustments shown in Figure 1, the Tac trough level was still inadequate (4.5 μg/L) at day 16, which resulted in an additional dose increase to 24 mg twice daily. A daily dose of 48 mg correlates with a dose of 0.8 mg/kg/day in our patient, which may potentially lead to toxic peak levels. To prevent potentially toxic peak levels, the dosing interval of Tac was shortened to 16 mg three times daily at day 17. Because of the lower doses per administration, lower peak levels will be reached. Subsequently, Tac trough levels will be higher due to a shorter elimination time of Tac.

The AUC is the best marker for total drug exposure and could be calculated based on a limited number of blood samples strategy using Bayesian estimation. At day 18, blood samples were drawn 30 minutes before the next dose and 1, 2, and 4 hours after Tac dosing; the measured concentrations were 12.3, 11.6, 12.8, and 28.9 μg/L respectively. Note that at day 18, a single dose of fluconazole 400 mg was administered because of its ability to inhibit CYP3A enzymes. The AUC_{0-8} was 240 μg*u/L, calculated with MW/Pharm, and the trough level was 12.3 μg/L. It should be taken into account that our patient was on a three times daily dosing regimen, which reflects an AUC_{0-8}. Our calculated AUC_{0-24} (720 μg*u/L) was higher than the target AUC_{0-24} (400-420 μg*u/L).[5] Guy-Viterbo et al[6] showed that fluconazole significantly increased Tac trough levels from day 2 to 30 post transplantation, especially in CYP3A5 expresser recipients. The combination of single-dose fluconazole administration and shortening of the dosing interval may have positively influenced the Tac exposure. However, our patient did not have a fungal infection, so multiple daily dosing of

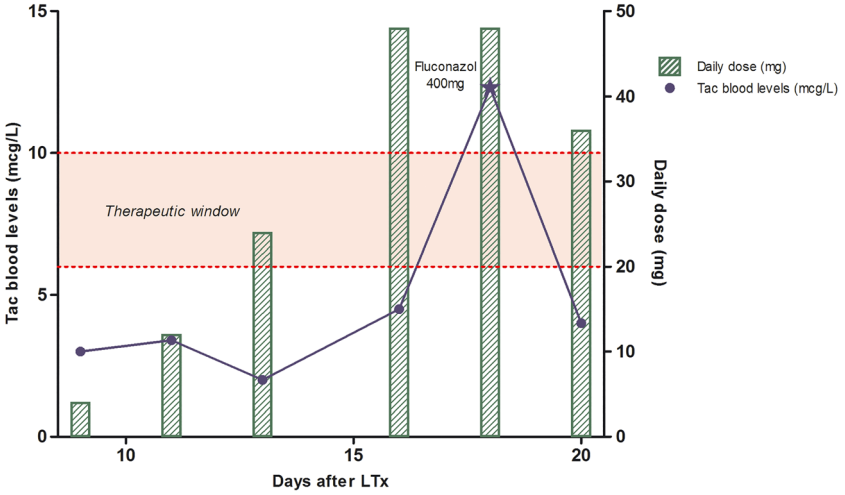

FIGURE 1 Tac trough levels in µg/L (blue line) and daily doses in mg (green bar) versus days after LTx

fluconazole to efficiently balance inhibition of CYP3A5 would not be appropriate. As biopsies of the liver graft were already taken, we genotyped both our patient and the donor liver graft after informed consent was obtained. Genomic DNA was extracted from whole blood of the patient and from the donor liver biopsy using the Total Nucleic Acid DNA isolation kit on a MagnaPure Compac (Roche Diagnostics, Mannheim, Germany). Genotyping of the CYP3A4*22 and CYP3A5*3, *6, and *7 SNPs was performed using the TaqMan® (ThermoFisher Scientific, CA, USA) genotyping assays according to manufacturer instructions. The results suggests that our patient is a CYP3A5 expresser (CYP3A5 *1/*1) with a normal CYP3A4 enzyme activity (CYP3A4 *1/*1B) explaining low Tac exposure. However, the results of the donor liver graft showed that the donor liver has a reduced CYP3A4 activity (CYP3A4 *1/*22) and nonfunctional CYP3A5 enzymes (CYP3A5 *3/*3). In theory, this genotype would cause higher Tac exposures in patients.[6]

Several studies showed that, in adult liver transplant patients, CYP3A5 expression in liver donor grafts and in transplant recipients resulted in higher Tac daily doses to achieve adequate Tac exposure. Initially, the recipient CYP3A activity seems to have the greatest influence on Tac pharmacokinetics, but this changes over time when the donor CYP3A activity becomes more important.[7-10] In the case of our patient, the metabolism of Tac in the intestine also had a more important effect on Tac pharmacokinetics than the metabolism of Tac in the donor liver in the first month after transplantation. However, these aforementioned studies mostly describe the influence of the transplant recipients' and donor liver grafts' CYP3A5 status on Tac metabolism. In this case, the donor liver graft was a CYP3A5 non-expresser but had a reduced CYP3A4 activity (CYP3A4 *1/*22), which have not yet been studied in combination with a transplant recipient CYP3A5 expresser. Therefore, we could hypothesize that the clearance of Tac by the donor liver is reduced because of its decrease in CYP3A4 expression and therefore more Tac is metabolized in the intestine, resulting in a substantially increased clearance because of its CYP3A5 expression. At day 31, our patient achieved adequate Tac levels (6.0 µg/L) with a dosing regimen of 10 mg Tac three times a day. If we had genotyped this patient before transplantation, we would have started with a dose of 0.3 mg/kg/day. This would have resulted in higher pre dose concentrations early after transplantation, however not as high as needed to reach the therapeutic window.

In conclusion, this case shows the difficulties of adjusting dosing regimens to obtain adequate Tac levels in patients with CYP3A genetic polymorphisms.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[11] and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.[12]

COMPETING INTEREST

There are no competing interests to declare.

Keywords

CYP3A5 polymorphism, liver transplantation, pharmacogenetics, tacrolimus, therapeutic drug monitoring

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