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LETTER TO THE EDITORS

Successful switch-over administration of intravenous-to-oral tacrolimus after isolated living-donor liver transplantation in a child with ultra short gut syndrome

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Dear Sirs,

We experienced a case of intravenous-to-oral tacrolimus administration after living-donor liver transplantation (LDLTx) for a patient with ultra short gut syndrome (USGS).

The case was a 17-year-old male patient suffering from liver failure induced by long-term parenteral nutrition (PN) while awaiting a suitable small bowel donor. As a neonate, his small bowel was completely removed because of midgut volvulus. The second portion of the duodenum was anastomosed to the ascending colon. In the course of this awaiting period, he underwent splenectomy because of pancytopenia induced by splenomegaly relating to hepatic fibrosis followed by long-term PN. During this postoperative period, subacute liver failure occurred (with serum total bilirubin levels over 30 mg/dl and Grade 3–4 hepatic encephalopathy) despite continuous hemodiafiltration and plasmapheresis. Considering the legal limitations (isolation of both liver and small bowel grafts from the same living donor is prohibited by law in Japan) and the risk of waiting for a deceased-donor small bowel graft, an isolated LDLTx using a left lateral segment liver graft from his father was performed after informed parental consent. After LDLTx, to prevent liver allograft rejection, we used continuous intravenous infusion (CIV) as a first induction of tacrolimus [starting at 1.0 mg/kg (graft weight) per day]. After therapeutic blood levels were achieved, oral administration [starting at 2.0 mg/kg (graft weight) per day] combined with CIV was started (Fig. 1). The sublingual route was not used in this case because we had not experienced the sublingual route yet. Two weeks after oral administration began, CIV was stopped. However, he was not a high risk for humoral or cellular rejection with positive crossmatch or positive donor-specific antibody, he had sometimes the suspicious rejection episodes during the first months. Despite three temporary CIV inductions because of both low trough levels of tacrolimus and suspicious episodes of mild rejection in laboratory data after switching to oral administration, the blood concentration of tacrolimus was eventually stabilized at 0.05∼0.08 mg/kg/day 65 days after transplantation.

We introduced CIV tacrolimus immunosuppressive therapy immediately after transplantation because we considered being able to control trough levels of tacrolimus strictly. After the therapeutic blood levels of tacrolimus were achieved with a combination of CIV and oral induction, finally, oral administration alone was started as previously reported [1]. There were three reasons for this. First, even in USGS patients, an important management issue is the need to achieve adequate immunosuppression to prevent liver allograft rejection because of abnormal gut function and, consequently, the unpredictable absorption of immunosuppressive drugs. Second, the patient suffered not only a preoperative chronic paralytic ileus condition but also intermittent epigastralgia induced by a duodenal ulcer during the early postoperative period resulting in little oral intake including oral medication and poor nutrition. This condition improved after administration of a proton pump inhibitor, and the combined induction of oral and CIV tacrolimus was started. Third, genomic study revealed CYP3A5 *1*3 allele in both donor and recipient. These genotype combinations have the possibility of difficulties to control strict blood tacrolimus concentration by only oral administration even in a normal gut patient. Thus, we selected CIV tacrolimus infusion at first not only to maintain the reliable therapeutic blood level of tacrolimus definitely, but also to avoid the unpredictable tacrolimus absorption from the alimentary tract without abnormal tacrolimus metabolism because of CYP3A5 polymorphism.

Recently, some studies reported that small intestinal enterocytes express high levels of the CYP3A4 family of metabolizing enzymes in the endoplasmic reticulum, which is responsible for tacrolimus phrmacokinetics [2–5]. A large fraction of the administered tacrolimus absorbed in the small intestine is either re-transported into the lumen, or metabolized via the first-pass effect. Lampen *et al.* showed that the intestinal metabolites formed after oral administration of tacrolimus were present at the highest concentrations in the duodenum and jejunum, where the drug is mainly absorbed, and declined as follows: duodenum > jejunum > ileum >

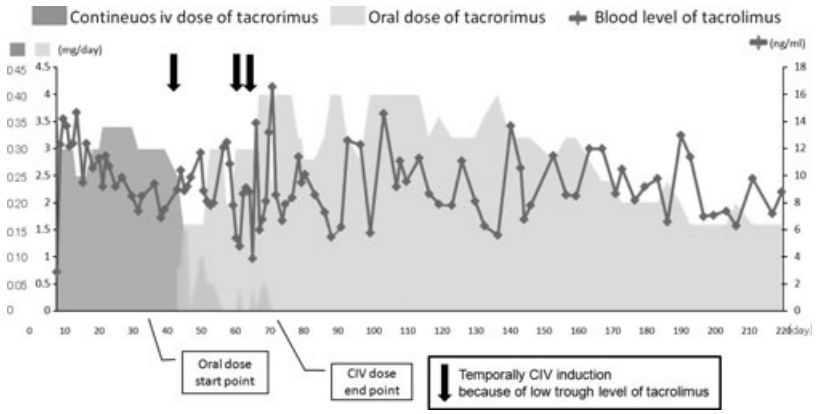

Figure 1 Consecutive data showing blood trough levels and administration doses of tacrolimus after both CIV and oral administration post-LDLTx. After switching to oral administration alone, the patient required temporary continuous intravenous infusion (CIV) induction at three time points because of low trough level of tacrolimus (black arrow). The trough levels were adequately controlled by oral administration alone by 65 days post-op and the dosage was decreased in stages.

colon > stomach [6]. This may represent the metabolic activity of oral tacrolimus in each segment of the gastrointestinal tract [6–8].

Following small bowel resection there is a reduced the first-pass effect, resulting in increased peak levels of tacrolimus. These results are supported by the paradoxical statement: ''The shorter the residual small intestine, the higher the oral tacrolimus blood concentration'' by Sano *et al.* [4]. These studies support the idea that stable blood tacrolimus concentrations may be achieved even in small bowel syndrome patients through oral administration alone; however, there are no reports that include patients without an intact jejunum and ileum. We successfully managed to maintain a satisfactory blood trough level of tacrolimus in our patient by oral administration alone. This may be because the paradoxical phenomenon described above is applicable to USGS patients keeping the balance between reduced first-pass effect and reduced tacrolimus absorption.

In conclusion, low dose oral administration of tacrolimus can achieve acceptable therapeutic levels, even in USGS after LDLTx, although it may need to be combined with appropriately timed CIV induction protocols according to the patient condition.

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References

1. Ueda M, Uemoto S, Inomata Y, Okajima H, Hashida T, Tanaka K, Yamaoka Y. A proposal of FK506 optimal dosing in living related liver transplantations. *Transplantation* 1995; **60**: 258.
2. Kolars JC, Schmiedlin-Ren P, Dobbins WO, Schuetz J, Wrighton SA, Watkins PB. Heterogeneity of cytochrome P450IIIA expression in rat gut epithelia. *Gastroenterology* 1992; **102**: 1186.
3. Shimomura M, Masuda S, Saito H, Sakamoto S, Uemoto S, Tanaka K, Inui K. Roles of the jejunum and ileum in the first-pass effect as absorptive barriers for orally administered tacrolimus. *J Surg Res* 2002; **103**: 215.
4. Sano N, Nio M, Ishii T, *et al.* Oral FK 506 blood levels are elevated in pig short bowel model: further investigations with co-administration of an intestinal CYP3A4 inhibitor. *Transplant Proc* 2002; **34**: 1050.
5. Uesugi M, Masuda S, Katsura T, Oike F, Takada Y, Inui K. Effect of intestinal CYP3A5 on postoperative tacrolimus trough levels in living-donor liver transplant recipients. *Pharmacogenet Genomics* 2006; **16**: 119.
6. Lampen A, Christians U, Guengerich FP, *et al.* Metabolism of the immunosuppressant tacrolimus in the small intestine: cytochrome P450, drug interactions, and interindividual variability. *Drug Metab Dispos* 1995; **23**: 1315.
7. Tamura S, Tokunaga Y, Ibuki R, Amidon GL, Sezaki H, Yamashita S. The site-specific transport and metabolism of tacrolimus in rat small intestine. *J Pharmacol Exp Ther* 2003; **306**: 310.
8. Moller A, Iwasaki K, Kawamura A, *et al.* The disposition of 14C-labeled tacrolimus after intravenous and oral administration in healthy human subjects. *Drug Metab Dispos* 1999; **27**: 633.