Effects of Concomitant Administration of Vonoprazan Fumarate on the Tacrolimus Blood Concentration in Kidney Transplant Recipients

Takanori Mei,* a Hiroshi Noguchi, a Kimitaka Suetsugu, b Yu Hisadome, a Keizo Kaku, a Yasuhiro Okabe, * a Satohiro Masuda, a and Masafumi Nakamura a

a Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University; 3–1–1 Maidashi, Fukuoka 812–8582, Japan; b Department of Pharmacy, Kyushu University Hospital; 3–1–1 Maidashi, Fukuoka 812–8582, Japan; and c Department of Pharmacy, International University of Health and Welfare Narita Hospital; 852 Hatakeda, Narita, Chiba 286–0124, Japan

Received April 20, 2020; accepted July 23, 2020

Vonoprazan fumarate (vonoprazan) is a new kind of acid suppressant with potent acid inhibitory effects. Therefore, it has been administered to kidney transplant recipients for treatment or prophylaxis of steroid ulcers, refractory peptic ulcers, and gastroesophageal reflux disease. Because tacrolimus, which is a well-established immunosuppressant for kidney transplantation, and vonoprazan share the CYP3A4 system for metabolism, drug interactions are anticipated upon simultaneous administration. We retrospectively analyzed 52 kidney transplant recipients who were converted from rabeprazole, which has a small effect on the tacrolimus trough blood concentration ($C_{\text{th}}$), to vonoprazan between August 2016 and July 2019. We compared the tacrolimus $C_{\text{th}}$/tacrolimus dose ($C_{\text{th}}/D$) before and after conversion and serum liver enzymes, serum total bilirubin, and the estimated glomerular filtration rate (eGFR). As a result, mean tacrolimus $C_{\text{th}}/D$ before and after conversion was 1.98 ± 0.2 and 2.19 ± 1.15 (ng/mL)/(mg/d), respectively, ($p < 0.001$). Additionally, mean aspartate transaminase (AST) before and after conversion was 18.6 ± 4.2 and 19.6 ± 5.21U/L, respectively, ($p = 0.037$). Mean alanine transaminase (ALT) before and after conversion was 15.8 ± 5.5 and 17.6 ± 7.1IU/L, respectively, ($p = 0.007$). Mean eGFR before and after conversion was 50.6 ± 14.4 and 51.4 ± 14.7mL/min/1.73m², respectively ($p = 0.021$). Mean AST, ALT, and eGFR were slightly but significantly elevated within normal ranges after conversion. In conclusion, our study suggests that the mean tacrolimus $C_{\text{th}}/D$ was elevated significantly by converting from rabeprazole to vonoprazan, but it had little clinical significance. Vonoprazan can be administered safely to kidney transplant recipients receiving tacrolimus.

Key words vonoprazan fumarate; tacrolimus; blood concentration

INTRODUCTION

Vonoprazan fumarate (vonoprazan) is a member of a new class of acid suppressants, namely potassium-competitive acid blockers that reversibly inhibit the gastric acid pump in a $K^+$-competitive manner.1 Because it has a potent acid inhibitory effect that is not less than that of common proton pump inhibitors (PPIs), vonoprazan has been recently administered to kidney transplantation recipients with refractory peptic ulcers or gastroesophageal reflux disease (GERD).2 Although vonoprazan is metabolized by CYP3A4, no report has examined the effect of vonoprazan on the tacrolimus blood concentration or its safety, which is a well-established immunosuppressant for kidney transplantation (KT).3,4

MATERIALS AND METHODS

We retrospectively analyzed 52 kidney transplant recipients who were converted from rabeprazole, which has a small effect on the tacrolimus trough blood concentration ($C_{\text{th}}$), to vonoprazan between August 2016 and July 2019. Exclusion criteria were: (i) patients with unstable renal functions within 3 months before conversion (patients with active allograft rejection or patients at less than 1 year after KT); (ii) patients whose liver functions were above the normal ranges at least once within 3 months before conversion [aspartate transaminase (AST) >30IU/L and/or alanine transaminase (ALT) >42IU/L for males and 231IU/L for females, and total bilirubin (T. Bil) >1.5mg/dL]; (iii) patients with unstable doses of tacrolimus (patients who had changed tacrolimus doses within 3 months before conversion); (iv) a different protocol of immunosuppressive drugs including twice daily tacrolimus and/or everolimus, which affected the tacrolimus blood concentration. All patients analyzed in this study were administered a once daily, prolonged release formulation of tacrolimus. Additionally, mycophenolate mofetil and methylprednisolone were not changed to other medications. The target tacrolimus $C_{\text{th}}$ was 4–6ng/mL. We also measured serum AST, ALT, T-bil, the estimated glomerular filtration rate (eGFR), and tacrolimus $C_{\text{th}}$/ dose ($C_{\text{th}}/D$) before and after conversion for 3 months. Serum AST and ALT were measured by the consensus method of the Japan Society of Clinical Chemistry.5 The normal range of AST is 13–30IU/L. The normal ranges of ALT for males and females are 10–42 and 7–23IU/L, respectively. Serum T-bil was measured by the bilirubin oxidase method. The normal range of T-bil is 0.4–1.5mg/dL. According to the pharmaceutical interview form,6 abnormal liver functions were defined as liver function test results over three times the upper limits. To evaluate baseline kidney functions, eGFR (mL/min/1.73m²) was calculated using the appropriate equation shown in a previous report.7 Tacrolimus $C_{\text{th}}$ (ng/mL) was monitored using a chemiluminescence immunoassay on the Architect-i1000 System (Abbott Japan, Tokyo, Japan).

Data are presented as the mean ± standard deviation for
normally distributed continuous variables, the median (interquartile range) for continuous variables that were not normally distributed, and the number for categorical variables. Mean serum AST, ALT, T-bil, eGFR, and tacrolimus $C_{u}/D$ for 3 months before and after conversion were used for analyses. The paired $t$-test was used to analyze differences in the mean AST, ALT, T-bil, eGFR, and tacrolimus $C_{u}/D$ before and after conversion. All statistical analyses were performed using R software. A $p$-value of $<0.05$ was considered as statistically significant. The static power of tacrolimus $C_{u}/D$ was also calculated. The study protocol was approved by the Ethics Committee of Kyushu University (IRB-No 24-54). This study is registered in the University Hospital Medical Information Network Clinical Trials Registry System (UMIN000008475)

RESULTS

The clinical characteristics of kidney transplant recipients who were converted from rabeprazole to vonoprazan are listed in Table 1. The reasons for conversion were as follows. Three patients were converted because of epigastric pain and three patients were converted because of a history of gastric or duodenal ulcers. Three patients had GERD, and three patients were administered anticoagulation drugs and converted to avoid gastric or duodenal bleeding. The reasons for the other patients ($n = 40$) were unknown. Table 2 shows the mean eGFR, serum AST, ALT, T-bil, and tacrolimus $C_{u}/D$ for 3 months before and after conversion. The mean tacrolimus $C_{u}/D$ before and after conversion was $1.98 \pm 1.00$ and $2.19 \pm 1.13$ (ng/mL)/(mg/d), respectively ($p < 0.001$, paired $t$-test). The static power of tacrolimus $C_{u}/D$ was 0.328. Three patients had liver enzymes above the normal limits (maximum values for AST and ALT after conversion were 35 and 50, respectively), and conversion† (month) 35 and 50, respectively), which recovered immediately. There were no adverse effects after conversion. Furthermore, there were no patients who were converted from vonoprazan to rabeprazole.

DISCUSSION

In this study, the mean tacrolimus $C_{u}/D$ when receiving vonoprazan was slightly but significantly higher than that when receiving rabeprazole ($p < 0.001$). Liver enzymes (AST and ALT) and eGFR were slightly but significantly elevated within normal ranges. Moreover, there were no adverse effects after conversion to vonoprazan. Therefore, vonoprazan may be administered safely to kidney transplant recipients providing that tacrolimus $C_{u}$ is monitored.

The reason for the elevation of tacrolimus $C_{u}/D$ after converting to vonoprazan is the different metabolisms of rabeprazole and vonoprazan (Fig. 1). Rabeprazole is mainly metabolized by a non-enzymatic pathway rather than CYP metabolism. Therefore, it has a lesser effect on the tacrolimus blood concentration than other PPIs that are metabolized by CYP metabolism in vivo. In contrast, vonoprazan and tacrolimus are both metabolized by CYP3A4 and may interact each other. It contributed to the fact that vonoprazan elevated the tacrolimus $C_{u}/D$. There is no report about the effects of vonoprazan on the metabolism of human CYP3A4 either in vitro or in vivo. However, in vitro and in vivo experiments in rats showed that vonoprazan interacts with other drugs that share CYP metabolism, including midazolam. Midazolam is a short-acting benzodiazepine that is metabolized to 1-hydroxy-midazolam and 4-hydroxy-midazolam by CYP3A4/5 in humans and CYP3A1 and/or 3A2 in rats. However, it is regarded as an ideal probe to ascertain in vivo CYP3A activity in humans. These findings may support our consideration that vonoprazan and tacrolimus are both metabolized by CYP3A4 and may interact each other. In contrast, Takahashi et al. reported that when a patient was converted from omeprazole to rabeprazole, the tacrolimus $C_{u}/D$ declined to approximately 0.7 (ng/mL)/(mg/d). Therefore, the effect of vonoprazan on tacrolimus appears to be smaller than that of omeprazole.

Tacrolimus is metabolized by both CYP3A4 and CYP3A5, and its blood level varies among patients with the CYP3A5 expressor status and defects. In general, the ethnic difference in the frequency of CYP3A5 defects is around 40, 10, and 80% in Asians, Africans, and Europeans, respectively. However, there is less information about CYP3A4 polymorphisms. Although there are a few reports showing that the effect of vonoprazan is different between CYP3A5 gene polymorphisms, it is considered that CYP3A5 does not affect vonoprazan metabolism in clinical situations. Based on these

### Table 1. Clinical Characteristics of Kidney Transplant Recipients Who Converted from Rabeprazole to Vonoprazan Fumarate

| Parameter | Recipients ($n = 52$) |
|-----------|----------------------|
| Age, years† | $55.7 \pm 13.0$ |
| Sex male: female | $35:17$ |
| Primary diseases (CGN: DM: Others) | $25:15:12$ |
| Height† (cm) | $165.3 \pm 9.4$ |
| Body weight† (kg) | $63.2 \pm 12.8$ |
| The duration between transplantation and conversion† (month) | $58.8 \pm 27.9$ |
| Tacrolimus dose† (mg) | $3.0 \pm 1.6$ |

†Mean ± standard deviation. Abbreviations: CGN, chronic glomerulonephritis; DN, diabetic nephropathy.

### Table 2. Mean AST, ALT, T-Bil, eGFR, and Tacrolimus Trough Concentration/Tacrolimus Dose (Tacrolimus $C_{u}/D$) for 3 Months before and after Conversion†

| Parameter | Before conversion | After conversion | $p$-Value |
|-----------|-------------------|-----------------|-----------|
| eGFR (mL/min/1.73m²) | $50.6 \pm 14.4$ | $51.4 \pm 14.7$ | 0.021 |
| AST (IU/L) | $18.6 \pm 4.2$ | $19.6 \pm 5.2$ | 0.037 |
| ALT (IU/L) | $15.8 \pm 5.5$ | $17.6 \pm 7.1$ | 0.007 |
| T.Bil (mg/dL) | $0.73 \pm 0.33$ | $0.72 \pm 0.32$ | 0.067 |
| Tacrolimus $C_{u}/D$ (ng/mL)/(mg/d) | $1.98 \pm 1.02$ | $2.19 \pm 1.15$ | <0.001 |

†Mean ± standard deviation. Abbreviations: eGFR: the estimated glomerular filtration rate, AST: aspartate transaminase, ALT: alanine transaminase, Tacrolimus $C_{u}/D$: tacrolimus trough concentration/tacrolimus dose.
findings, the drug interaction between tacrolimus and vonoprazan in the present study was mainly focused on CYP3A4-mediated metabolism regardless of CYP3A5 functions.

The main side effect of vonoprazan is constipation (1.0%) and diarrhea (0.7%). Additionally, because vonoprazan is metabolized by the liver, 0.2% of patients had reversible abnormal liver functions over three times the upper limits in a previous trial. In this study, no patients had constipation or diarrhea. Mean liver enzyme (AST and ALT) levels were significantly elevated by 1–2 IU/L within normal range. It was statically significant, but did not appear to be clinically important. Three patients had liver enzyme elevation above the normal limit, but they were all under three times the upper limits and recovered immediately. Although tacrolimus C0/D was elevated, eGFR was also slightly elevated. The reason for this was unknown. There were also no adverse effects after conversion.

This study had several limitations. First, it was a retrospective, observational cohort study in a single center. Second, the sample size and power were small. Therefore, the study may have been underpowered. Third, this study had only one-way conversion from rabeprazole to vonoprazan. Furthermore, we did not evaluate the benefits of converting to vonoprazan in the digestive system. However, to the best of our knowledge, there has been no study about the effects of vonoprazan on the metabolism of tacrolimus blood concentration. M-I* is the first metabolite of tacrolimus. SULT2A1**: Sulfotransferase 2A1. (Color figure can be accessed in the online version.)

CONCLUSION

Our study suggests that the mean tacrolimus C0/D was significantly elevated by about 0.2 (ng/mL)/(mg/d) by converting from rabeprazole to vonoprazan, but it had little clinical significance. Therefore, vonoprazan can be administered safely to kidney transplant recipients receiving tacrolimus.

Acknowledgments We thank Yasuka Ogawa, medical assistant, for performing the data collection. This work was supported in part by a Grant-in-Aid for Scientific Research (KAKENHI) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan (Grant No. 18H02588 to S. Masuda).

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

1) Sugano K. Vonoprazan fumarate, a novel potassium-competitive acid blocker, in the management of gastroesophageal reflux disease: safety and clinical evidence to date. Ther. Adv. Gastroenterol., 11, 1756283X17745776 (2018).
2) Echizen H. The first-in-class potassium-competitive acid blocker, vonoprazan fumarate: Pharmacokinetics and pharmacodynamic considerations. Clin. Pharmacokinet., 55, 409–418 (2016).
3) Shapiro R, Jordan ML, Seamlebury VP, Vivas C, Fung JJ, McCawley J, Randhawa P, Demetris AJ, Irish W, Mitchell S, Hakala TR, Simmons RL, Starzl TE. A prospective randomized trial of FK506-based immunosuppression after renal transplantation. Transplantation, 59, 485–490 (1995).
4) Iwasaki K. Metabolism of tacrolimus (FK506) and recent topics in clinical pharmacokinetics. Drug Metab. Pharmacokinet., 22, 328–335 (2007).
5) Itagaki F, Homma M, Yuzawa K, Nishimura M, Naito S, Ueda N, Ohkohchi N, Kobda Y. Effect of lansoprazole and rabeprazole on tacrolimus pharmacokinetics in healthy volunteers with CYP2C19 mutations. *J. Pharm. Pharmacol.*, 56, 1055–1059 (2004).

6) Isoda K, Takeuchi T, Kotani T, Hirano-Kuwata S, Shoda T, Hata K, Yoshida S, Makino S, Hanafusa T. The proton pump inhibitor lansoprazole, but not rabeprazole, the increased blood concentrations of calcineurin inhibitors in Japanese patients with connective tissue diseases. *Intern. Med.*, 53, 1413–1418 (2014).

7) Kotani K, Maekawa M, Kanno T. Reestimation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio based on JSCC consensus method—changes of criteria for a differential diagnosis of hepatic disorders following the alteration from Karmen method to JSCC method. *Nihon Shokakibyo Gakkai Zasshi*, 91, 154–161 (1994).

8) e-IF (Pharmaceutical Interview Forms). Pharmaceuticals and Medical Devices Agency.: <https://www.pmda.go.jp/english/index.html>, Approved in December 2014. Revised October 2019.

9) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. *Am. J. Kidney Dis.*, 53, 982–992 (2009).

10) Wang Y, Wang C, Wang S, Zhou Q, Dai D, Shi J, Xu X, Luo Q. Cytochrome P450-based drug–drug interactions of vonoprazan in vitro and in vivo. *Front. Pharmacol.*, 11, 53 (2020).

11) Wang X, Lee WYW, Zhou X, Or PMY, Yeung JHK. A pharmacodynamic-pharmacokinetic (PD–PK) study on the effects of Danshen (Salvia miltiorrhiza) on midazolam, a model CYP3A probe substrate, in the rat. *Phytomedicine*, 17, 876–883 (2010).

12) Takahashi K, Motohashi H, Yonezawa A, Okuda M, Ito N, Yamamoto S, Ogawa O, Inui K. Lansoprazole–tacrolimus interaction in Japanese transplant recipient with CYP2C19 polymorphism. *Ann. Pharmacother.*, 38, 791–794 (2004).

13) Brunet M, van Gelder T, Asberg A, et al. Therapeutic drug monitoring of tacrolimus-personalized therapy: second consensus report. *Ther. Drug Monit.*, 41, 261–307 (2019).

14) Sugimoto M, Ban H, Hira D, Kamiya T, Otsuka T, Inatomi O, Bamba S, Terada T, Andoh A. Letter: CYP3A4/5 genotype status and outcome of vonoprazan-containing *Helicobacter pylori* eradication therapy in Japan. *Aliment. Pharmacol. Ther.*, 45, 1009–1010 (2017).

15) Touw DJ. Clinical implications of genetic polymorphisms and drug interactions mediated by cytochrome P-450 enzymes. *Drug Metabol. Drug Interact.*, 14, 55–82 (1997).

16) Yamasaki H, Kawaguchi N, Nonaka M, Takahashi J, Morohashi A, Hirabayashi H, Moriwaki T, Asahi S. *In vitro* metabolism of TAK-838, vonoprazan fumarate, a novel potassium-competitive acid blocker. *Xenobiotica*, 47, 1027–1034 (2017).