
Oral

[O26-4] O26-4: Pharmacogenomics (2)

Chairs: Tsuyoshi Fukuda, USA / Taisei Mushiroda, Japan

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[O26-4-4] Impact of cytochrome P450 2C19 polymorphisms on the pharmacokinetics of tacrolimus when coadministered with voriconazole

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Keywords: tacrolimus, voriconazole, drug interaction, CYP2C19 polymorphism, CYP3A

Background

Tacrolimus is commonly administered concurrently with voriconazole in order to prevent fungal infections early after allogeneic hematopoietic stem cell transplantation. Voriconazole inhibits cytochrome P450 (CYP) 3A that metabolizes tacrolimus, and the exposure of voriconazole depends on the CYP2C19 genotype. The frequencies of nonfunctional *CYP2C19* alleles are higher in Asians than in whites and blacks. The objective of this study is to determine the effect of *CYP2C19* polymorphisms on the pharmacokinetics of tacrolimus when coadministered with voriconazole and to assess the extent to which this interaction is impacted by the *CYP2C19* genotype in healthy Japanese subjects.

Methods

A single-center, open, cross-over study with two treatment phases was conducted. Eighteen healthy male volunteers, including 6 CYP2C19 extensive metabolizers (EMs, *1/*1), 6 intermediate metabolizers (IMs, *1/*2 or *1/*3) and 6 poor metabolizers (PMs, *2/*2, *2/*3 or *3/*3) were enrolled in this study. A single oral dose of 3 mg tacrolimus was administered alone or in combination with 200 mg voriconazole twice daily at steady state after 3-day pretreatment. Serial venous blood samples were collected, and whole blood concentrations of tacrolimus and plasma concentrations of voriconazole were measured by ELISA and validated HPLC-UV, respectively.

Results

When tacrolimus was coadministered with voriconazole, a significant increase in area under its concentration-time curve (AUC_{0-24}) was observed for all genotypes. AUC_{0-12} of voriconazole in IMs and PMs were significantly higher than that in EMs ($P < 0.05$ and $P < 0.01$, respectively). Consequently, AUC_{0-24} of tacrolimus in combination with voriconazole in IMs and PMs were also significantly higher than that in EMs ($P < 0.05$).

Conclusions

CYP2C19 genotypes influence the exposure of tacrolimus when coadministered with voriconazole, although tacrolimus is mainly metabolized by CYP3A.