Interaction of the FLT3 Inhibitor Gilteritinib with Xenobiotic Uptake Transporters

Dominique A. Garrison, Zahra Talebi, Yan Jin, Muhammad Erfan Uddin, Alice A. Gibson, Alex Sparreboom, Sharyn D. Baker

Division of Pharmaceutics and Pharmacology, The Ohio State University, Columbus, OH

**Objective:**

Gilteritinib is a kinase inhibitor approved for relapsed/refractory FLT3-mutated acute myeloid leukemia. The pharmacokinetic properties of gilteritinib are characterized by extensive differences in exposure between patients receiving the same therapeutic regimen, and this high degree of inter-individual variability may have important toxicological ramification. Gilteritinib is believed to be primarily eliminated via CYP3A4-mediated metabolism but mechanisms of hepatocellular uptake and its interaction with xenobiotic transporters remain poorly understood. In the present investigation, we re-examined the contribution of CYP3A-mediated elimination to gilteritinib exposure and characterized the transporter-mediated drug-drug interaction potential with gilteritinib.

**Methods:**

Gilteritinib transport was studied *in vitro* using HEK293 cells stably transfected with human OATP1B1, its murine orthologue OATP1B2, as well as the OCT1, OCT2, and MATE1 transporters. Uptake studies were performed to evaluate the effects of gilteritinib on substrate- and concentration-dependent uptake of the prototypical radiolabeled substrates estradiol-17β-d-glucuronide, tetraethylammonium (TEA), and metformin, followed by liquid scintillation counting. Pharmacokinetic studies were performed with a single oral dose of gilteritinib (10 mg/kg; n=5 per group) in adult wild-type mice and sex- and age-matched mice that are CYP3A-deficient, OATP1B2-deficient, OCT1/2-deficient, or MATE1-deficient via repeat blood sampling (6 samples over 8 hours). Concentrations of gilteritinib were determined using a validated LC-MS/MS method, and pharmacokinetic parameters were calculated by non-compartmental analysis using Phoenix WinNonlin v8.0.

**Results:**

Compared to wild-type mice, the systemic exposure to gilteritinib was not significantly altered in CYP3A-deficient mice (1423 ± 142 vs 1468 ± 147 ng.h/mL), suggesting that the clearance of gilteritinib in mice is largely independent of CYP3A function. *In vitro* studies demonstrated that gilteritinib is an inhibitor of the hepatic uptake transporter OATP1B1 (IC50, 2.23 µM), and the interaction of gilteritinib with this transporter was verified by the demonstration that the peak concentration (Cmax) and area under the curve (AUC) of gilteritinib were significantly increased (~1.4-fold), in OATP1B2-deficient mice compared with wild-type mice. In addition, we found that gilteritinib is a potent inhibitor of the hepatic transporter OCT1 (IC50, 300 nM) as well as OCT2 (IC50, 150 nM) and MATE1 (IC50, 5 nM), transporters involved in the renal tubular excretion of cationic drugs. In line with this observation, we found that OCT1/2-deficiency and MATE1-deficiency was associated with altered systemic exposure to gilteritinib (1.1-to 1.5-fold).

**Conclusions:**

This study suggests that CYP3A-deficiency in mice is not associated with a profound phenotypic change in the pharmacokinetic handling of gilteritinib. This unexpected finding suggests that the contribution of CYP3A-mediated metabolism to previously reported drug-drug interactions of gilteritinib with CYP3A4-inhibitory azole antifungals, such as itraconazole, is low and may instead be mechanistically linked with OATP1B-mediated transport modulation. This possibility is currently under further investigation in a transgenic mouse model with hepatic expression of human OATP1B1. In addition, the ability of gilteritinib to potently inhibit the function of OCT2 and MATE1 suggests that caution is warranted when gilteritinib is given in combination with agents that are renally eliminated via these pathways.

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