Model-informed Prediction of Pediatric Drug Interaction with Ritlecitinib

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Introduction. Ritlecitinib is an oral, selective dual inhibitor of JAK3 and TEC family kinases approved for severe alopecia areata. It exhibits time-dependent inhibition (TDI) of cytochrome P450 3A (CYP3A) and 1A2 (CYP1A2) in vitro and undergoes multi-pathway clearance without a single route contributing >25%. Given frequent co-medication in adolescents, quantifying perpetrator drug–drug interaction (DDI) risk in pediatrics is clinically relevant.

Aims. To predict the magnitude of ritlecitinib-mediated changes in exposure (AUC and Cmax) for sensitive CYP3A and CYP1A2 substrates in pediatric subgroups and to contextualize these effects versus adults.

Methods. A physiologically based pharmacokinetic (PBPK) model was developed in PK-Sim (version 11.2) using adult pharmacokinetics, in vitro TDI parameters for CYP3A and CYP1A2, and disposition via glutathione conjugation and CYP oxidation. The model was qualified by reproducing adult probe DDI data at a high dose and scaled to the approved regimen. Age-appropriate physiology and enzyme ontogeny functions for CYP3A and CYP1A2 were applied. Virtual trials simulated co-administration with midazolam and caffeine at standard probe doses in adolescents 12–17 years (primary) and children 6–11 years (exploratory). Outcomes were exposure ratios versus control (AUC and Cmax). Sensitivity analyses varied hepatic function, ontogeny percentiles, and adherence patterns.

Results. The adult qualification reproduced probe interactions within prespecified acceptance, with midazolam AUC ratio (AUCR) at 2.7 and Cmax ratio (CmaxR) at 1.8, with caffeine AUCR at 2.7 and CmaxR at 1.1. In children 6–11 years, predicted ratios for midazolam and caffeine, were increased, reflecting developmental differences in CYP ontogeny. Predicted effects on CYP2B6 (efavirenz) and CYP2C9 (tolbutamide) were small and not clinically meaningful. Across sensitivity analyses, the largest changes were determined to be from variations from different ontogeny profiles.

Discussion. Model-informed translation indicates that, at the approved dose, ritlecitinib-mediated interaction may remain clinically relevant for sensitive or narrow-therapeutic-index CYP3A and CYP1A2 substrates, supporting careful selection or monitoring of co-medications.

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