Physiologically based pharmacokinetic combined JAK2 occupancy modelling to simulate PK and PD of baricitinib with kidney transporter inhibitors and in patients with hepatic/renal impairment

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Abstract

Our aim is to build a physiologically based pharmacokinetic and JAK2 occupancy model (PBPK-JO) to simultaneously predict pharmacokinetic (PK) and pharmacodynamic (PD) changes of baricitinib (BAR) in healthy human when co-administration with kidney transporters OAT3 and MATE2-K inhibitors, and in patients with hepatic and renal impairment. Probenecid and vandetanib were selected as OAT3 and MATE2-K competitive inhibitors, respectively. Here, we have successfully simulated PK and JAK2 occupancy profiles in human by PBPK-JO model. Moreover, this modelling reproduced every observed PK data, and every mean relative deviation (MRD) were below 2. The simulation demonstrated that oral dose of BRA should be reduced to half when co-administration with probenecid. The prediction suggested also vandetanib was unlikely to affect PK and PD of BAR. In simulations of hepatic and renal impairment patients, the predictions suggested that significant changes in PK and PD of BAR occurred. However, there was a lower fold increase in JAK2 occupancies than in PK in patients relative to healthy individuals. In other words, administration dose adjustment of BAR in patients with hepatic or renal impairment should combine PK and PD changes of BAR, instead off only considering PK alteration.

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