Evaluation of the impact of missing a dose of mycophenolate mofetil based on population pharmacokinetic modeling and proposition of a mitigation strategy

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Background. Mycophenolate mofetil (MMF) is crucial to prevent graft rejection after transplantation. Missed doses lead to suboptimal exposure to mycophenolic acid (MPA) and compromise graft and patient outcomes. This study aimed to investigate the impact of missed doses of MMF on exposure to MPA and explore mitigating strategies to prevent prolonged underexposure.

Methods. A published population pharmacokinetics (PK) model for MMF in adult kidney transplant recipients (Rong et al. 2019) was implemented in R software version 4.3.2. The MPA PK profiles of 1000 patients without omission were simulated, and the model implementation was validated by comparing $AUC_{0\text{-}12h}$ values to those published. Subsequently, we simulated PK profiles after missed doses, based on three dosing schemes (500, 750 and 1000 mg BID), and estimated their impact on the following MPA $AUC_{0\text{-}12h}$. Various dose mitigation strategies were then tested, with the objective of restoring the initial $AUC_{0\text{-}12h}$ (prior to the missed dose). The impact of missed doses was then assessed by: (i) comparing the AUC following the oversight compared to the initial $AUC_{0\text{-}12h}$; (ii) evaluating the time required to reach the initial AUC.

Results. The mean estimated $AUC_{0\text{-}12h}$ were 31.2, 48.8 and 62.4 h.mg/L for the dosing schemes of 500, 750 and 1000 mg BID, while 44.5, 6.5 and 2.1% of the $AUC_{0\text{-}12h}$ were below the lower target of 30 h.mg/L. After a missed dose, the mean $AUC_{0\text{-}12h}$ decreased to 18.1, 27.2 and 36.2 h.mg/L, while the proportion of $AUC_{0\text{-}12h}$ <30 h.mg/L increased to 92.9, 56.1 and 23.2%. The mean $AUC_{0\text{-}12h}$ over the following 4 days after omitting the dose approximately 20% lower than the initial $AUC_{0\text{-}12h}$. A full dose intake within the first 6 hours of the dosing interval or a half dose within the next 6 hours limited the duration of underexposure to one day.

Conclusions. We propose a strategy to limit the impact of MMF dose omission in kidney transplant patients, which we will test in other solid organ transplant populations, in order to propose a harmonized strategy for all solid organ transplant recipients.

Keywords. Mycophenolate mofetil, population pharmacokinetics, missed doses, kidney transplantation.