Missed or delayed doses of extended-release tacrolimus in transplantation: impact on exposure and mitigation strategies

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Background. In a lifelong treatment such as with immunosuppressants, there is a high risk of missing a dose, inducing underexposure and loss of efficacy. Strategies limiting the impact of missed doses of immediate-release tacrolimus have already been proposed. Our objective was to find such strategies for prolonged-release tacrolimus (PR-tacrolimus).

Methods. Three population pharmacokinetic models developed in stable kidney and liver transplant recipients on PR-tacrolimus (Moes et al. 2015, Benkali et al. 2010, Martial et al. 2021) were implemented in R software version 4.3.2. Tacrolimus pharmacokinetic profiles of 1000 patients at steady state (SS) were simulated, with doses targeting trough concentrations (C_0) of 5 or 7.5 µg/L. Various scenarios were considered, from a 3-hours delayed dose to a completely missed dose. The effect of a missed dose on tacrolimus exposure was evaluated on the following area under the curve over 24 hours ($AUC_{0\text{-}24h}$) and on the C_0. The relative difference (RD) between SS and up to five days after the missed dose was calculated for C_0 and $AUC_{0\text{-}24h}$. Different dose adjustments scenarios allowing the restoration of exposure as fast as possible were tested.

Results. A 3-hour delayed dose induced a variation of +1 to +14% on the following C_0 and -1 to -4% on the following $AUC_{0\text{-}24h}$, depending on the models. A missed dose resulted in a variation of -12 to -65% on the following C_0 and -24 to -67% on the following $AUC_{0\text{-}24h}$, while five days were necessary for both exposure indices to reach their initial SS values. The best strategies restoring appropriate exposure depended on the dosing interval and were the following: immediate intake of the full dose for a delay of less than 12 hours; intake of 150% of the original dose at the time of the next scheduled dose, for a 12 to 24-hour delay.

Conclusions. Pharmacokinetic simulations provided valuable data on how to handle delayed or missed doses in kidney and liver transplant recipients receiving PR-tacrolimus. These recommendations should be applied in order to minimize the risk of graft rejection and adverse effects.

Keywords. Prolonged-release tacrolimus, population pharmacokinetics, delayed dose, missed dose, renal transplantation, liver transplantation.