Tacrolimus Bayesian dose adjustment in a large population of paediatric renal transplant recipients

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Abstract

Background: The Immunosuppressive drug Bayesian dose Adjustment website (ISBA) offers an online expert system routinely used for estimating the area under the curve (AUC) of immunosuppressive drugs through pharmacokinetic modelling and Bayesian estimation, and proposing dose adjustments to reach predefined exposure targets. We retrospective analysed the ISBA database to describe tacrolimus pharmacokinetics and exposure, evaluate the efficiency of ISBA dose recommendations, and propose tacrolimus AUC_{0-12h} target ranges in paediatric kidney allograft recipients.

Methods: We analysed 1935 requests for tacrolimus dose adjustment in 419 patients aged <19 years treated with immediate-release tacrolimus, posted by 21 French renal transplantation centres. We studied the time evolution of tacrolimus exposure, the correlations between C0 and AUC_{0-12h} at different periods post-transplantation and the efficiency of dose recommendation to avoid underexposure and overexposure and decrease between-patient AUC variability.

Results: Between-patient AUC variability was large (CV%=45-47%), while within-patient variability was smaller (32.3% overall, 25.8% over a 3-month time window), at odds with common belief. The AUC_{0-12h} ranges were calculated from the consensual C_0 ranges using linear regression. C_0/dose, Cmax/dose and AUC/dose significantly increased over time to reach a maximum at 1-year post-transplantation, and then decreased slightly. In contrast, the AUC/C_0 ratio did not significantly vary.

Lower interquartile ranges and a significantly higher proportion of AUCs within targets were observed when the ISBA recommended dose was actually applied (p<0.0001).

Conclusion: ISBA efficiently help to reduce tacrolimus underexposure or overexposure. We propose AUC_{0-12h} target ranges for paediatric patients, very close to those previously reported for adults. Estimating the AUC/C_0 ratio may help determine personalized C_0 targets.

Keywords: Renal transplantation, immunosuppressant, tacrolimus, therapeutic drug monitoring, paediatric adjustment