Poster

[P25-8] P25-8: Immunosuppressive drugs (3): Biomarkers and pharmacokinetics

Chair: Hideyuki Motohashi, Japan

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[P25-8-3] Pharmacokinetic of tacrolimus in Mexican adult patients with renal transplant: population analysis with NONMEM

Silvia Romano[1], Juan Eduardo Resendiz[2], Susanna Medellin[3], Rosa Milan[4], Perla Nino[5], Javier Isordia[6]

(1.Universidad Autonoma de San Luis Potosi, 2.Universidad Autonoma de San Luis Potosi, 3.Universidad Autonoma de San Luis Potosi, 4.Universidad Autonoma de San Luis Potosi, 5.Universidad Autonoma de San Luis Potosi, 6.Hospital Centraldr Ignacio Morones Prieto)

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Background

Tacrolimus (TAC) is the calcineurin inhibitor most used because it shows lower incidence of adverse events and survival improvement in short-term, after renal transplantation. The aim of this study was to analyze the pharmacokinetics of TAC in renal transplant patients, using a mixed-effects modelling to propose a dosage regimen for Mexican population.

Methods

A total of 65 patients attended by Transplantation Unit (TU) at the Hospital Central “Dr. Ignacio Morones Prieto” in San Luis Potosí (México) were included in this study. Informed consent was retrieved and all procedures performed were in accordance with the ethical standards of the institutional research committee. Trough blood concentrations versus time was best described by a one-compartment open model with first-order elimination rate; the influence of sex, age, weight, height, body mass index, serum creatinine, creatinine clearance, urea, glucose, blood urea nitrogen, hematocrit and concomitant pharmacotherapy on TAC clearance (CL) was evaluated through NONMEM (NONlinear Mixed Effects Model) software version 7.2.

Results

Final population pharmacokinetic model obtained was CL= 30.1, 20.5 and 16.0 L/h, for the genetic polymorphism CYP3A5*1*1, CYP3A5*1*3 y CYP3A5*3*3 respectively, with a typical value of hematocrit (39%) and assuming a distinct relative bioavailability for each generic trademark of TAC administered during the current study. The influence of hematocrit was demonstrated to be inverse to TAC CL, following an allometric power function. Internal validation of the final model, using the Bootstrap technique (resampling of 200) and the external validation (n = 13) demonstrated the stability and the precision of the pharmacokinetic parameters for the final model. Stochastic simulations were performed to propose a dosage regimen based on hematocrit CYP3A5 genotype and generic formulation of TAC.

Conclusions

A population pharmacokinetic model was successfully developed on Mexican adult patients with renal transplant and the influence of hematocrit, CYP3A5 genotype and generic formulation on dosage regimen and trough blood concentrations, was demonstrated.