

Early impact of donor CYP3A5 genotype and Graft-to-Recipient Weight Ratio on tacrolimus pharmacokinetics in pediatric liver transplant patients

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Background and objectives
Tacrolimus (TAC) pharmacokinetics is influenced by the donor CYP3A5 genotype and the age of pediatric liver recipients. However, an optimization of a genotype-based algorithm for determining TAC starting is needed to earlier achieve stable target levels. As the graft itself is responsible for its metabolism, the Graft-to-Recipient Weight Ratio (GRWR) might play a role in TAC dose requirements.

Materials and Methods
A single-center study was carried out in a cohort of 49 pediatric recipients to analyse the impact of patient and graft characteristics on TAC pharmacokinetics during the first 15 post-transplant days.

Results
Children <2 years received grafts with a significantly higher GRWR (4.2%) than children between 2–8 (2.6%) and over 8 (2.7%). TAC concentration/weight-adjusted dose ratio was significantly lower in recipients from CYP3A5*1/*3 donors or with extra-large (GRWR>5%) or large (GRWR 3–5%) grafts. The donor CYP3A5 genotype and GRWR were the only significant predictors of the TAC weight adjusted doses. Patients with a GRWR>4% had a higher risk of acute rejection, observed in 20/49 (41%) patients.

Conclusions
In conclusion, TAC starting dose could be guided according to the donor CYP3A5 genotype and GRWR, allowing for a quicker achievement of target concentrations and eventually reducing the risk of rejection.

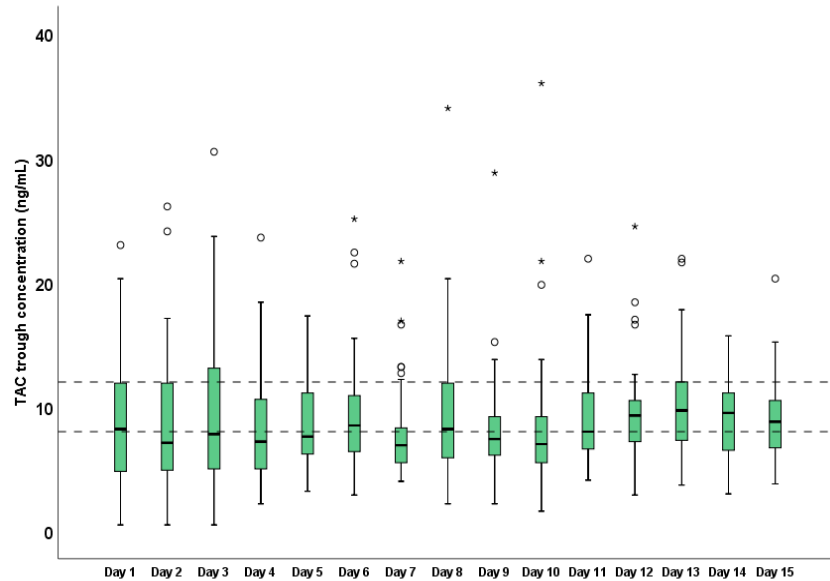


Figure 1 Daily TAC blood concentration after liver transplant. TAC, tacrolimus.

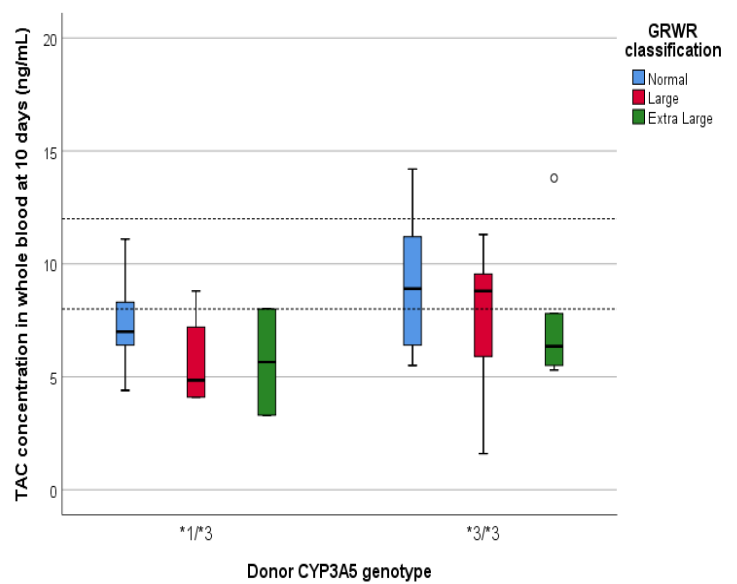


Figure 2 TAC blood concentrations on the 10th post-transplant day stratified by GRWR and the donor CYP3A5 genotype. TAC, tacrolimus; GRWR, Graft-to-Recipient Weight Ratio.

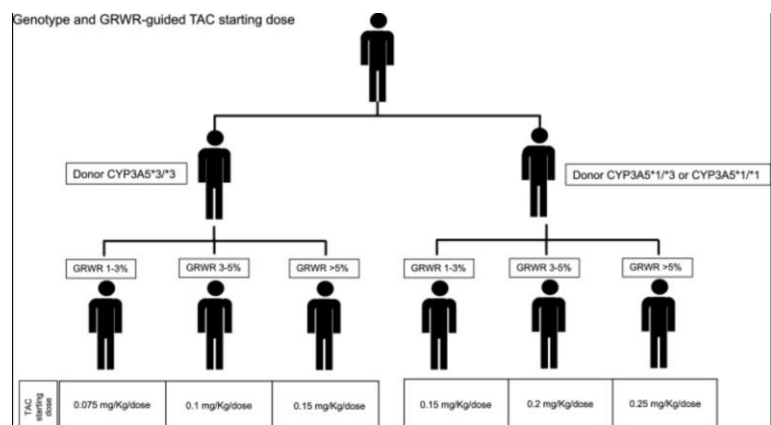


Figure 3 Proposal for an algorithm for a genotype and GRWR guided TAC starting dose. TAC, tacrolimus; GRWR, Graft-to-Recipient Weight Ratio.