Immunomonitoring of Tacrolimus in healthy volunteers: the first step from PK- to PD-based therapeutic drug monitoring

A.E. in 't Veld[1], H.W. Grievink[1], M. Saghari[1], F.E. Stuurman[1], M.L. de Kam[1], B.C.M. de Winter[2], J. Burggraaf[1], A.F. Cohen[1], M. Moerland[1]

[1]*Centre for Human Drug Research, Leiden, the Netherlands*

[2] *Department of hospital pharmacy, Erasmus Medical Center, Rotterdam, the Netherlands*

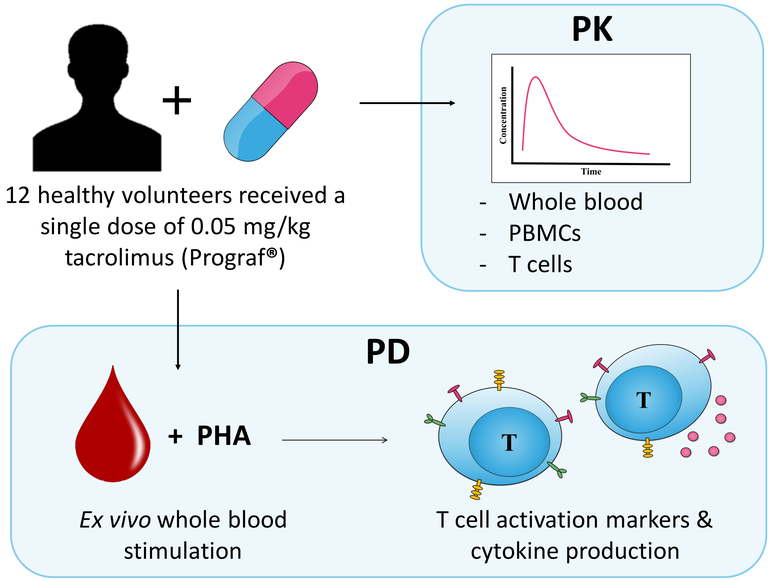
Introduction

To prevent allograft rejection after kidney transplantation, patients need long-term treatment with calcineurin inhibitors (CNI). CNI-treatment (e.g. Tacrolimus) has a small therapeutic window and a large inter-patient variability in clinical effect. Even though PK-based therapeutic drug monitoring is routinely performed, toxicity and rejection of the transplanted organ still occurs.

Aim

To develop functional immune tests for quantifying the immunosuppressive state in individuals, which can help optimize tacrolimus dosing strategies.

Methods



Results

- PK in T cells was much lower than in PBMCs (Fig. 1A).
- Tacrolimus concentrations correlated well between whole blood and T cells (Fig. 1B).
- Tacrolimus inhibited PHA-induced IL-2 and IFN-γ production, and CD154 and CD71 expression (Fig. 2).
- The maximal tacrolimus effect was observed at a concentration of 21.4 ± 6.2 µg/L (1.5 hrs post-dose), and was in line with tacrolimus effect in vitro (Fig.2).

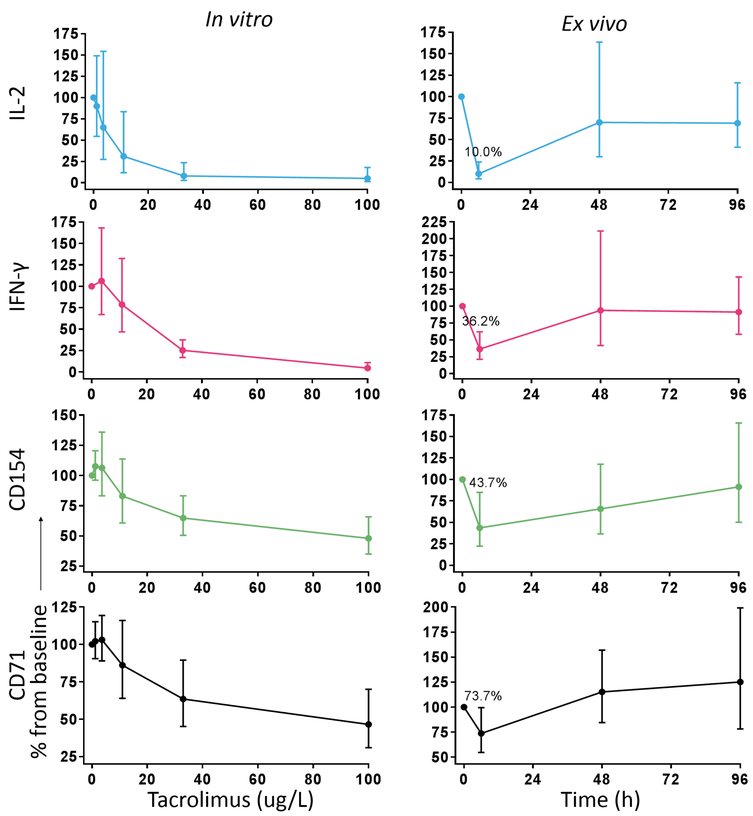


Figure 2: In vitro and ex vivo tacrolimus effect (cytokine production, and cell surface marker expression).

Conclusions

- The selected whole blood-based assays were feasible for quantification of tacrolimus activity in individual subjects.
- A future study in transplant patients will evaluate the relationship between pharmacodynamic activity and the clinical effect, aiming for future PD-based therapeutic drug monitoring.

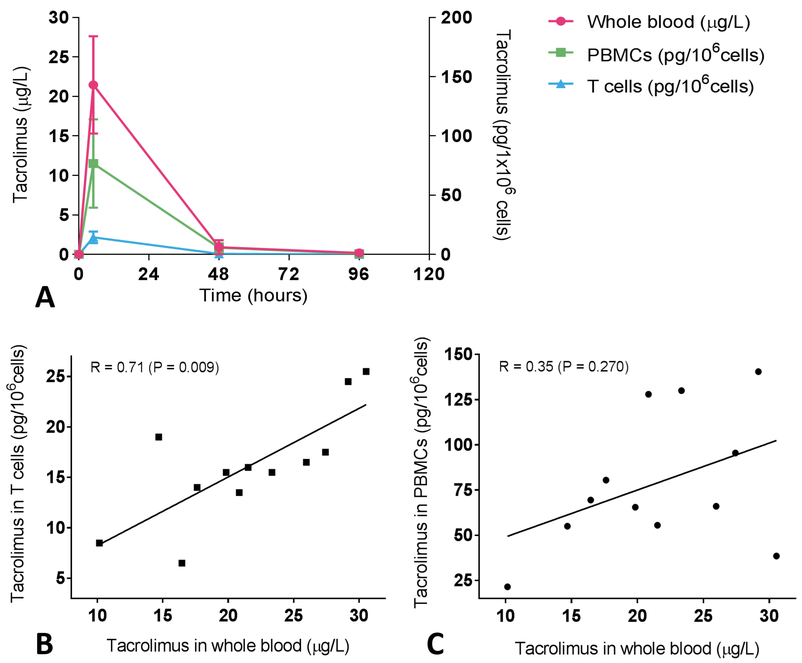


Figure 1: PK profile in whole blood, PBMCs and T cells (A), and the correlation between the different PK parameters (B,C).

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Centre for Human Drug Research

Centre for Human Drug Research | Zernikedreef 8 | 2333 CL Leiden | The Netherlands | Tel +31 71 52 46 400 | info@chdr.nl | www.chdr.nl