Pharmacodynamic monitoring of cyclosporin A activity using *ex vivo* T cell function assays

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Introduction

Therapeutic drug monitoring (TDM) of immunosuppressive treatment is currently standard of care after solid organ transplantation. TDM is mostly used for individualized dosing of calcineurin inhibitors (i.e. tacrolimus and cyclosporin A), since these are known for their large pharmacokinetic intrapatient variability and small therapeutic window. Although the incidence of acute rejection has strongly decreased after implementation of TDM, there are still many transplantation patients that experience severe side effects after several years of treatment, indicating that the current monitoring strategy need further optimization.

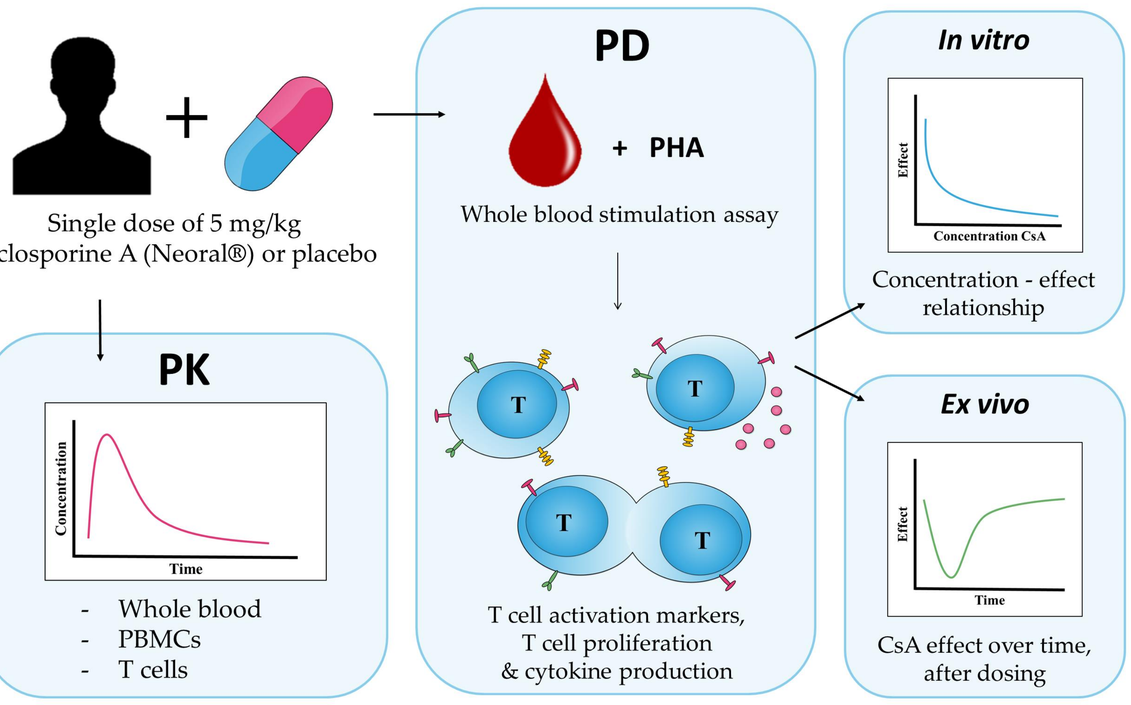
Aim

To identify clinically relevant biomarkers for a pharmacodynamic-based monitoring approach for treatment with calcineurin inhibitors

Results

- At 2 hours post-dose, the highest whole blood concentration of Cyclosporine A (CsA) was found (1615.3 µg/L) – Figure 1
- CsA strongly inhibited PHA-induced IFN-γ and IL-2 production (93% and 73% respectively), and the expression of CD154 and CD71 on T cells (86% and 52% respectively), but did not have a strong inhibitory effect on T cell proliferation – Figure 2 and 4B
- CsA strongly inhibited all markers i*n vitro*, with an Emax reaching 100% inhibition for IL-2 and IFN-γ production, and CD154 expression – Figure 3
- The *in vitro* effect of CsA showed a clear correlation with the *ex vivo* drug effect – Figure 4A and B

Methods



Conclusions

- The selected whole blood-based assays were feasible for the quantification of drug effect of CsA in healthy volunteers.
- A future study will evaluate these readout measures in kidney transplantation patients receiving a combination of immuno-suppressive drugs.

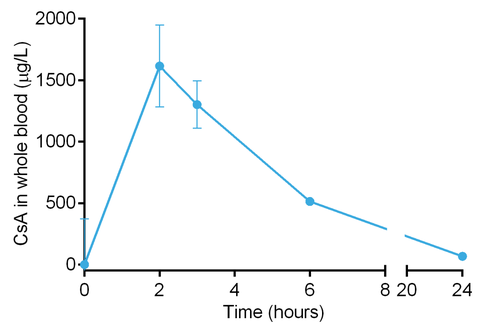


Figure 1: Concentration of Cyclopsorine A in whole blood at 0, 2, 3, 6 and 24 hours post-dose.

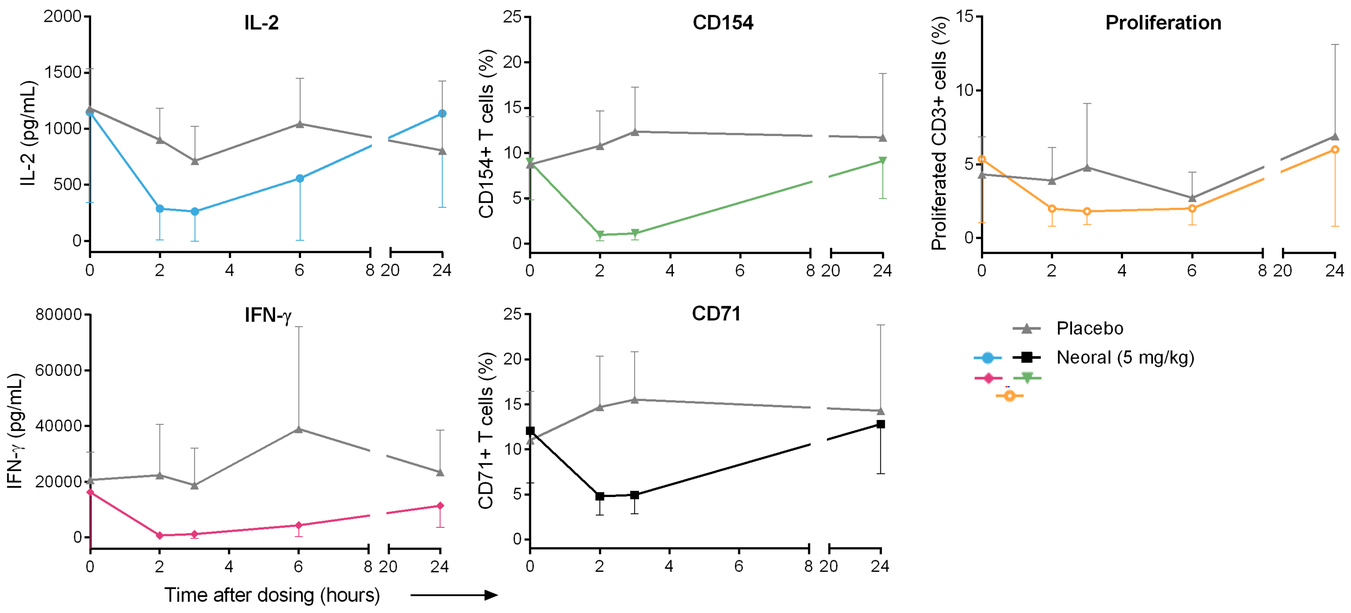


Figure 2: Ex vivo effect of cyclosporine A on cytokine production and cell surface marker expression

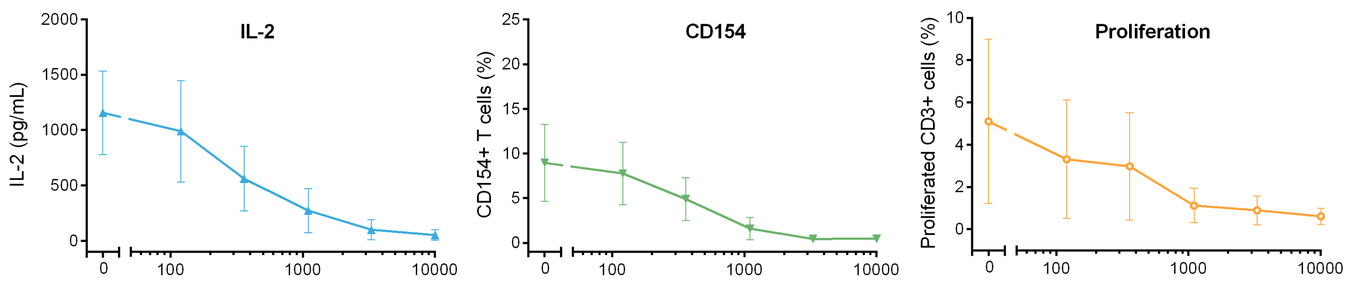


Figure 3: In vitro effect of cyclosporine A on cytokine production and cell surface marker expression

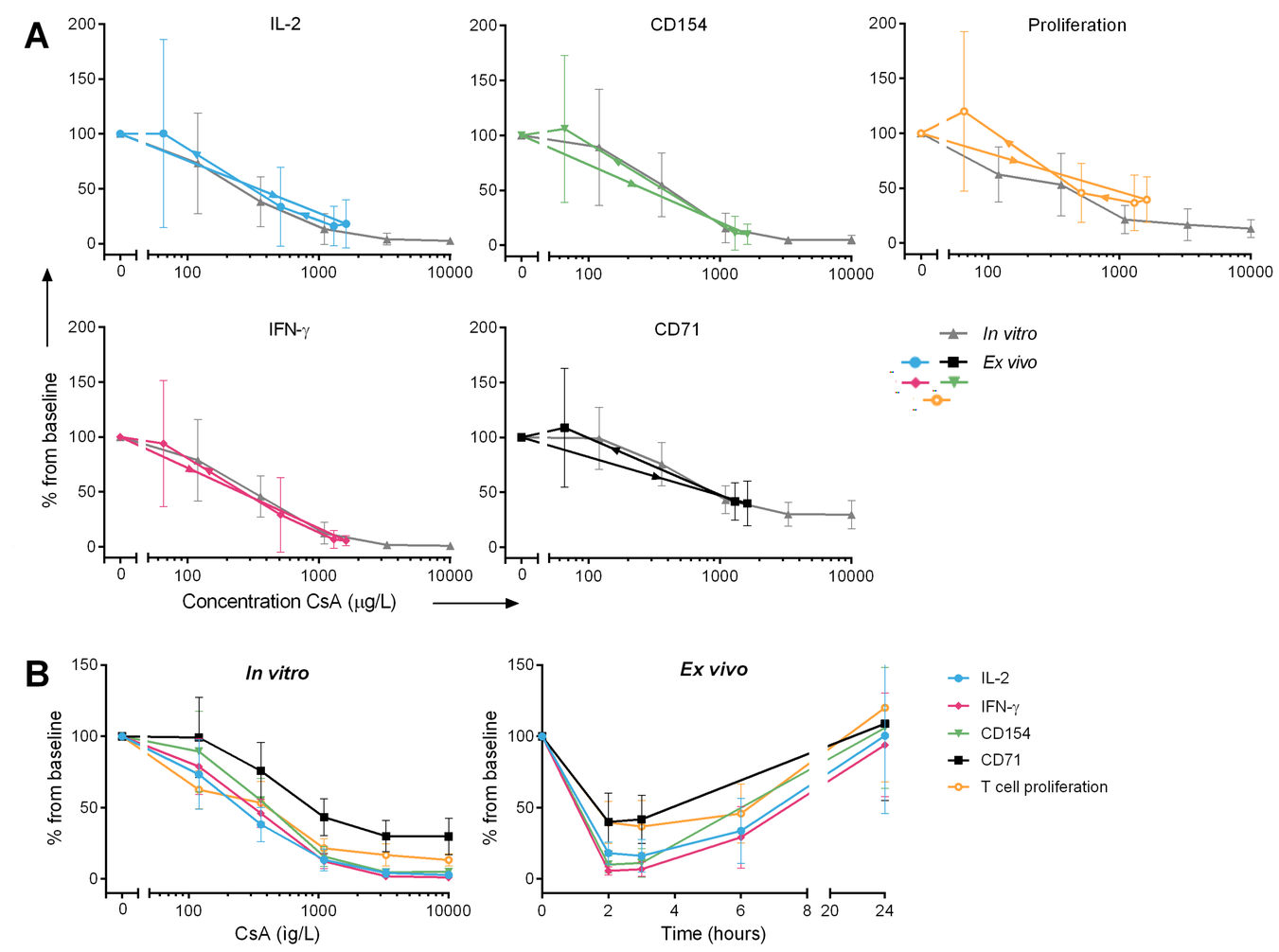


Figure 4: Correlation of in vitro and ex vivo effect of Cyclosporine A on cytokine production, cell surface marker expression and T cell proliferation (A).
In vitro and ex vivo effect of Cyclosporine A on all markers shown in figure 2 and 3, expressed as percentage from baseline (B).

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