INFLUENCE OF CYCLOSPORIN INFUSION DURATION ON EFFICACY IN PAEDIATRIC BONE MARROW TRANSPLANTATION: ANALYSIS BY A PBPK MODEL

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Objectives
In bone marrow transplantation (BMT), cyclosporin is used to prevent the graft versus host disease (GVHD). In our hospital, more frequent and severe GVHD were observed with continuous infusion than with twice daily infusion (2 h every 12 h), given the same daily dose (mg/kg) (table I). The team of Rowland has built a physiologically based pharmacokinetic (PBPK) model of cyclosporin in rats (fig. 1) and clearly showed that cyclosporin distribution presents several sources of non-linearity [1]. Our hypothesis is that the difference of efficacy of cyclosporin between both types of infusion is linked to a difference of tissue distribution of the target organs of GVHD (skin, intestine and liver). The objective of this study was to compare, with a global PBPK model, exposure of these organs to cyclosporin for each type of infusion.

Methods
The rat PBPK model of Rowland was scaled up to human adult and adjusted to children. The scaling was based on physiological data and allometric equations. The model was implemented in ADAPT II. The paediatric PBPK model was fitted individually (bayesian MAP estimator) to cyclosporin blood concentrations from 61 paediatric patients (31 and 30 with intermittent and continuous infusion, respectively). Both groups were comparable for demographics, BMT indication (table II) and initial dosing regimen. Using the adjusted PBPK model, the AUCs in blood and target organs were calculated for each child.

Results
Kinetic profiles simulated in blood and all organs with the rat PBPK model were similar to the experimental data [1].

The study showed that mean AUCs were significantly greater for the blood and GVHD targeted organs at the beginning of the treatment (0-24 hours) when cyclosporin was administered by intermittent rather than continuous infusion (p < 0.05 in each case) (fig. 3). The ratio of mean AUCs 0-24h (intermittent / continuous) was 1.25 (blood), 1.42 (skin), 1.10 (intestines), 1.25 (liver).

Conclusion
The PBPK model in children showed that the day 1 exposure to cyclosporin was more important in the GVHD target organs when it was administered by intermittent infusion, which is consistent with the greater efficacy of intermittent infusion in prevention of GVHD.