Determination of effective blood concentrations of cyclosporine in the treatment of severe aplastic anemia in children

M. Philippe[1], E. Hénin[2], Y. Bertrand[3], D. Plantaz[4], S. Goutelle[5], N. Bleyzac[1]

[1]Pharmacy Department, Pediatric Hematology and Oncology Unit, IHOP, France ;
[2]Departement of Clinical Pharmacology & Clinical Trials, Hospices Civils de Lyon, France ;
[3]Transplantation Unit, Pediatric Hematology and Oncology Unit, IHOP, Lyon, France ; [4]Pediatric Hematology and Oncology Unit, CHU Grenoble, Grenoble, France ;
[5]Pharmacy Department, Groupement hospitalier de gériatrie, Lyon, France.

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Introduction

Optimal immunosuppressive therapy in acquired severe aplastic anemia (SAA) remains to be refined, especially cyclosporine (CsA) use. Current recommendations state that CsA trough blood concentrations (TBC) should be maintained between 200 and 400 ng/mL despite the lack of supporting data. This study aimed at quantifying relationships between exposure to CsA and hematological response, and at determining the optimal CsA TBC target.

Materials and methods

23 pediatric patients with SAA treated with CsA were retrospectively analyzed. **Nonlinear mixed effects modelling** approaches were used to develop a Pharmacokinetic-Pharmacodynamic model. The **pharmacokinetic model** described the relationships between CsA doses and TBC. The **pharmacodynamic model** allowed to estimate boundaries for optimal CsA effects, neutrophils being used as biomarker of response. A **time-to-event model** linked effective concentration to time-to-therapeutic success (TTR). **Simulations** were subsequently performed using the model to evaluate the chance of therapeutic success according to various CsA TBC target, and thus estimate the optimal CsA exposure. Time-to-therapeutic success was externally predicted in **two additional patients** not included in the model building

Results

The median (min-max) age and weight were: 8.5 (8-15) years, and 34 (9.8-79.3) kg, respectively. 15/23 patients responded to the IST (65.2%) with a median time of response of 69 days (min 19- max 182). CsA TBC were adequately described by a two-compartment model (**Fig. 1**) with first order absorption, a lag-time and a linear elimination. The optimal target range of CsA TBC was estimated between 87 and 120 ng/mL (relative standard error < 5%). Model-based simulations showed that CsA TBC should be maintained around 100 ng/mL to expect a maximal response rate (**Fig. 4**). Using the model, TTR could adequately be predicted for two new patients (**Fig. 5**).

Cyclosporine population Pharmacokinetic parameters in SAA children.

Parameter	Typical values (%rse)	Interindividual variability (% CV)
F	0·386	0 (fixed)
Tlag (h)	0·648	0 (fixed)
ka (h^{-1})	0·829	0 (fixed)
V_1 ($L.(34\ kg)^{-1}$)	37·5 (59)	30
Q ($L.h^{-1}.(34\ kg)^{-0.75}$)	2·7 (64)	66·2
V_2 ($L.(34\ kg)^{-1}$)	1690 (50)	30
Cl ($L.h^{-1}.(34\ kg)^{-0.75}$)	7·2 (28)	31·4
a (mg/L)	0·03 (15)	-
b (%)	25 (14)	-

F=bioavailability; Tlag=lag time; ka=absorption rate constant; V1=volume of distribution of the central compartment; V2=volume of distribution of the peripheral compartment; Q=intercompartment clearance; Cl=total body clearance; a=additive error; b=proportional error; rse=relative standard error; CV=coefficient of variation.

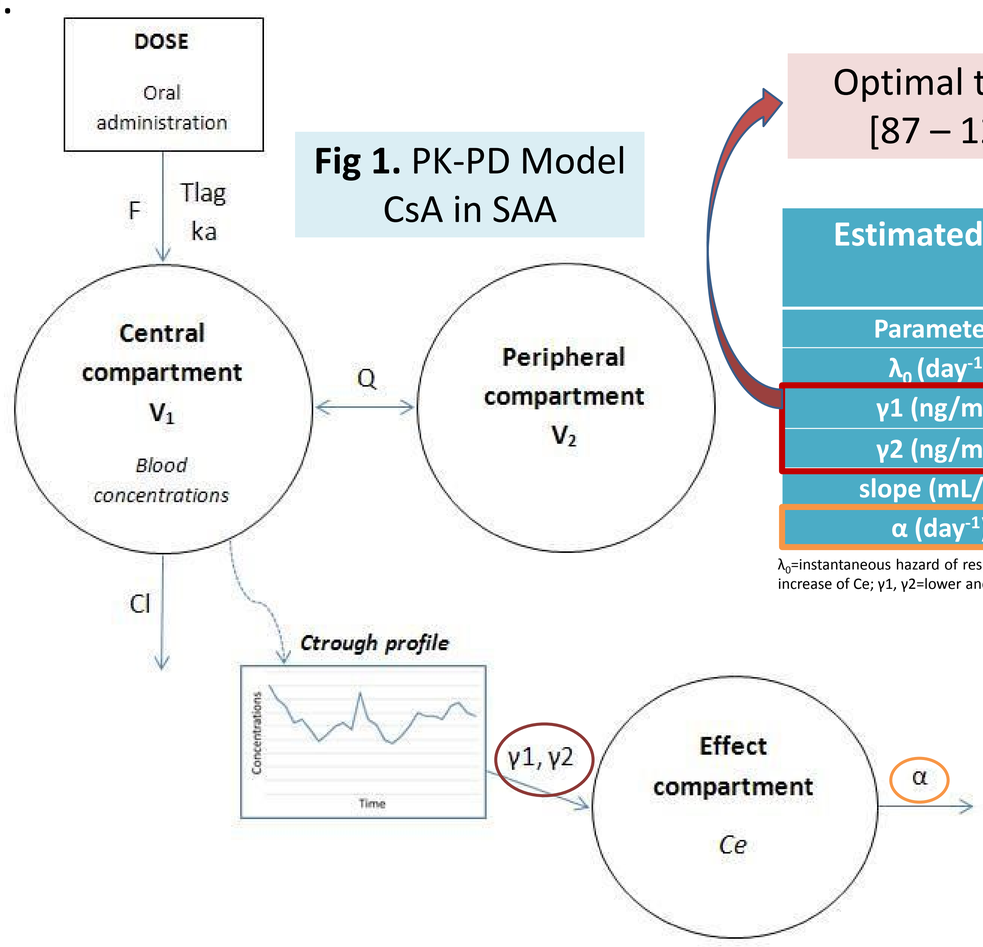

Fig 1. PK-PD Model CsA in SAA

Optimal target range: [87 – 120 ng/mL]

Estimated parameters of Time-to-therapeutic success model

Parameters	Typical value (%rse)
λ_0 (day^{-1})	0·0027 (58)
γ1 (ng/mL)	87 (3)
γ2 (ng/mL)	17·2 (102)
slope (mL/ng)	87 (3)
α (day^{-1})	0·028 (107)

λ_0=instantaneous hazard of response without treatmentslope=rate of increase of the instantaneous hazard for one unit increase of Ce; γ1, γ2=lower and upper bounds of CsA TBC ; ; α=elimination rate constant of effective concentration.

$$T_{1/2\,(effect)} = \frac{ln2}{\alpha} = \mathbf{25\ days}$$

Validation PK

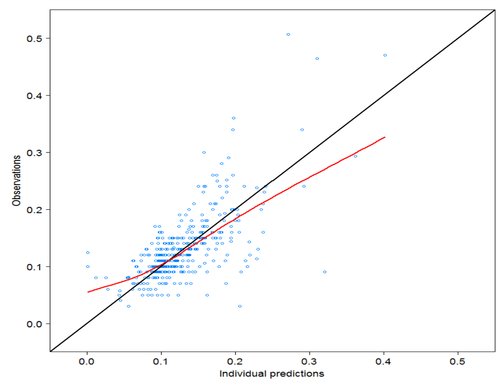

Fig 2. Individual predictions versus observed concentrations.

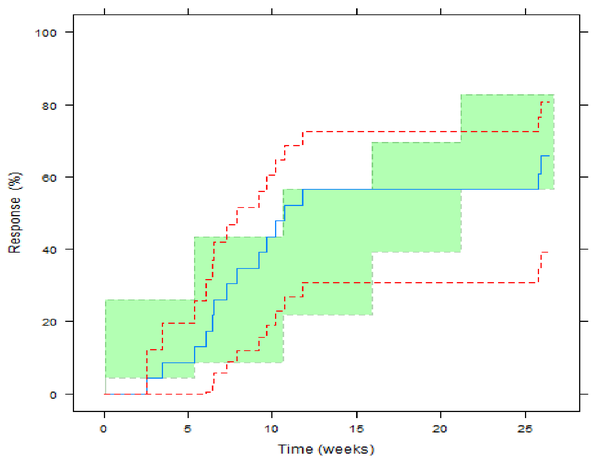

Fig 3. Visual predictive checks of the probability of response over time

Simulations

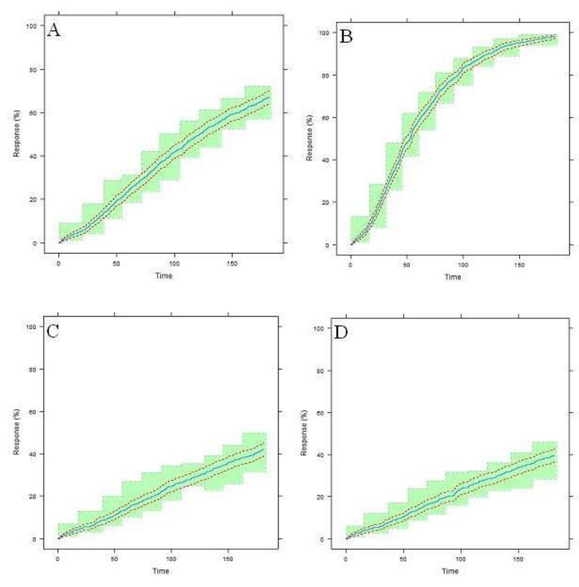

Fig 4. Profiles of simulated probability of treatment response with different TBC targets: 80 (A), 100 (B), 150 (C), and 200 ng/mL (D) with a variability of 10%.

External validation

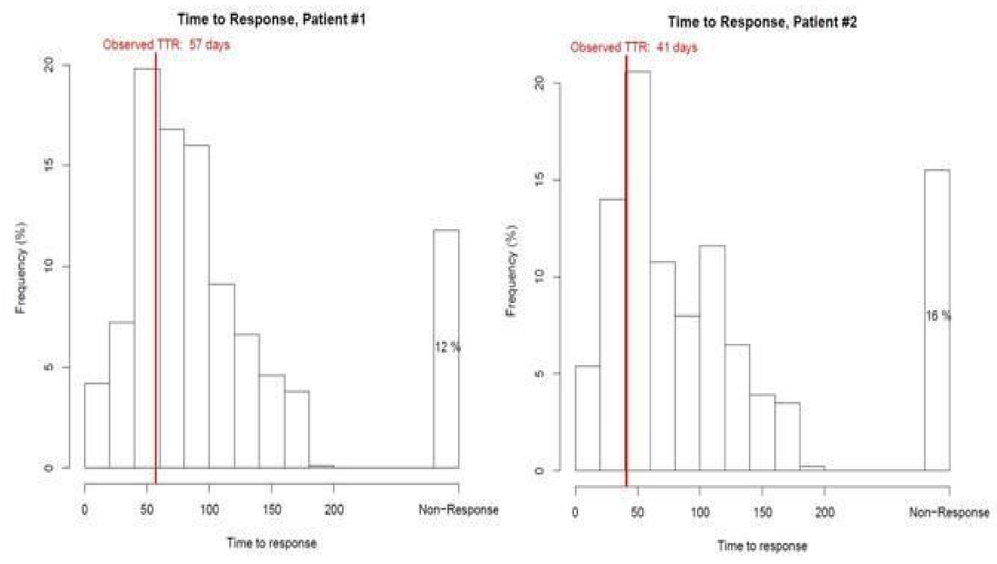

Fig 5. Predicted distribution of the TTR (histogram) and observed time-to-therapeutic success (red line) in two external patients

Conclusion

This original modelling approach was successful in describing the relationship between CsA TBC and the neutrophil response in patients with SAA. While further research in a larger population is necessary to confirm our findings, this work suggest that a CsA TBC target of 100 ng/mL, much lower than that currently recommended, would be associated with a better response rate in children with SAA. These results are in agreement with the SAA physiopathology, the involvement of regulatory T-cells (Treg) and concentration-dependent effect of CsA on Treg via IL-2.