DEVELOPMENT OF A POPULATION PHARMACOKINETIC MODEL OF CYCLOSPORINE

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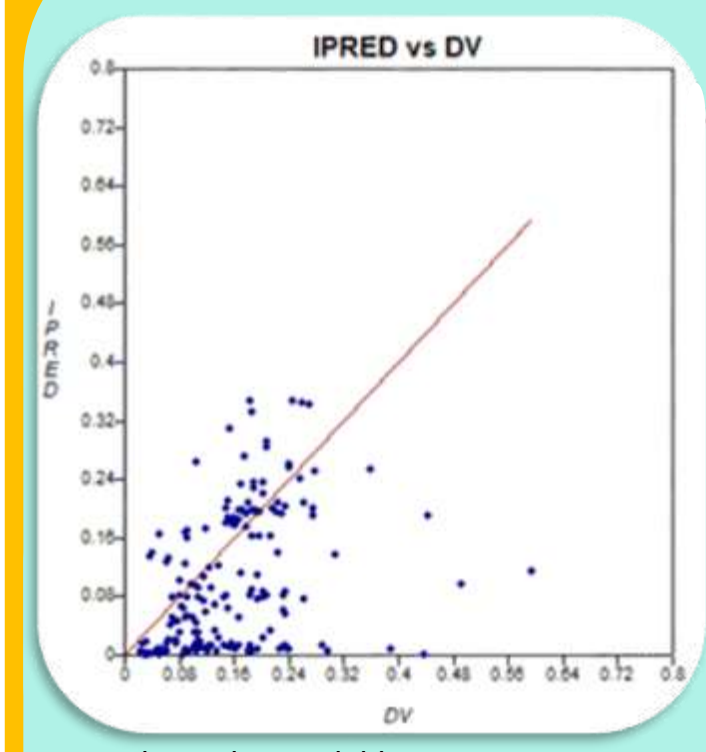
Aim and objectives

- Design a population pharmacokinetic model of cyclosporine.
- Analyze the influence of the recorded covariates.

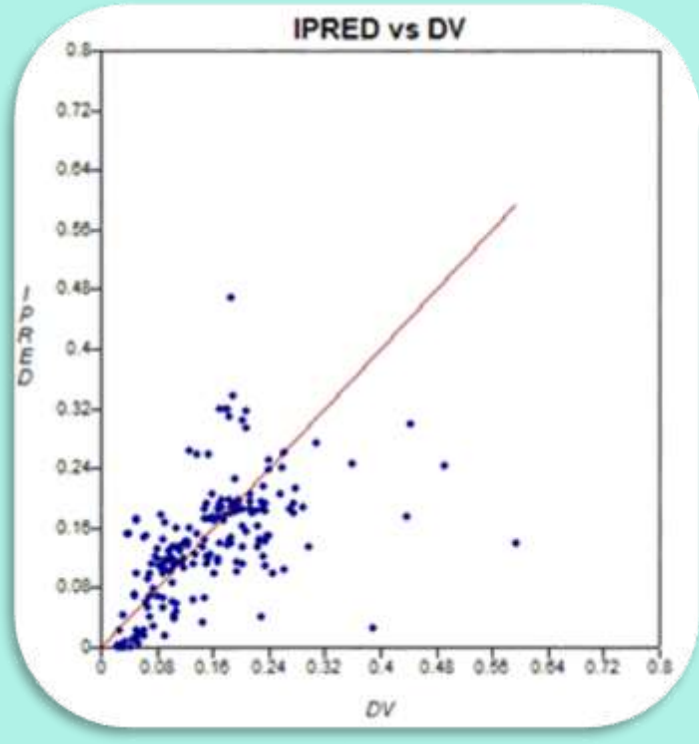
Materials and methods

- **Design**: Retrospective observational study between January 2016 and April 2022.
- **Inclusion criteria**: patients hospitalized at Severo Ochoa University Hospital treated with cyclosporine.
- **Exclusion criteria**: Patients hospitalized in the ICU and outpatients were excluded.
- **Data recorded**: date, time and value of the CSC, route of administration, doses administered, sex, age, weight, hematocrit, albumin, serum creatinine and concomitant treatment.
- **Analysis**: the one- and two-compartmental models were tested with 4 estimations: first order, first order with interaction, first order conditional and first order conditional with interaction. The influence of the covariates was evaluated, selecting those that showed a statistically significant reduction in the objective function (OFV).

One-Compartment Model



Two-Compartment Model



DV: dependent variable
IPRED: individual predictions

Background and importance

Cyclosporine is an immunosuppressive drug with complex pharmacokinetics, a narrow therapeutic interval and dose-related adverse effects (nephrotoxicity, hepatotoxicity, and neurotoxicity).

Amiodarone, verapamil and macrolides increase cyclosporine serum concentrations (CSC), whereas phenytoin, carbamazepine and rifampin decrease CSC.

Therefore, therapeutic drug monitoring of cyclosporine is of great importance in routine clinical practice.

Results

N=29 patients
66,7% **female**

- ✓ **Age**: 65 years-old (28-92)
- ✓ **Mean weight**: 75.1 kg (42.5-125)
- ✓ **Serum creatinine**: 1.12 mg/dL (0.33-4.41)
- ✓ **Serum albumin**: 3.5 g/dL (2.3-4.6)
- ✓ **Hematocrit**: 32.6% (13.4-48.5)
- ✓ **None** of the patients received the registered drugs

OFV	
One-compartment model	Two-compartment model
-663,636	-654,430

Two-compartment model: variables **age and weight** showed influence on **clearance**, but without **statistically significant differences**.

No covariate showed an **effect** on the **volume of distribution.**

Better correlation between the CSC and those predicted, therefore the analysis of the covariates was continued with the two-compartment model.

Conclusion and relevance

- ✓ The two-compartment model with first order conditional estimation with interactions showed a better goodness of fit.
- ✓ The development of a pharmacokinetic model of cyclosporine assists clinicians to establish an effective and safe dosing regimen.
- ✓ Further studies are needed to better analyze the population pharmacokinetics of cyclosporine.

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