Population Approach to Assess the Relationship of Cyclosporin Exposure and Renal Dysfunction in Japanese Patients with Rheumatoid Arthritis

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Background

Therapeutic drug monitoring (TDM) for cyclosporin

- ✓ **Efficacy:** Immunosuppressive effect (suppressing T-cell functions)
- ✓ **Safety:** Renal dysfunction, Hypertension
- ✓ **Pharmacokinetics:** Large inter-subject variability
- ✓ **Pharmacodynamics:** Narrow therapeutic window

→ **Drug Monitoring in clinical use**

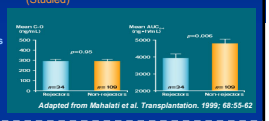
Background

PK/PD studies for TDM

Clinical events (efficacy & safety) ⇔ (Studied) Exposure in drug monitoring days (C0, AUC_{0-4}, C2)

(Example)

Exposure at 2 - 4 days after start of Neoral® dosing vs Acute rejection during 3 months after transplantation



Adapted from Mahalati et al. Transplantation. 1999; 68:55-62

Clinical events (efficacy & safety) ? (Not studied) Exposure from start of dosing to clinical events (accumulative AUC, mean conc.)

Investigation on exposure / renal dysfunction relationship in Japanese patients with rheumatoid arthritis

Clinical study design

Dosage

0 - 4 weeks: 2.5mg/kg/day (b.i.d)

4 - 24 weeks: Adjust daily dose based on efficacy and safety

Pharmacokinetics

Sparse sampling, PPK analysis

Efficacy

ACR20 (American College of Rheumatology criteria)

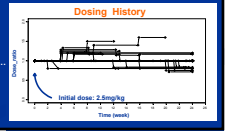
Safety (AE: adverse events)

Renal dysfunction, Hypertension, …

Background and administered doses

Number of patients (M / F)	50 (13/ 37)
Age (years)	58 ± 10
Body weight (kg)	52.9 ± 9.3
Number of blood samples	527
Dose (mg/kg) start	2.50 ± 0.14
period	2.56 ± 0.25
end	2.54 ± 0.44
Treatment period (week)	21.3 ± 5.3

Dosing History



Population PK analysis

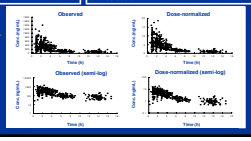
Factor tested for oral clearance (CL) in fixed model

- ✓ Age, Gander, Body weight
- ✓ White blood cell
- ✓ Red blood cell, Hemoglobin, Hematocrit, Total cholesterol
- ✓ Blood urea nitrogen, Serum creatinine
- ✓ Total bilirubin, ALT, AST, alkaline phosphatase
- ✓ Methotrexate treatment history

Test method

- ✓ NONMEM (V.1.1), (ADVAN4, TRANS4: 2-compartment model with first-order absorption)
- ✓ Compaq Visual Fortran (6.6)
- ✓ FOCE INTERACTION method
- ✓ Inter-patient variability : Log-normal distribution model
- ✓ residual variability : Proportional model
- ✓ Log-likelihood ratio test (p<0.05), forward selection

Drug concentration-time profiles

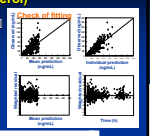


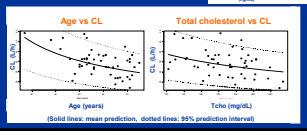
Covariates of oral clearance (age, total cholesterol)

$CL = 28.0 \cdot (Age/58.5)^{-0.525} \cdot (Tcho/192.5)^{-0.402}$ [L/h]

V2	= 41.2	[L]
Ka	= 0.541	[h^{-1}]
Q	= 17.8	[L/h]
V3	= 247	[L]

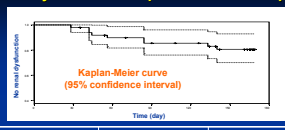
(Age: years, Tcho - total cholesterol: mg/dL)





(Solid lines: mean prediction, dotted lines: 95% prediction interval)

Renal dysfunction / exposure relationship



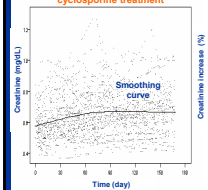
	Adverse event (No)	Adverse event (Yes)
N (M/F)	41 (11/30)	9 (2/7)
Age (years)	58 ± 10	61 ± 10
WT (kg)	51.7 ± 9.5	58.0 ± 6.5
Total dose (mg/kg) *	385 ± 95	193 ± 104
Average daily dose (mg/kg) *	2.58 ± 0.26	2.67 ± 0.22
Total AUC_{0-4} (μg·h/mL) # *	676 ± 251	512 ± 363
Mean concentration (ng/mL) # *	169 ± 64	128 ± 91 (p=0.067) *

#: Calculated with the PPK model Mean +- SD, *: Cox proportional hazards model analysis

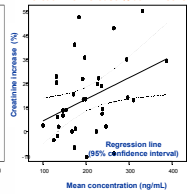
*: from start of dosing to the incidence in patients with AE or to the last available visit in patients without AE

Serum creatinine during cyclosporine treatment

Time course of serum creatinine during cyclosporine treatment



Mean blood concentration vs creatinine increase % at 24 weeks



Summary

- ✓ Age and total cholesterol were significant covariates for oral clearance, but 95 % prediction interval for each correlation curve was wide due to inter-individual variability.
- ✓ The population PK model, which fitted closely observed blood concentration-time data, enabled us to simulate exposure in each patient, i.e., total AUC, and mean blood concentration from start of dosing to the incidence in patients with the adverse event (AE) or to the last available visit in patients without the AE.
- ✓ Renal dysfunction is related to mean blood concentration rather than total doses, average daily doses, or total AUC.