Hospital pharmacometrics contributing to the treatment of connective tissue diseases with low dose cyclosporine A

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Background
Cyclosporine A (CsA) has been used for the treatment of connective tissue diseases more than two decades. However, during the treatment with CsA, drug concentration-dependent adverse events such as renal disorder have appeared frequently. Recent studies reported low dose CsA therapy for connective tissues, which was adjusted to ensure minimum blood concentration approximate 80-150 ng/mL, was effective and less toxic. In the present study, a population pharmacokinetic analysis and a dosing simulation were performed to clarify the pharmacokinetics of low dose CsA in connective tissue disease patients.

Methods
Routine clinical data including blood drug concentrations were collected from patients treated with low dose CsA. A one-order absorption and one-order distribution and elimination model was adopted as a pharmacokinetic model, and a nonlinear mixed effects model was used to analyze the population pharmacokinetic models. The parameter values were standardized for a body size of 70 kg using an allometric scaling and normal fat mass (NFM) which reflected the effect of the body composition. A dosing-simulation was performed for assumed patients with various age and body size.

Results
The study involved 36 patients who contributed 89 observations. In the final model, absorption rate constant (Ka), clearance (CL/F) and a volume of distribution (Vd/F) were explained by:

\[ Ka (h^{-1}) = 0.77 \]

\[ CL/F (L/h) = 24.8 \times \exp(-0.00534 \times (AGE-60)) \times (NFM/NFMstd)^{0.75} \]

\[ Vd/F (L) = 150 \times (NFM/NFMstd) \]

NFMstd represents NFM standardized for a body size of 70 kg. Age was identified as an influential covariate on CL/F and NFM was superior to total body weight as the size descriptor of pharmacokinetic parameters.

Conclusions
The dosing-simulation based on final model showed the maintenance of CsA concentrations at 80-150 ng/mL was possible with high probability by dose adjustment according to age and body size. The present model will represent a significant contribution to considering dosing regimen for individual patients with connective tissue disease.