

Model-based Precision Dosing for Pediatric Patients

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Scope of the lecture:

The scope of my presentation is to describe my research experience as a young scientist at Cincinnati Children's Hospital Medical Center including the role of our Clinical Pharmacology Division in a large pediatric academic medical center in terms of collaborative activities with multidisciplinary clinical and research groups. My talk will be specifically focusing on the implementation of a model-based pharmacokinetically (PK)-guided precision dosing strategy of sirolimus in pediatric patients with complicated vascular anomalies.

Learning objectives:

1. Describe examples of the implementation of model-based PK-guided dose individualization with Bayesian adaptive control in pediatric patients
2. Highlight how clearance in the pediatric population can be characterized by growth and development (or maturation) of relevant organ functions
3. Describe examples of applying pharmacometrics to identify age-appropriate dosing regimens in very young children such as neonates and infants

Extended abstract:

Infants and children differ physiologically from adults and experience rapid changes in growth and development over the course of their childhood.¹ Lack of clinical data in the pediatric population has been well recognized as a problem and the lack of age-appropriated evidence-based dosing guidelines remains an important unmet need in clinical practice for many medications. Model-based (or model-informed) precision dosing has been advocated for many years², however the approach has not been widely implemented at the bedside.³ Recent advances in the science of quantitative pharmacology and pharmacometrics have resulted in the improvement of model-based approaches to better describe and understand important age-related factors influencing drug disposition and response in pediatric patients. In this symposium, my talk will present an example of the strategy of model-based dose optimization of sirolimus in pediatric patients with complicated vascular anomalies.

Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) that is increasingly being investigated or prescribed off-label in the pediatric population. Sirolimus has been approved in many countries for the prophylaxis of organ rejection in patients receiving renal transplantations. Moreover, it has been investigated as a potential new targeted therapy of various diseases such as tuberous sclerosis complex (TSC), neurofibromatosis (NF) and vascular anomalies (VA). Based on such exploratory studies, sirolimus was recently approved for the treatment of lymphangioleiomyomatosis (LAM) in Japan.

Due to lack of pediatric data, sirolimus dosing in many of the clinical trial was largely extrapolated from adult studies. The biggest unmet challenge in sirolimus therapy for pediatric patients was to identify safe and effective dose ranges in patients across the age spectrum from newborns to adolescents. In the first concentration-controlled Phase 2 study of sirolimus in pediatric patients with VA, we conducted a real-time model-based dose individualization strategy for all patients to optimally achieve target concentration attainment (Figure).^{4,5} Dose adjustments to target a sirolimus pre-dose concentration of 10-15 ng/mL were based on concentration measurements in combination with Bayesian adaptive control using a previously developed PK model in pediatric patients with NF.⁶ Throughout the trial, over 670 sirolimus blood concentration data points were obtained from 52 pediatric patients aged 3 weeks to 18 years (24 patients were younger than 2 years-old). Using these data, developmental changes in sirolimus clearance were characterized and described as a function of allometrically-scaled body weight (growth) and age (development).⁷ Thereafter, age-dependent sirolimus clearance estimates and steady-state trough concentrations were simulated using the established developmental PK model. Based on the simulations, eight different dosing strata (mg/m^2) were identified for patients in the 0 to 24 months of age cohorts with the shortest age range set to one month for practical purposes.⁸ Finally, the sirolimus population PK model was updated for patients with VA using the collected data in the Phase 2 study, which has now been prospectively utilized for Bayesian estimations for patients not participating in the clinical trial.

In conclusion, we present an example of development and implementation of model-based dose optimization in pediatric patients. This type of model-informed precision dosing will provide a foundation for ongoing efforts to further define the exposure-response relationship for different drugs across the pediatric age spectrum.

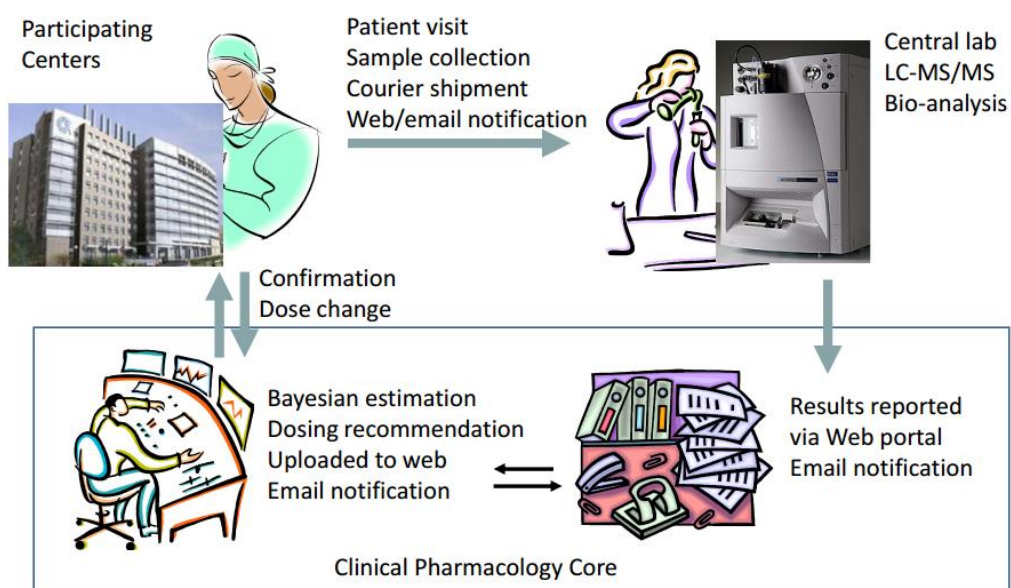


Figure. Outline of the different steps in the sirolimus precision dosing process from patient visit and sampling, sample shipment, analysis, reporting of assay results and the final communication of the model based dosing recommendations (Reused from Mizuno et al.⁵)

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References

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