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Oral

## [O27-2] O27-2: Pharmacometrics (2)

Chairs: Fumiyoishi Yamashita, Japan / Toshimi Kimura, Japan

Wed. Sep 27, 2017 11:15 AM - 12:00 PM Room C1 (1F)

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## [O27-2-3] Model-informed precision dosing of sirolimus in children with vascular anomalies: pharmacokinetic-guided dose adjustment and design of age-appropriate starting dosing regimens

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### Background

Sirolimus is the first drug to demonstrate efficacy for complicated vascular anomalies (VA). The majority of VA patients present in childhood including in the neonatal period. However, dosing information for this pediatric population is limited. In a prospective concentration-controlled Phase 2 trial, we conducted PK-guided dosing using Bayesian adaptive control to achieve optimal target attainment.<sup>1</sup> The aims of this study were 1) to evaluate the outcomes of PK-guided dose titration in the trial and 2) to identify age-appropriate sirolimus starting doses for children with VA across the age spectrum from newborns to adolescents based on PK model-based simulations.

### Methods

Patients enrolled in the Phase 2 study (NCT00975819) were initiated on sirolimus at 0.8 mg/m<sup>2</sup> twice daily (BID). Subsequent dose adjustments to target a pre-dose concentration of 10-15 ng/mL were based on concentration measurements in combination with real-time Bayesian adaptive control using MW/Pharm with a previously developed pediatric PK model.<sup>2</sup> Using 676 concentrations collected throughout the two-year clinical trial, the sirolimus PK model was updated for VA patients including neonates/infants with NONMEM. Sirolimus clearance was described as a function of age (maturation) and allometrically-scaled body weight (body size) as previously described.<sup>3</sup> Starting doses were identified based on simulated trough concentrations to maximize the likelihood of target attainment for each age cohort.

### Results

Data on 52 patients aged 3 weeks-18 years were available for analysis. Target attainment after 2-3 months of therapy was 94%. In the majority of patients, sirolimus dose had to be increased. The mean sirolimus dose (BID) to achieve the target was 1.8 (range: 0.8-2.9) mg/m<sup>2</sup> for patients >2 years. In patients aged 0-2 years, the required doses were lower than in older patients and increased with age; indicating maturation of clearance. Based on the simulated age-dependent clearances and concentration targets, nine different dosing steps (0.4–1.6 mg/m<sup>2</sup> for patients aged 0-2 years and 1.8 mg/m<sup>2</sup> for patients >2 years) were identified.

### Conclusions

This study describes a model-informed precision dosing strategy for sirolimus in patients with VA to rapidly achieve optimal target attainment. This strategy has now been successfully implemented for external patients. A prospective evaluation is being planned.

References:

1. Adams DM et al. *Pediatrics*. 2016;137(2):e20153257
2. Scott JR et al. *Ther Drug Monit*. 2013;35(3):332-7
3. Emoto C et al. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(8):411-7