Modeling & Simulation in Pediatric Drug Development: Application of Pharmacometrics to Define the Right Dose for Children

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- Ranked in Top 3 of pediatric programs in the U.S
- 628 beds; >15,000 employees; 822 faculty
- Operations of $2.1 Billion
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- 628 beds; >15,000 employees; 822 faculty
- Operations of $2.1 Billion
- 7 Million square feet of facilities; 14 off-site facilities
- Over 1.4 Million sq.ft. of research space
- $200 Million in Research Funding per year ($140 Million from the NIH)
Objectives

• Describe the use of developmental pharmacometrics to design informative pediatric trials
• Present examples of the application of modeling & simulation in pediatric drug studies
• Illustrate the potential of M&S to generate age-appropriate pediatric dosing information
Power of Modeling & Simulation

https://www.youtube.com/watch?v=o2ntCRCgpUM

The benefits of modeling and simulation in drug development: July 27, 2014
Promise of Modeling & Simulation

PK/PD driven decision support

Informative Designs -> Improved Outcomes

https://www.youtube.com/watch?v=o2ntCRCgpUM
The benefits of modeling and simulation in drug development: July 27, 2014
Reasonable to assume (pediatrics vs. adults)

- similar disease progression?
- similar response to intervention?

**NO**

Conduct PK studies
Conduct safety/efficacy trials*

**NO**

Is there a PD measurement** that can be used to predict efficacy?

**NO**

Reasonable to assume *similar concentration-response (C-R)* in pediatrics and adults?

**YES**

Conduct PK studies to achieve *levels similar to adults*
Conduct safety trials

**YES**

Conduct PK/PD studies to get C-R for PD measurement
Conduct PK studies to achieve target concentrations based on C-R
Conduct safety trials

Neonates: birth up to 1 month
Infants: 1 month up to 2 years
Children: 2 years up to 12 years
Adolescents: 12 years up to 16 years

Lesko 2003 www.fda.gov/

Should modeling and simulation methods be considered in all pediatric drug development programs? – (VOTE) YES: 13; NO: 0; ABSTAIN: 0

Can dose(s) for the adolescent (>12 years) population be derived using adult data without the need for a dedicated PK study? – (VOTE) YES: 12; NO: 1

Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time? – (VOTE) YES: 7; NO: 6
36% (16/45) of partial extrapolation product reviews describe the use of M&S in the development program.

Source: Dionna Green, Ped Clin Pharm Staff
Adapted from Dr. Gilbert Burckart, PBPK Workshop FDA-CERSI, 2014

http://pediatrics.aappublications.org/content/128/5/e1242
Applying Pharmacometrics in Adults & Children

Descriptive Population Analysis & Modeling

Clinical data
Population PK/PD & covariate exploration

Top-down

Prior Knowledge
PK/PD Model

Clinical Trial Simulation

Scenario Analysis
Dose Selection

Learn, Confirm & Apply

Impact of Development on Drug Disposition

- Metabolic capacity
- Water distribution
- GI function

Body composition
Renal function

Impact of Size and Maturation

**Size Increases**
- Body weight
- Organ size

**Developmental Changes**
- CYP3A & transporter protein expression

**Population PK PBPK model**

Case study - Application of M&S to study design

Teduglutide PK/PD in Neonates with Short Bowel Syndrome

• Teduglutide - a synthetic glucagon-like peptide-2 analog
  – evaluated for treatment of short-bowel syndrome (SBS)

• Design Pediatric multiple-dose Phase-I clinical study
  – determine safety, efficacy and PK of teduglutide in pediatric patients with SBS aged 0-12 months

• Application of clinical trial simulations
  – Assume similar exposure-response (E-R) in pediatrics and adults (FDA pediatric decision tree)
  – Modeling approach for age-weight distribution across age categories

• Goal was to optimize likelihood of achieving target exposure and therapeutic effect
  – based on observations in adult patients

Development of Pediatric Population Model

- **Structural PK model**
  - Based on adult, healthy subject, and pediatric data

- **Size component**
  - Allometric scaling of clearance (CL) and volume of distribution (V)

- **Maturation function**:
  - Include glomerular filtration rate maturation as part of clearance change over time
  - And/or drug metabolizing enzyme maturation function(s)

Generating Realistic Covariates

- Short bowel syndrome patients have body weights below the 5th percentile of their respective age groups.
- Check with data from our short bowel syndrome patients.
- Specific modeling technique (GAMLSS) was used to simulate age-matched body weights values below the 5th percentile.

GAMLSS: Generalized Additive Models for Location, Scale and Shape
Clinical Trial Simulation - results

Teduglutide dosing strategy to achieve optimal target attainment

- Percentages of patients with steady-state teduglutide exposure within the targeted window of efficacy
- Dose reductions of 55, 65, 75, and 85% in the 0–1-, 1–2-, 2–3-, and 3–6-month age groups, vs. the optimal dosing regimen in the 6–12-month age group.

Informative PK/PD Study Design

- **How many patients?**
  - Required number of patients for statistically robust estimation of PK/PD relationship(s)
  - Precision criteria to derive sample size for pediatric PK studies

- **How many samples per patient?**
  - Precision criteria and simulations

- **Best times to sample**
  - Optimal sampling times

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Effect of number of subjects on clearance estimates

- 500 replicates with n=5, 10, 15, 20, 25 & 30 subjects were simulated
- Mean CL/F was calculated as the arithmetic mean of empirical Bayesian estimates of individual CL/F per trial

Simulation of drug exposure at different dose levels

Obs, observed in adult studies; Sim, predicted exposure in children and adolescents

AAPS Translational Sciences 101

Top-down

Clinical data
Empirical approaches
Population PK-PD & covariate exploration

Descriptive population analysis & modeling

Age appropriate Models & Algorithms

Mechanistic approaches
In vitro-in vivo extrapolation (IVIVE) & Physiologically-based pharmacokinetics (PBPK)

Drug data

Physiological Parameters
Adult & Pediatric populations

Pediatric Phase 1/2 studies - Implementation of Pharmacometrics

- Study of the mTOR Inhibitor Sirolimus in Neurofibromatosis Type-1 Related Plexiform Neurofibromas
- Pilot study of sirolimus plus multiagent chemotherapy for relapsed/refractory acute lymphoblastic leukemia/lymphoma
- Assessing Efficacy and Safety of the mTOR Inhibitor Sirolimus in the Treatment of Complicated Vascular Anomalies – patients 0-18 years of age

Maturation of drug clearance
- PBPK Simulations vs. Clinical observations -

Allometrically scaled Clearance vs. Age

Separation of size and maturation

$\text{CL}_{\text{PREDICTED}} = \text{CL}_{\text{STD}} \left( \frac{\text{WT}}{\text{WT}_{\text{STD}}} \right)^{3/4}$

Individual clinical observations (N=21, 0 to 3 years-old patients)
- Median PBPK predicted profile
- 25 to 75 percentiles
- 5 to 95 percentiles

Abstract for the 21st International Workshop on Vascular Anomalies (ISSVA 2016)  
April 26-29, 2016, Buenos Aires, Argentina

Title: Developmental Pharmacokinetics of Sirolimus: implications for dosing in neonates and infants with vascular anomalies

Authors: Tomoyuki Mizuno, PhD, Chie Emoto, PhD, Tsuyoshi Fukuda, PhD, Paula Mobberley-Schuman, Adrienne Hammill MD PhD, Denise M. Adams, MD, Alexander A. Vinks, PharmD, PhD

Purpose: We recently reported sirolimus to be efficacious and well tolerated in patients with complicated vascular anomalies. Nevertheless dosing information for this pediatric population is very limited, especially for neonates and infants. The purpose of this study was to characterize the developmental trajectory of sirolimus clearance in very young patients using data from our pharmacokinetically guided clinical trial. In addition, we developed an age-appropriate dosing algorithm to facilitate achievement of the appropriate sirolimus target concentrations.

Methods: A total of 316 sirolimus pre-dose concentrations were obtained from 24 patients aged 3 weeks to 4 years participating in a concentration-controlled sirolimus Phase 2 study in children with complicated vascular anomalies. Sirolimus pharmacokinetic (PK) parameters were calculated using Bayesian estimation with a recently published population PK model (MW/Pharm, Mediware, Czech Republic). Allometrically scaled sirolimus clearance was modeled as a function of age using a sigmoidal E_max model (NONMEM 7.2, ICON, USA). Using the developmental PK model, sirolimus doses required to reach a trough target concentration of 10-15 ng/mL were simulated across the different age groups from 0-24 months.

Results: Allometrically scaled sirolimus clearance increased with age up to 24 months. The non-linear relationship between age and allometrically scaled clearance was well described by the sigmoidal E_max model. Based on the developmental PK model, predicted sirolimus maintenance doses were estimated as 0.4, 0.6, 0.9, 1.3 and 1.6 mg/m^2 every 12 hours for the 1, 3, 6, 12 and 24 months age groups, respectively.

Conclusion: This study quantitatively described the relationship between sirolimus clearance and age in neonates and infants. An age-appropriate dosing algorithm was developed that will facilitate sirolimus target concentration attainment. This algorithm in combination with therapeutic drug monitoring will allow precision dosing in very young children receiving sirolimus treatment for complicated vascular anomalies.
Target Controlled Drug Management

Participating Centers

Patient visit
Data & sample collection
UPS shipment
Web/email notification

Centralized LC-MS/MS Bio-Analysis

Confirmation
Dose change

Bayesian estimation
Dosing recommendation
Uploaded to web portal
Email notification

Results reported via Web portal
Email notification

http://clinicaltrials.gov/ct2/show/NCT00634270
Pharmacokinetically Guided Dosing of Sirolimus

Pilot study in refractory acute lymphoblastic leukemia/lymphoma

PK model-based prediction for a 8y old, 29.8 Kg male patient (BSA 1.0 m²).
Loading dose: 5.4 mg, administered as 1.8mg q8h on day 1; maintenance dose of 1.8 mg BID.
Predicted concentrations (open circles) per protocol on days 1, 4, 9, 16, 23, and 28.
Pre-dose trough target 10-12 ng/mL; range 10-15 ng/mL (dotted lines)
Concluding remarks

• Modeling and simulation are powerful tools for the design of informative PK/PD studies in neonates, infants and children.
• With relative sparse data, and application of literature information it is possible to make (initial) informed decisions on pediatric study design.
• Implementation of D-optimal design will increase information content and improve the cost-effectiveness of studies.
• PBPK (and PD) will improve our understanding of important ontogeny effects and help identify those studies that have to be performed to support pediatric drug development.
• Model-based dosing (Bayesian estimator) is the way forward in concentration controlled trials in pediatric drug development and clinical precision dosing in children.
Acknowledgements

Cancer & Blood Diseases Institute
• Denise Adams, MD
• Maureen O’Brien, MD
• & Hemangioma and Vascular Malformation Program

Supported by: T32 HD069054; R01 FD004363

Clinical Pharmacology
• Tsuyoshi Fukuda, PhD (福田剛史)
• Chie Emoto, PhD (江本千恵)
• Laura Ramsey, PhD
• Min Dong, PhD
• Tomoyuki Mizuno, PhD (水野知行)
• Kana Mizuno, PhD (水野佳奈)
• David Hahn, PhD
• Brooks McPhail, PhD
• Rajiv Balyan, PhD
• Joshua Euteneuer, MD
ご清聴、本当にありがとうございました。
本発表や私共のプログラムに関して、ご不明な点やご質問がございましたら、下記までご連絡ください。

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また、発表の機会を与えていただきまして 独立行政法人医薬品医療機器総合機構
ならびに慶應義塾大学、運営委員の先生方に深謝いたします。