Modeling & Simulation in Pediatric Patients: Top down, Bottom Up, and What it All Means Clinically

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Outline

• Describe how growth and maturation of relevant processes are predictive of pediatric drug disposition
• Highlight how pharmacometrics can facilitate the development of informative pediatric clinical studies
• Describe examples of the application of modeling and simulation and Physiologically-Based Pharmacokinetics (PBPK)
Systems Pharmacology for Drug Discovery and Development: *Paradigm Shift or Flash in the Pan?*

- **Network/pathway models**
  - Model complexity determined by low-level organization
  - Model selection rarely performed

- **PBPK models**
  - ePD models

- **(Semi)mechanistic PK/PD models**

- **Heuristic models**

  - Middle-out: what we know
    - Model complexity determined by existing information
    - Model selection based on function

  - Bottom-up: reductionism

  - Top-down: intact system
    - Model complexity determined by high-level organization
    - Model selection based on statistics

References:

Vicini & van der Graaf. Clinical Pharmacology & Therapeutics (2013); 93 5, 379–381
Why Pediatric Pharmacometrics?

• To develop informative models based on pharmacology, physiology and disease for quantitative analysis of interactions between drugs and patients
• To collect informative PK, PD, PG data with a focus on variability across populations
• To better predict and control exposure and response in individual patients
• Achieve paradigm shift in way we perform clinical trials and individualized therapeutics in children

Continuing Paradox of Drug Development

- Clinical trials provide evidence of efficacy and safety at usual doses in populations.

- Physicians treat individual patients who can vary widely in their response to drug therapy.

[Diagram showing diverse outcomes: Efficacious & Safe, Adverse Drug Reaction, No Response.]
Applying Pharmacometrics in Pediatrics

Clinical data
- Population PK/PD & covariate exploration

Top-down

Descriptive Population Analysis & Modeling

- Prior Knowledge
- PK/PD
- Model
- Clinical Trial Simulation
- Scenario Analysis
- Dose Selection
- Learn & Confirm
Clinical Trial Simulation: Phase-I neonates

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.

Mycophenolates - One Dose Does Not Fit All
Large variability at standard doses

MPA AUC (mg • hr/L)

Kidney

MMF Dose, 1 g BID

Target

Dose, 1000 mg twice a day

MPA: Mycophenolic acid
AUC: Area under the concentration-time curve


Consensus papers:
Van Gelder et al. 2006; Kuypers et al. 2011
Rationale for Developing of a Bayesian Estimator

- Large between patient variability
- Substantial within patient variability
  - Complex absorption process
  - Enterohepatic recycling
- Clearance changes first 3-6 months post-transplant
- Pre-dose concentration does not allow accurate estimation of drug exposure


BCS Class II substance with strong pH-dependent solubility profile
Descriptive Modeling of PK variability

Final model prediction: $R^2=0.27$
Posthoc Bayesian estimates: $R^2=0.70$

Allometric scaling equations

$CL_{pediatric} = CL_{adult} \times \left( \frac{WT}{70} \right)^{0.75}$

$V_{pediatric} = V_{adult} \times \left( \frac{WT}{70} \right)^{1.0}$

Mechanism based approach to MPA disposition

Small intestine

Liver

Blood

Steroids

MPA

MPAG

CyA

MPA-glucuronide

CyA, cyclosporine

MMF, mycophenolate mofetil
MPA, mycophenolic acid
MPAG, MPA-glucuronide
CyA, cyclosporine
Predicting MPA Enterohepatic Recycling

**GastroPlus™ 8.0 - Physiochemical properties with ADMET Predictor™ 6.0**

Metabolism parameters based on *in vitro* UGT1A9 data - EHC process included


Data from:布尔林奇格等. 1996: 1.5g MMF (IV infusion and oral administration in 12 healthy volunteers)
Combination therapy shows early promise against stubborn leukemia

In early-stage studies, combining mTOR inhibitors with chemotherapy appears far more effective against T-cell acute lymphoblastic leukemia (T-ALL) than stand-alone treatment. Read More at www.cincinnatichildrens.org (Sept 2013)
Phase I/II - Model-based concentration-Controlled Studies

• Study of the mTOR Inhibitor Sirolimus in Neurofibromatosis Type-1 Related Plexiform Neurofibromas

• Assessing Efficacy and Safety of the mTOR Inhibitor Sirolimus in the Treatment of Complicated Vascular Anomalies – patients 0-18 years of age

• Pilot study of sirolimus plus multiagent chemotherapy for relapsed/refractory acute lymphoblastic leukemia/lymphoma
Target Controlled Drug Management

Participating Centers

Patient visit
Sample collection
UPS shipment
Web/email notification

Centralized LC-MS/MS Bio-Analysis

Confirmation
Dose change

Bayesian estimation
Dosing recommendation
Uploaded to web
Email notification

Results reported via Web portal
Email notification
Sent out

http://clinicaltrials.gov/ct2/show/NCT00634270
Clinical evidence ontogeny - sirolimus

Separation of size and maturation

\[ CL_{PREDICTED} = CL_{STD} \cdot \left( \frac{WT}{WT_{STD}} \right)^{3/4} \cdot MF \]

Emoto C. et al. 2014 submitted
Applying Pharmacometrics in Pediatrics

**Top-down**

- Descriptive population analysis & modeling

**Bottom-up**

- Clinical data
  - Empirical approaches
    - Population PK-PD & covariate exploration

**Mechanistic approaches**

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

**Drug data**

**Pharmacogenomics**

**Physiological Parameters**

- Adults & Pediatric populations

**Dosing scenarios**

1. Scenario 1
2. Scenario 2
3. Scenario 3

**Dosing**

Pharmaco-genomics
IVIVC confirmation of ontogeny

**In vivo data**

- $p < 0.01$
- $p < 0.03$

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<thead>
<tr>
<th>Age group (years)</th>
<th>CL (L/hr/70kg)</th>
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<tbody>
<tr>
<td>&lt;1</td>
<td>10</td>
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<td>1</td>
<td>15</td>
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<tr>
<td>2</td>
<td>20</td>
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<tr>
<td>3≤</td>
<td>25</td>
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**In vitro data**

- $N=8$
- $N=3$
- $N=4$

<table>
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<tr>
<th>Age group (years)</th>
<th>CL_{int} of sirolimus (µL/min/mg)</th>
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<tbody>
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<td>&lt;0.5</td>
<td>4000</td>
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<tr>
<td>2</td>
<td>3000</td>
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<tr>
<td>4</td>
<td>5000</td>
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<tr>
<td>Adults</td>
<td>6000</td>
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Substrate depletion assay with human microsomes and recombinant CYP3A7: CYP3A4, CYP3A5, CYP3A7 and CYP2C8; montelukast and ketoconazole as inhibitors.

Emoto C. et al. 2014 submitted
Sirolimus metabolic pathways in children

Pediatric PBPK model development

Adapted from Leong et al with some modifications.

### Drug-dependent parameters for Sirolimus

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<th>Value</th>
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<tr>
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<tr>
<td>f&lt;sub&gt;u,p&lt;/sub&gt;</td>
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<tr>
<td>Caco-2</td>
<td>3.1×10&lt;sup&gt;-6&lt;/sup&gt; cm/s</td>
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<tr>
<td>CL&lt;sub&gt;int,3A4&lt;/sub&gt;</td>
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<tr>
<td>f&lt;sub&gt;u,m&lt;/sub&gt;</td>
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Simcyp Peds, Version 13

**Adult PBPK model**

- Drug-dependent parameters
- Systems-dependent parameters (Adults)

**Pediatric PBPK model**

- Drug-dependent parameters
- Systems-dependent parameters (Pediatric)

- Perform sensitivity analysis to characterize residual clearance with available pediatric data
- Update ontogeny profiles for each CYP3A isoform


Vision of PBPK models in candidate selection and drug development

Concluding remarks

• Top-down statistics-based approaches alone are insufficient as they do not provide mechanistic basis for extrapolation

• Despite the promise of PBPK as a powerful tool, there still are significant knowledge gaps, and a great amount of work will need to go into developing fully predictive pediatric PBPK models
  – DME and transporter ontogeny profiles

• Given the limited pool of experts in PBPK modeling and the lack of formal comparisons of existing PBPK software, it would be desirable to develop guidance or best practice documents for PBPK modeling using existing experience and databases

• But - “It is here and it can only get better” (Malcolm Rowland)

➢ With next steps toward PBPK-PD
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