Dose selection and benefit-risk assessment in chronic paediatric diseases

Oscar Della Pasqua
Points to consider in a paediatric development plan: what is the right dose?

Model-based PK and PKPD bridging

Extrapolation studies and risk assessment

Extrapolation studies: Benefit-risk balance

Conclusions & recommendations
ICH E11 – DECISION TREE FOR PAEDIATRIC STUDIES

- Will the drug be used in a special population (ethnic group or rare disease)?
  - Yes
    - Is the indication the same as in the current label?
      - No
        - Is the disease process similar to the current indications?
          - Yes
            - Is the outcome of therapy likely to be similar in the new population?
              - No
                - Does efficacy correspond with blood levels in adult?
                  - Yes
                    - PK & safety data
                      (Efficacy/safety extrapolated from reference population)
                  - No
                    - PK & safety data
                      (Efficacy/safety extrapolated from reference population)
              - No
                - Is the dose-conc. relationship likely to match that of the current indication?
                  - Yes
                    - PK & safety data
                      (Efficacy/safety extrapolated from reference population)
                  - No
                    - No clinical development
    - No
      - Is the dose-conc. relationship likely to match that of the current indication?
        - Yes
          - PK & safety data
            (Efficacy/safety extrapolated from reference population)
        - No
          - No clinical development
If a paediatric medicine is to be approved, which are the long term net benefits?

FIGURE 2.2 SOURCE: Drawing by Richter; ©1988 The New Yorker Magazine, Inc.
### Adverse Drug Reactions – 15 drugs ~ 41% of case reports

#### Table: Top 15 Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug Name</th>
<th>Drug Name*</th>
<th>Cases</th>
<th>Medical Use*</th>
<th>Psych*</th>
<th>Most Frequent ADE</th>
<th>2d Most Frequent ADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Infliximab</td>
<td>REMICADE</td>
<td>1772</td>
<td>Crohn's Disease</td>
<td>N</td>
<td>Crohn's disease</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>2</td>
<td>Montelukast</td>
<td>SINGULAIR</td>
<td>944</td>
<td>Asthma</td>
<td>Y</td>
<td>Suicidal ideation</td>
<td>Aggression</td>
</tr>
<tr>
<td>3</td>
<td>Somatropin</td>
<td>NUTROPIN</td>
<td>606</td>
<td>GH deficiency</td>
<td>N</td>
<td>Headache</td>
<td>Convulsion</td>
</tr>
<tr>
<td>4</td>
<td>Baclofen</td>
<td>LIORESAL</td>
<td>579</td>
<td>Muscle spasticity</td>
<td>N</td>
<td>Hypertonia</td>
<td>Drug ineffective</td>
</tr>
<tr>
<td>5</td>
<td>Isotretinoin</td>
<td>CLARAVIS</td>
<td>447</td>
<td>Acne</td>
<td>Y</td>
<td>Suicidal ideation</td>
<td>Depression</td>
</tr>
<tr>
<td>6</td>
<td>Methylphenidate</td>
<td>CONCERTA</td>
<td>418</td>
<td>ADHD</td>
<td>Y</td>
<td>Sudden death</td>
<td>Aggression</td>
</tr>
<tr>
<td>7</td>
<td>Lamotrigine</td>
<td>LAMICTAL</td>
<td>335</td>
<td>Epilepsy</td>
<td>Y</td>
<td>Convulsion</td>
<td>Stevens-Johnson synd</td>
</tr>
<tr>
<td>8</td>
<td>Lisdexamfetamine</td>
<td>VYVANSE</td>
<td>314</td>
<td>ADHD</td>
<td>Y</td>
<td>Suicidal ideation</td>
<td>Aggression</td>
</tr>
<tr>
<td>9</td>
<td>Aripiprazole</td>
<td>ABILIFY</td>
<td>297</td>
<td>Bipolar disorder</td>
<td>Y</td>
<td>Weight increased</td>
<td>Dystonia</td>
</tr>
<tr>
<td>10</td>
<td>Ibuprofen</td>
<td>MOTRIN</td>
<td>242</td>
<td>Pyrexia</td>
<td>N</td>
<td>Hypersensitivity</td>
<td>Renal failure acute</td>
</tr>
<tr>
<td>11</td>
<td>Etanercept</td>
<td>ENBREL</td>
<td>231</td>
<td>Juvenile arthritis</td>
<td>N</td>
<td>Injection site pain</td>
<td>Vomiting</td>
</tr>
<tr>
<td>12</td>
<td>Atomoxetine</td>
<td>STRATTERA</td>
<td>227</td>
<td>ADHD</td>
<td>Y</td>
<td>Suicidal ideation</td>
<td>Chest pain</td>
</tr>
<tr>
<td>13</td>
<td>Quetiapine</td>
<td>SEROQUEL</td>
<td>210</td>
<td>Bipolar disorder</td>
<td>Y</td>
<td>Weight increased</td>
<td>Tardive dyskinesia</td>
</tr>
<tr>
<td>14</td>
<td>Levetiracetam</td>
<td>KEPPIRA</td>
<td>206</td>
<td>Epilepsy</td>
<td>Y</td>
<td>Convulsions</td>
<td>Drug ineffective</td>
</tr>
<tr>
<td>15</td>
<td>Risperidone</td>
<td>RISPERDAL</td>
<td>195</td>
<td>Bipolar disorder</td>
<td>Y</td>
<td>Aggression</td>
<td>Weight increased</td>
</tr>
</tbody>
</table>

* Most frequently cited in case reports. **Psychiatric side effects > 25% of reports.

GH = Growth hormone. ADHD = Attention deficit hyperactivity disorder. Additional note in Methods Summary.
**EMA: BENEFITS AND RISKS**

<table>
<thead>
<tr>
<th>Favourable Effects</th>
<th>Uncertainty of Favourable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavourable Effects</td>
<td>Uncertainty of Unfavourable Effects</td>
</tr>
</tbody>
</table>

**Definitions**

*Favourable effects* are any beneficial effects for the target population (often referred to as “benefits” or “clinical benefits”) that are associated with the product.

*Unfavourable effects* are any detrimental effects (often referred to as risks, harms, hazards both known and unknown) that can be attributed to the product or that are otherwise of concern for their undesirable effect on patients’ health, public health, or the environment.

*Uncertainties about both types of effects* arise from variation, important sources of bias, methodological flaws or deficiencies (including GCP, compliance, etc.), unsettled issues, and limitations of the data set, e.g., due to sample size, study design, or duration of follow-up.
Points to consider in a Paediatric Development Plan

Model-based PK and PKPD bridging

Extrapolation studies and risk assessment

Extrapolation studies: Benefit-risk balance

Conclusions & recommendations
Pediatric Dose Selection

DR Abernethy¹ and GJ Burckart¹

Selection of a drug dose in pediatrics is generally based on no or incomplete pharmacokinetic data. Traditionally, allometric, or scaling, techniques have been used; however, they have inherent limitations and may not make optimal use of the drug-specific clinical pharmacokinetic information that is available. Modeling is a tool that helps approach this problem.

A Model-Based Approach to Dose Selection in Early Pediatric Development

M Cella¹, F Gorter de Vries¹, D Burger², M Danhof¹ and O Della Pasqua¹,³

Clinical Pharmacology & Therapeutics, 2010
PK BRIDGING STUDY – ADULT DATA INTEGRATION

- **Amount**: F1, fraction of Dose
- **1** Depot Cpt
- **2** Central Cpt: Cp (s)
- **Ka(θ)**
- **ALAG2 (θ,η)**
- **Duration D2 (θ,η)**
- **Amount**: F2=1-F1
- **Vd (θ,η), Cl (θ,η)**

Population pharmacokinetic model (common to all populations)
Pharmacokinetic and Pharmacodynamic Basis for Effective Argatroban Dosing in Pediatrics

Rajanikanth Madabushi, PhD, Donna S. Cox, PhD, Mohammad Hossain, Phl Duane A. Boyle, PharmD, Bela R. Patel, PhD, Guy Young, MD, Young-Moon Choi,
DOSE SELECTION AND BENEFIT-RISK ASSESSMENT IN CHRONIC PAEDIATRIC DISEASES

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Conclusions & recommendations
As defined in the draft EMA concept paper, extrapolation may be generally defined as “extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product”
Modeling and Simulation as a Tool to Bridge Efficacy and Safety Data in Special Populations

L Harnisch¹, T Shepard², G Pons³,⁴ and O Della Pasqua⁵

The registration and approval of novel medicines have traditionally been based on evidence arising from large prospective trials. Such an approach is often not possible or unsuitable to evaluate the benefit-risk balance in special populations (e.g., children, ethnic groups, rare diseases). Inferences by modeling and simulation can play a major role in evidence synthesis. A framework is proposed that promotes its acceptability and the basis for decision making during development, registration, and therapeutic use of drugs.

CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e28; doi:10.1038/psp.2013.6; advance online publication 27 February 2013
Adherence to therapy

• Inadequate adherence to the prescribed dosing regimen is one of the major causes of viral failure.

• The impact of poor adherence to antiretroviral therapy has never been evaluated in a systematic manner in children.

• Do different regimens alter the clinical implications of poor adherence to antiretroviral drugs?
Does an increase in dosing interval from twice to once daily increases the risk of clinical failure?

**Clinical Implications of Poor Adherence**

**Dose/Dosage scheme**

**PK**
- Ritonavir
- Plasma concentrations
- Concentration vs. Time

**PK**
- Lopinavir
- Plasma concentrations
- Concentration vs. Time

**PD**
- Inhibition of infection rate
- Inhibitory effect vs. Time

**Disease model**
- Endpoint
  - Viral load
  - CD4+ count

The previously simulated inhibitory effect ($\gamma(t)$) is used in this model.
Assumption: 40% of patients showing variable adherence
Clinical implications of poor adherence

**Twice daily**

**Once daily**

Treatment interruptions
Points to consider in a Paediatric Development Plan

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Conclusions & recommendations
A FRAMEWORK FOR BR ASSESSMENT IN CHILDREN

**DRUG-DISEASE MODELS**
(Clin Trial Simulations)

- Account for possible correlations:
  *Multidimensionality*

- Preference and weighting
  *Clinical relevance of response variables*

- *Use of simulation scenarios:*
  *Generate new evidence*

**Quantitative BR Analysis**
(MCDA)
CLINICAL TRIAL SIMULATIONS - TREATMENT RESPONSE

Disease + Drug + Population + Endpoint Measurement

Placebo Effect + Compliance + Dropout

Dosing Regimen + Protocol Design + Data Analysis

Response / Effect Size = Efficacy endpoints

Safety endpoints
• A method to combine endpoints with different scales into a **uniform** ‘response’:
  – Utility function
  – Comparative weighting
  – Preference scores

• Not technically complex

• No inferential statistics (p-values)

• **Probability-weighted utility scores**
  – Highest score suggests the best decision/choice
1. Establish the **decision context**
2. Identify the **endpoints or measures** of interest
3. Identify **objectives and criteria**:
   - Identify criteria for assessing the consequences for each outcome
   - Organise criteria by clustering them under high-level and lower-level objectives in the hierarchy
4. Assess the expected performance of each option against the criteria (**‘preference value’**):
   - Describe the consequences of each outcome
   - Score the options on the criteria
   - Check the consistency of the preference values on each criterion
5. Assign **weights** for each criterion to reflect their relative importance to the decision
6. Calculate **weighted scores** at each level in the hierarchy and calculate overall weighted scores
7. Examine the **results** and conduct **sensitivity analysis**
Objectives:

- To demonstrate the feasibility of a model-based approach for the evaluation of benefit-risk balance.

- To explore the implications of different dosing regimens on long-term response of iron chelation therapy (long term BRB)

Iron Accumulation

Methods: Endpoints and Parameters

Treatment of interest: deferoxamine

- **Favourable effects**
  - Serum ferritin levels (PKPD model)
    - *change from baseline (%)*
    - *percentage of responders (%)*
  - Prevention of long-term disease complications (%)
    - *Hypothyroidism (hazard model)*
    - *Diabetes mellitus (hazard model)*

- **Unfavourable effects**
  - Acute drug specific AEs (%)
    - *Arthralgia/myalgia* (very common and dose-dependent)
    - *Anaphylaxis* (rare and dose-independent)
Hypothyroidism

Model performance in comparison with literature data

Borgna-Pignatti et al.  
Belhoul et al.  
Mehrvar et al.  
Aydinoc et al.  
Shamshirzar et al.  
Kyriakou (Italy) et al.  
Kyriakou (TIF) et al.

Dashed line: clinical data
METHODS: CLINICAL TRIAL + FOLLOW UP

- Patient population: paediatric patients affected by transfusion-dependent haemoglobinopathies

- **Phase III randomised trial design**
  - Sample size: 150 patients per treatment arm
  - Age: 10 (2-17)
  - Age groups:
    - 2-6 years = 30
    - 6-12 years = 70
    - 12-17 years = 50
  - Body weight: 32 (12-62)
  - Gender: 50% males
  - Baseline ferritin levels: 3000 (1000-8500)
  - Number of samples per year: 5

- Duration: follow-up for **5 and 10 years**
- Treatment: iron chelator **deferoxamine**
- Dosing regimen: changes with each scenario (see options)
1- PKPD model describing the effects of transfusion and iron chelation on ferritin levels

2 – Covariate models describing the effects of compliance and dropout on treatment response

3 - Hazard models describing the effects of disease progression and chelation therapy on the incidence of co-morbidities

4 - Hazard models describing dose-related and dose-unrelated adverse events

- **Scenario 1:** FIXED DOSE REGIMEN
  - Reference: fixed dose 45 mg/kg/day 5/7

- **Scenario 2:** WEIGHT-BANDED DOSING REGIMEN

- **Scenario 3:** FERRITIN-GUIDED DOSING REGIMEN
  - Individualised regimen based on serum ferritin levels
Data

• Summary data for each endpoint are used as input for the MCDA software
• Mean and CI were used (250 simulations per individual)
1) Favourable effects vs. Unfavourable effects

2) Favourable effects

3) Unfavourable effects
DO THE CALCULATIONS!

\[ U_i = \sum_{j=1}^{k} w_j S_{ij} = w_1 S_{i1} + w_2 S_{i2} + \cdots + w_k S_{ik} \]
RESULTS: 1 YEAR FOLLOWUP (TYPICAL CLINICAL TRIAL)

Criteria Contribution

- Score
- Fixed Dose 45

- Hypothyroidism
- Diabetes
- Anaphylaxis
- Arthralgia/Myalgia
- Ferritin Response

Score 33.30
Extrapolation: 5 Year Follow-up

Criteria Contribution

Score

- Weight-based >40 kg
- Weight-based 20-40 kg
- Weight-based <20 kg
- Ferritin > 5000
- Ferritin 2500-5000
- Fixed Dose 60
- Fixed Dose 50
- Fixed Dose 45
- Fixed Dose 40
- Ferritin <2500
- Fixed Dose 30

- Hypothyroidism
- Diabetes
- Anaphylaxis
- Arthralgia/Myalgia
- Ferritin Response
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Extrapolation studies: Benefit-risk balance

Conclusions & recommendations
• **Extrapolation** must be considered in the context of evidence synthesis

• **Extrapolation can be used to replace or complement data**, especially when exploring scenarios for which clinical evidence may not be available or limited.

• **Drug-disease models** can and should be used in conjunction with **clinical trial and not-in-trial simulations** to extrapolate paediatric data

• A (model-based) **extrapolation** framework provides a robust basis for the evaluation of benefit-risk balance in paediatric diseases

• **Models do not make decisions**, people do.
Experts:

1. Paediatrician / ex-PDCO member
2. Paediatric haematologist
3. Paediatric haematologist
4. Paediatric haematologist
5. Paediatric haematologist/oncologist
6. Biostatistician
7. Clinical Pharmacologist
8. Paediatric Clinical Pharmacologist
9. Epidemiologist