Clinical Pharmacology Considerations for Pediatric Dose Selection – FDA Perspective

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Overview

• Terminology
• Current Experience in IBD
  – Infliximab for pediatrics and adults
• Clinical Pharmacology Considerations
  – IBD in general
  – Pediatric dose selection
  – Biologics
Terminology

• Exposure Metrics: Pharmacokinetic (PK)
  – AUC: area under the concentration-time curve
  – Trough concentration: pre-dose drug concentration, $C_{\text{min}}$

• Response Metrics
  – Pharmacodynamic (PD) markers
  – Clinical endpoints, surrogate endpoints

• Exposure-Response (E-R) Relationship
  – PK-PD response
  – PK-clinical endpoint response
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Current Experience:
Infliximab in Pediatric & Adult IBD

- Pediatric development strategy utilized partial extrapolation.
- Similar PK
  - AUC, C_{min}, C_{max} (CD); C_{min}, C_{max} (UC)
- Similar efficacy at 5 mg/kg dose

Clinical remission

**Crohn's Disease**

- % subjects in clinical remission

<table>
<thead>
<tr>
<th></th>
<th>W10</th>
<th>W30</th>
<th>W54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ped</td>
<td>60</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Adult (ACCENT I)</td>
<td>50</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>

**Ulcerative Colitis**

- % subjects in clinical remission

<table>
<thead>
<tr>
<th></th>
<th>W8</th>
<th>W30</th>
<th>W54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ped</td>
<td>N~60</td>
<td>N~20</td>
<td>N~20</td>
</tr>
<tr>
<td>Adult (ACT 1)</td>
<td>N=55</td>
<td>N=20</td>
<td>N=9</td>
</tr>
</tbody>
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Rutgeert 2005, Hyams 2012

Clinical response
Current Experience:

Infliximab E-R in Pediatric & Adult UC

- **Maintenance regimen** – not feasible due to small sample size
  - N= 9 with data @ Week 54

- **Induction regimen** - Week 8 concentration & response
  - Similar E-R for clinical response (ped vs. adult) by logistic regression
  - 95% confidence interval overlapped over a range of concentrations; median values appear higher in pediatrics.

**Note:** 10 mg/kg in adults showed 62% response rate
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General Considerations for IBD

• Two (or three) dose regimens to establish
  – Induction treatment
  – Maintenance treatment
  – Dose intensification after loss of response during maintenance

• Challenges / Opportunities
  – Biologics have widely varying dosing frequencies.
  – Lacking PD markers is a limiting factor for efficient dose ranging.
  – Sample size limitation is a major challenge to E-R evaluation.
    • Induction responder re-randomization → maintenance
    • Maintenance loss of response → dose intensification
  – Assessment of effectiveness in dose intensification is limited.
    • e.g., no control group in addition to small sample size
Pediatric IBD Dose Selection Guided by Exposure-Response Evaluations

• Leverage adult trial E-R data
  – Assess E-R for each indication independently.
  – Assess E-R for each treatment, including dose intensification.
  – Establish population PK/PD model; foundation for pediatric data evaluation.

• Conduct Phase 2 dose-ranging to select doses for Phase 3 confirmation
  – Assess similarity in PK as it may differ in pediatric and adult.
  – Strive for early E-R evaluation using PD markers, if feasible.
  – Collect adequate pediatric PK/PD data to verify similarity to adults.

• Assess E-R in phase 3 study with 2 or more dose levels
  – Especially useful in the absence of a placebo control group.
Opportunities for Pediatric Dose Selection

• Utilize advanced tools in data analysis
  – e.g., population PK/PD modeling given limited pediatric PK sampling
  – Adequate PK sampling is still needed.

• Maximize information with limited PK(/PD) sampling
  – Verify appropriateness to rely on adult data and PK model, and
  – Establish E-R.
  – If needed, consult experts or discuss with reviewers in OCP.

• Develop age-appropriate formulation
  – New formulation, new strength, new delivery device, … etc.
  – Clinical PK/PD comparability study may be required if analytical comparability results reveal substantive differences from the marketed formulation.
Special Considerations for Biologics

• Immunogenicity assessment is essential.
  – Immunogenicity can impact PK, PD, efficacy, and safety.
  – Extrapolation is not feasible.
• Immunogenicity data interpretation may require drug concentration data.
• Analytical challenges for anti-drug antibody assays
  – High circulating drug concentrations can influence assay results.
  – Determine PK concentration in immunogenicity samples when drug interference is suspected.
• Analytical challenges for drug assays
  – Design assays to measure drug concentration relevant for drug activity/effect and E-R evaluations.
Take-away Messages

• Properly leverage adult data requires dose-ranging in pediatric population.
  – When PK/PD data are needed for partial extrapolation.

• Biologics specific - immunogenicity assessment
  – Immunogenicity may impact on treatment outcome
  – Data interpretation may be affected by assay limitations
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