Use of Exposure-Response Information in Pediatric Drug Development

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Acknowledgements

Metrum Research Group Scientists

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FDA-UMD CERSI Workshop Organizers, Panelists and Participants

Pediatric Trial Participants
Exposure Matching is Not the Topic of Discussion


- “A dose-response study is one kind of adequate and well-controlled trial that can provide primary clinical evidence of effectiveness.”

- “Exposure-response information can support the primary evidence of safety and/or efficacy.“

- “In general, the more critical a role that exposure-response information is to play in the establishment of efficacy, the more critical it is that it be derived from an adequate and well controlled study (see 21 CFR 314.126), whatever endpoints are studied.”
Hypothetical True Exposure-Response Relationship

- Typical Individual
- Population Variability
Ideal E-R Study Design Characteristics

Predictor or independent variable (exposure):
- adequate range to describe relationship
- randomly assigned
- known without error (or negligible error)
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Design-driven range in predictor (e.g. randomized to dose or exposure) is key.
Ideal E-R Study Design Characteristics: Individual E-R

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### RA and pJIA Trial Designs: Adequate for E-R?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult trials</th>
<th>Doses in pivotal RA</th>
<th>Pediatric trial</th>
<th>Dose in pivotal PJIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>DB, PC</td>
<td>2 doses</td>
<td>RW</td>
<td>1 BSA based dose</td>
</tr>
<tr>
<td>Golimumab SC</td>
<td>DB, PC</td>
<td>2 doses</td>
<td>RW</td>
<td>1 BSA based dose</td>
</tr>
<tr>
<td>Infliximab</td>
<td>DB, PC</td>
<td>3 doses</td>
<td>DB, PC</td>
<td>1 WGT based dose</td>
</tr>
<tr>
<td>Etanercept</td>
<td>DB, PC</td>
<td>3 doses</td>
<td>RW</td>
<td>1 WGT based dose</td>
</tr>
<tr>
<td>Abatacept IV</td>
<td>DB, PC</td>
<td>3 doses</td>
<td>RW</td>
<td>1 WGT based dose</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>DB, PC</td>
<td>2 doses</td>
<td>RW</td>
<td>2 WGT based doses</td>
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</table>

*Slide courtesy of Renu Singh. FDA/UMD CERSI pJIA Drug Development Workshop - October 2, 2019*
Imagine a design with narrower exposure range:
- exposures resulting from single dose level (X mg)
- variability in exposure due to inter-subject variability in PK
- Unknown correlation between response and PK (confounded E-R; e.g. higher CL with more severe disease)
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Predictor or independent variable (exposure):

- inadequate range to describe relationship
- not randomly assigned – actually an outcome
- known with some error
PK/PD - Dosing

Single Dose Level

- Dosing with GLM 30 mg/m² every 4 weeks resulted in GLM levels similar or higher compared to adults with RA
- Immunogenicity
  - Did not affect GLM levels with exception of patients with high titers of ADA
  - Did not affect efficacy unless titers were >1:1000 (n=6)
- There is no identified mechanistic basis for prolonged PD effect in anti-TNF agents

Exposures sufficient to saturate target

Bioanalysis with the same PK assay (MSD)
- Week 16 GO-KIDS SC golimumab 30 mg/m² + MTX Q4W
- Week 76 & 104 GO-FORWARD SC golimumab 50 mg + MTX Q4W
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Is the apparent exposure-response relationship confounded by disease severity?
Strong Interest in Understanding Causal E-R Relationships

The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

Jun Yang, PhD1, Hong Zhao, PhD1, Christine Garnett, PharmD1, Atiqur Rahman, PhD1, Jogasao V. Gobburu, PhD1, William Pierce, PharmD2, Genevieve Schechter, MD1, Jeffery Summers, MD1, Patricia Keegan, MD1, Brian Booth, PhD1, and Yaning Wang, PhD1

2012

Exposure–Response Relationship of T-DM1: Insight Into Dose Optimization for Patients With HER2-Positive Metastatic Breast Cancer

J Wang1, P Song1, S Schrieber1, Q Liu1, Q Xu1, G Blumenthal1, I Amiri Kordestani1, P Cortazar1, A Ibrahim1, R Justice1, Y Wang1, S Tang1, B Booth1, N Mehrotra1 and A Rahman1

2015

FDA Approval Summary: Ramucirumab for Gastric Cancer

Sandra J. Casale1, Ibilola Fashoyin-Aje1, Steven J. Lemery1, Lillian Zheng2, Runyen Jin2, Hongshen Li2, Liang Zhao3, Hui Zhang3, Huanyu Chen3, Kun He3, Michele Dougherty3, Rachel Novak3, Sarah Kennett3, Sacha Khasar3, Whitney Helms3, Patricia Keegan1, and Richard Pazdur1

2015
Concern About Confounded Causal Inference is Not New

**Pitfalls in Retrospective Analysis in Search of Concentration-Effect Relationships**

Carl Peck, Tom Ludden
Leiden University, The Netherlands, and CDER, FDA, USA

1994

**Intention-to-treat analysis and the goals of clinical trials**

Lewis B. Sheiner, MD, and Donald B. Rubin, PhD

1995

**Diagnostics for confounding in PK/PD models for oxcarbazepine**

Jerry R. Nedelman, Donald B. Rubin and Lewis B. Sheiner

2007
Possible Solutions to Confounded Exposure-Response

- Case matching or model-based adjustment for confounding
  - Not practical for small sample size
- Randomize exposure across population through randomized dose range
  - Broad range needed for accurate inferences, may not be practical
  - 2 doses may be diagnostic for confounded E-R
  - MCPMOD approach may be useful
- Within-individual exposure-response designs
- Make inferences from randomized dose-response designs (avoid E-R)
- Use biomarkers or mechanistic understanding to guide dose selection
Imagine a design with narrower exposure range:

- exposures resulting from 2 randomized dose levels (X mg O mg)
- variability in exposure due to inter-subject variability in PK and study design
- Unknown correlation between response and PK (confounded E-R)
- Acknowledge that adequate and well controlled exposure-response studies are very difficult and probably impractical in pediatric development programs.

- Understand that apparent exposure-response relationships resulting from inadequate designs lead to misguided inferences.

- Adapt decision-making in this context.
• Is this step necessary for extrapolation?

• Are we really learning what we think we are learning?

• Or, are we simply demonstrating similarity of disease-exposure relationship?
Related References

- Resulting exposure-response relationships are misleading
Population Exposure-Response w/ Single Dose Level

- One solution: Obtain within-individual E-R (e.g. crossover) analyzed with mixed-effects modeling
Population Exposure-Response w/ Single Dose Level

- Another solution: Population E-R with broad dose-range