The Use of Exposure-Response With Therapeutic Proteins in Pediatric Drug Development

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Exposure Matching is Not the Topic of Discussion Today


Guidance for Industry

Exposure-Response Relationships — Study
Design, Data Analysis, and Regulatory
Applications

- “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

- **Response**
- **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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  - adequate range to describe relationship
  - randomly assigned
  - known without error (or negligible error)

Design-driven range in predictor (e.g. randomized to dose or exposure) is key.
<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>
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<tbody>
<tr>
<td>Adalimumab</td>
<td>DB, PC</td>
<td>2 doses</td>
<td>RW</td>
<td>1 BSA based dose</td>
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<tr>
<td>Golimumab SC</td>
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<td>2 doses</td>
<td>RW</td>
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<tr>
<td>Infliximab</td>
<td>DB, PC</td>
<td>3 doses</td>
<td>DB, PC</td>
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<tr>
<td>Etanercept</td>
<td>DB, PC</td>
<td>3 doses</td>
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<tr>
<td>Abatacept IV</td>
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<td>RW</td>
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<td>Tocilizumab</td>
<td>DB, PC</td>
<td>2 doses</td>
<td>RW</td>
<td>2 WGT based doses</td>
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Slide courtesy of Renu Singh. FDA/UMD CERSI pJIA Drug Development Workshop - October 2, 2019
Observed (not Design-Driven) Population E-R

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
Observed (not Design-Driven) Population E-R

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- exposures resulting from single dose level (X mg)
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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, Jagarao Y. Gobburu, PhD1, William Pierce, PharmD1, Genevieve Schechter, MD2, Jeffery Summers, MD2, Patricia Keegan, MD2, 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 Schriber1, Q Liu1, Q Xu1, G Blumenthal1, L Amiri Kordestani1, P Cortazar1, A Ibrahim1, B Justice1, Y Wang1, S Tang1, B Booth1, N Mehrotra1, and A Rahman1

2015

FDA Approval Summary: Ramucirumab for Gastric Cancer

Sandra J. Czejka1, Ibiola Fashoyin-Aje1, Steven J. Lemery1, Lillian Zhang2, Runyan Jin2, Hongshan Li2, Liang Zhao2, Hong Zhao2, Hui Zhang2, Huanyu Chen2, Kun He2, Michelle Dougherty2, Rachel Novak2, Sarah Kennett2, Sachia Khasar2, Whitney Helms2, Patricia Keegan1, and Richard Pazdur2

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

Intention-to-treat analysis and the goals of clinical trials
Lewis B. Sheiner, MD, and Donald B. Rubin, PhD

Diagnostics for confounding in PK/PD models for oxcarbazepine
Jerry R. Nedelman, Donald B. Rubin and Lewis B. Sheiner

1994
1995
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
- Most of these solutions are impractical in pediatric clinical trials – rely on thorough E-R design and analysis in adults
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.
Acknowledgements

Metrum Research Group Team

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Related References