The use of modeling & simulation to facilitate an understanding of pediatric dose-exposure-response for small molecules and biologics.

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Is the pediatric disease similar to adult disease?
  • Quantitative Systems Pharmacology Models

What is the relationship between dose and exposure in children?
  • (Population) Pharmacokinetic Models

What is the relationship between exposure and response in children?
  • Pharmacokinetic-Pharmacodynamic Models

Will a pediatric trial meet stated goals & learnings?
  • Clinical Trial Simulation
Bayesian Modeling Methods in Pediatrics

**PEDICATRIC PHARMACOLOGY**

**PRIOR KNOWLEDGE**

**NEW DATA**

- Adult model and parameters
- Link between pediatric and adult PK-PD, efficacy, toxicity
- Prior knowledge of (patho)physiology, therapeutic area
- New PK-PD, efficacy, toxicity data from pediatric patients

**INFLUENTIAL FACTORS**

- Magnitude of inter-individual variability
- Quality of data (residual/measurement error)
- Quantity of new data (no. of individuals & data points)
- Uncertainty in prior model and parameters

\[
p(\theta | Y) = \frac{p(\theta)p(Y | \theta)}{p(Y)}
\]

Thomas Bayes. An essay towards solving a problem in the doctrine of chances, (1764).

“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.”
Ideal Design of Exposure-Response Studies

Design-driven range in predictor (e.g. randomized to dose or exposure) is key.

Predictor or independent variable (exposure):
- adequate range to describe relationship
- randomly assigned
- known without error (or negligible error)
Drug and Indication
- Anti IL-17A human mAb
- Adult patients with:
  - Plaque psoriasis
  - Psoriatic arthritis
  - Ankylosing spondylitis
- Induction dose (adults):
  - 150/300 mg qw x5, then q4w

Questions
- What dose is appropriate in pediatric population?
- Should different weight groups get different doses?
  - How to compose weight groups?
  - What dose to give each group?
- How might we conduct therapeutic drug monitoring?

Model
- Published in FDA Clin Pharm Review
  - 125504Orig1s000
- Two-compartment PK
  - Weight is only covariate on clearances and volumes
- Endpoint is PASI75
- Turnover-type PD model for PASI

https://www.metrumrg.com/interactive-apps-decision-making/
Interactive Simulation & Visualization w/ Cloud Computing

Web Browser Interface

EC2 Clusters

Shiny by RStudio

mrgsolve

Rcpp
C++
ODEpack

qapply

https://www.metrumrg.com/interactive-apps-decision-making/
Model Inputs

Pediatric dose (mg)
75

Weight groups (kg)

Model Results Up to Date
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