Design of PK/PD Studies

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Background

Pediatric studies in infectious diseases

Main area of experience: TB, HIV, malaria and other parasites

Characteristics: High pediatric disease burden; Combination therapy; Comorbidities; Often in low-resource environment; Often poorly understood exposure-efficacy/safety in adults

New combinations (TB-HIV)
Different levels of drug resistance
Bridging to new populations (Asian, African, South America)
New target exposures adults (rifampicin)
New treatment schedules (dose, frequency)
New indications (prophylaxis)
New formulations (fixed dose combinations)
New drugs (bedaquiline, delamanid)
This presentation

• Illustrating pediatric trial design components of a new agent

  – Trial focusing on PK information to achieve exposure similarity with adults and generation a safety data base
  – Model-informed design for model-based analysis
  – Sequential de-escalation of age-cohorts
  – Basic case with options & extensions
Workflow for pediatric studies

- Adult NLME PKPD Model
  - Scale
    - Adjust
      - Design
        - Power
  - Conduct
    - Reassess
  - Analyze
    - Develop weight-banded dosing
Workflow for pediatric studies

- **Adult NLME PKPD Model**
  - Scale
    - Adjust
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  - Conduct
    - Reassess
  - Analyze

- Develop weight-banded dosing
PKPD model from adults to children

Steps in basic PK scaling:

1. Determine size model based on allometry
2. Use maturation function based on known route of elimination if age-range includes <2 years
3. Add formulation effects and organ function model if needed in study population
PKPD model from adults to children

• Pharmacokinetics: allometry & maturation functions [1,2]

\[ V_{\text{typ}} = V_{\text{std}} \cdot \frac{BW}{70} \]

\[ CL_{\text{typ}} = CL_{\text{std}} \cdot \left( \frac{BW}{70} \right)^{0.75} \cdot MF \cdot OF \]

BW: body weight
MF: maturation function
OF: organ function

• MF: empirical function to describe age-related increase apart from size

\[ MF = \frac{PCA^s}{PCA_{50}^s + PCA^s} \]

Renally cleared: Rhodin et al. [3]
Metabolized: Johnson et al. [4]

Scale
PKPD model from adults to children

Example: Comparison of scaling approaches for vancomycin (main elimination by glomerular filtration)[1,2]

[1] Parameter value from:

[2] Growth data from:
PKPD model from adults to children

- Other PK aspects:
  - Absorption (pH, motility, ...)
  - Binding proteins
  - Body composition
- PBPK models
  - Integrating multiple developmental/size/disease differences
- Disease
  - Same infecting organisms
  - Differences in disease manifestation
- PD aspects:
  - Exposure-response often missing in adults but assumed similar

Workflow for pediatric studies

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Develop weight-banded dosing

Adult NLME PKPD Model
Adjust

Dose adjustment to target exposure/effect

- Target adult exposure on standard doses
  - Homogeneous exposure across and within cohorts is the typical goal
- Define target
  - Which exposure metric(s), at what time, from what source (trial results, model-based analysis, preclinical)
- Generally only discrete set of doses/formulations available
  - Expected variability in exposure similar to adults acceptable
- Conflict:
  - Successful achievement of target exposure with low variability will result in minimal information about exposure-response
  - Learning will focus on efficacy/safety at adult exposure not on learning about exposure-response and possible differences compared to adults
Methodology:

1. Simulate exposure/effects using
   - Available doses
   - Scaled PK(PD) model
   - Relevant age-weight distribution
     • Growth curves (WHO, CDC)
     • Empirical in-house data bases
2. Check predicted results with clinical team
3. Adjust dosing per cohort if needed
4. Repeat if necessary

Adjust
Dose adjustment to target exposure/effect
Final dose recommendations may differ from studied doses for a number of reasons:

- Study dosing is mainly age-banded, dosing preferably weight-banded
- Final pediatric PK model (on which dosing is based) differ from prior PK model(s)
- Exposure-response found to be different
- Formulation changes between study doses and dosing recommendations
  - Fixed dose combinations
  - Dedicated pediatric formulations
Workflow for pediatric studies
• Many constraints in study design:
  – Ethical
  – Practical
  – Cost
  – ...

• Study design important for expected data quality:
  – Scope of model
  – Model identifiability
  – Parameter precision
• Large set of design parameters:
  – Dosing strategy modifications
    • Within-subject variation favourable for characterising nonlinear
      PK and exposure-response
  – What to observe
    • Total and/or unbound concentration, matrix
    • Parent and/or metabolites
    • Biomarkers, Safety, Efficacy
  – Observations
    • Number, timing, difference in times between subjects
    • Importance of design increases with sparsity per individual
  – Covariates to collect
  – ...

Design
Methodology:

1. Determine set of ethically attractive and clinically feasible candidate designs

2. Perform clinical trial simulations (CTS) for candidate designs using scaled model & planned doses
   - intended analysis method (estimation method)

3. Evaluate performance of designs using multiple metrics (model identifiability, parameter precision, convenience, study costs, ...)

Design
Workflow for pediatric studies

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Power study for required parameter precision

• Sample size needs to be chosen to fulfill precision criteria:
  “.. target a 95% CI within 60% and 140% of the geometric mean estimates of clearance and volume of distribution … in each pediatric sub-group with at least 80% power.” [1]

• Considerations:
  – Choice of PK parameters
  – “within 60% and 140% of the geometric mean”
  – Estimation of CIs
  – CIs at which ages/weights
  – Use of prior information in analysis

• CL
  – Relates mainly to $C_{\text{average}}$ and $C_{\text{min}}$
  – More complex with non-linear elimination

• V
  – Determines fluctuations, not $C_{\text{average}}$
  – With distribution, multiple V terms, differently related to $C_{\text{max}}$ and $C_{\text{min}}$

• Ka
  – Rate of absorption related to $C_{\text{max}}$
• What prior adult information/data is to be used in the analysis of pediatric data?
  – No use of prior information/data in analysis
  – Assumption of same structural PK model
  – Prior information from adults based on assumption of continuity
    (parameter values for children approach those of adults as age increases)
  – Prior information on selected or all parameters
  – Full or partial use of the adult information
Asymptotic covariance matrix
- Suggested approach in Wang et al.
- Assumes symmetry in imprecision around point estimates

Case Bootstrap
- Gold standard in large studies
- Underestimates interindividual variability in small studies

Sampling-Importance-Resampling
- Promising new method [1]

Likelihood profiling
- Appropriate for mapping CIs, but difficult to implement in powering

Power
What weights to calculate CIs for

• Median weights in each age cohort
  – According to CDC suggested by Wang et al.
  – Disease population specific median weight
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Adult NLME PKPD Model
Reassessment after each cohort

• To assess exposure
  – Is exposure sufficiently similar to target to provide relevant safety information?

• To assess agreement with expected data information
  – Was the data as informative as expected?
  – Study additional subjects

• To determine doses for next (younger) cohort
  – Update PKPD model with new data
  – Reassess planned doses
Reassessment
after the first X patients of a cohort

• It may be too late to learn about study (PK) problems after an entire cohort been studied

• Assess agreement with target exposure
• If necessary,
  – Update PKPD model
  – Propose new doses
Reassessment after each patient

- Assess agreement with target exposure/response

- If outside desired range,
  - Calculate individual PKPD parameters
  - Propose new doses or treatment interruption
Workflow for pediatric studies

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Adult NLME PKPD Model
Extensions & alternatives to the proposed workflow

Scale & Adjust:
• Utilize model/parameter uncertainty from adults

Design & Power:
• Use optimal design methodology
  – Maximize overall parameter precision using D-optimality
  – Maximize precision for specific parameters using Ds-optimality
  – Use global optimal design with parameter uncertainty from adult model
  – Power study using Fisher information matrix

CTS for verification
Extensions & alternatives to the proposed workflow

Reassess & Analyze:
Model-based adaptive optimal design with automatic stopping [1]

- Interim analysis after every cohort
- Update of design for next cohort
- Stopping if precision is sufficient

Model-informed study design for model-based analysis is a multi-step procedure, each step has many options and potential for further development.

Multiple pharmacometric tools available to guide planning and analysis of pediatric trials. Extensions to 'basic' workflow can reduce assumptions and increase robustness.

Extrapolations:
- Assumption that target exposure is the same as in adults
- Assume that safety at recommended doses are similar to that of study doses
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