Role of Model-Informed Drug Development (MIDD) in Accelerating and Optimizing Dose Dose Selection

Transforming Pediatric Drug Development in Systemic Lupus Systemic Lupus Erythematosus (SLE)

FDA–University of Maryland CERSI Public Workshop

Accelerating Product Development for Pediatric Systemic Lupus Erythematosus

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Disclosures

- Full-time employee of Flagship Pioneering
- Stockholder in Lilly, Merck, Takeda, and Novartis
- All material presented is from the public domain and cited accordingly

Today

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02	Dosing in Children
03	Predicting and Assessing Pharmacokinetics in Children
04	Target Concentrations & Concentrations & Exposure-Response Analysis
05	Belimumab: An Illustrative Example
06	Role of MIDD for New Therapies

MIDD is not just about models and mathematics — it increases scientific confidence, minimizes pediatric trial pediatric trial burden, and shortens development timelines.

Pediatric SLE: An Ideal Application for MIDD

15–20%

of lupus cases are childhood-onset

More Severe

Pediatric disease is often more aggressive than adult SLE
SLE

Rare Disease

Makes large Phase 3 pediatric trials difficult to conduct

What is MIDD?

Model-Informed Drug Development integrates:

- Clinical Pharmacology
- Pharmacometrics
- Systems Biology
- Regulatory Science

…to inform dose selection, trial design, and extrapolation.

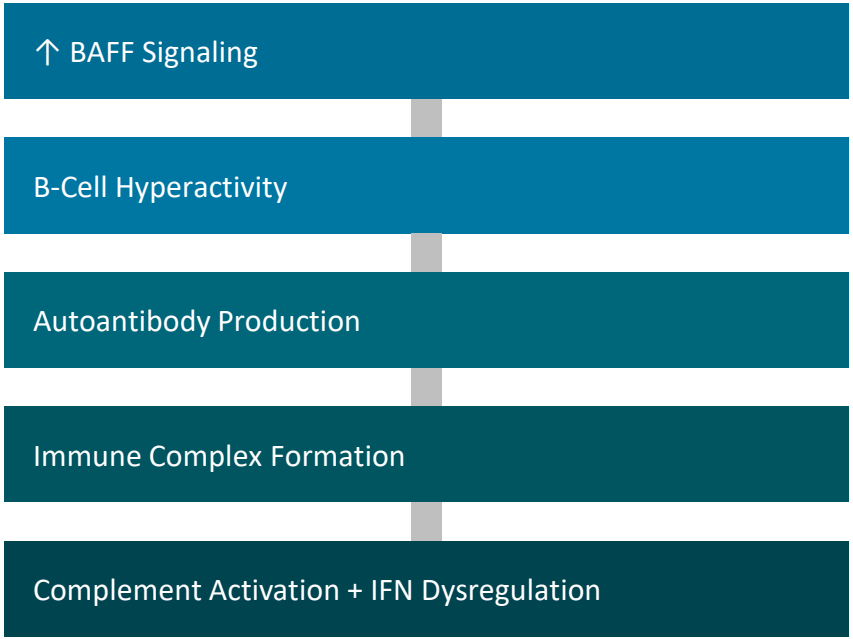
Nat Rev Rheumatol 6, 538–546 (2010)

Scientific Basis for Extrapolation in Pediatric SLE

Pediatric efficacy can be extrapolated when:

- Disease progression is sufficiently similar between adults and children
- Mechanism of action is expected to be comparable
- Similar drug concentrations produce similar clinical benefit

Shared Disease Pathophysiology

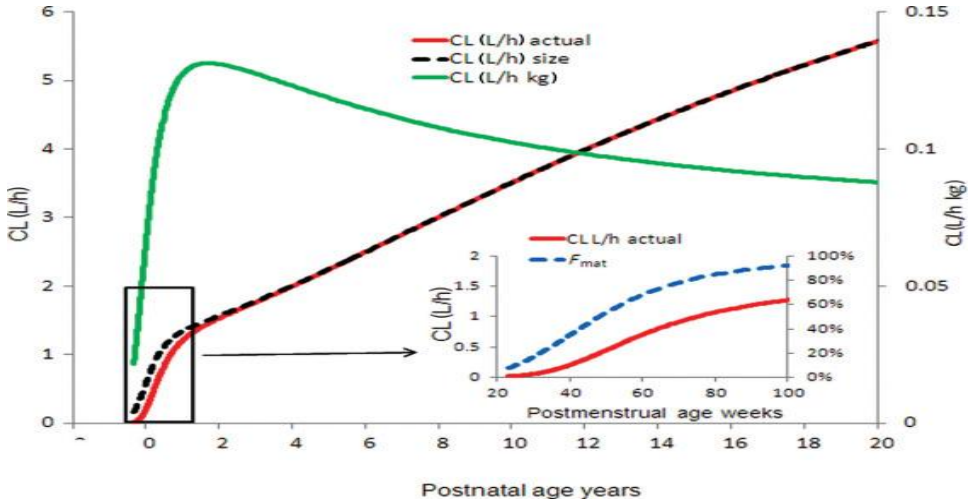


MIDD provides a quantitative *and predictive framework that makes pediatric extrapolation possible*

Dosing in Children: Pharmacokinetics

Key Question
What dose in a child achieves adult-equivalent (similar) concentrations concentrations ?

- Clearance scaled by allometry and maturation function
- Organ maturation modifies volume of distribution and protein protein binding
- PBPK models integrate developmental physiology across age across age groups



J Pharmaceutical Sciences 2013;102(9):2941–2952

Dosing in Children: Exposure-Response (ER) Analysis

Key Question: What concentration in a child will result in the same therapeutic effect as in adults?

ER Analysis Provides

- Dose selection across age groups
- Effective concentration thresholds
- Reduction in trial size
- Improved safety assessments

ER Analysis Characterizes [Effect of dose over Time] Time]

- Concentration *with response,*
- Biomarker
- Clinical Efficacy Endpoints
- Safety Outcomes

Dosing in Children, Clin Pharmacol Ther (2010); Stat Methods Med Res 2020;29(9):2583–2602

Dosing in Children: Exposure Matching Framework

1 **Adult ER Data**

Dose-ranging data characterize the therapeutic window

2 **Pharmacokinetic Scaling and Modeling**

Account for body weight and covariates (maturation); *often* weight-based dosing in younger children

3 **Simulation & Bayesian Methods**

Explore designs and sample sizes; adult data informs pediatric pediatric trials.

4 **Exposure Matching**

Align drug concentrations in a child with adult efficacy and and safety targets

5 **Dose Optimization**

Identify optimal doses

6 **Confirmation**

Pediatric PK data confirm and refine model predictions; bridge predictions; bridge to new formulations

Zhang Y et al. (2020). Exposure-Response Assessments in Studies Submitted to the US FDA. Clin Pharmacol Ther, 108:90–98

Belimumab: An Illustrative Example

Targets BAFF — mechanism well understood from extensive adult clinical development

1 Adult Efficacy Data

Established therapeutic benefit & ER

2 Target Concentrations

Identified by age group (weight-based)

3 PK Scaling

Predicted pediatric doses from adult data data

4 PK Assessment

Evaluated across age cohorts

5 PLUTO Trial

Verified extrapolation assumptions

INDICATIONS AND USAGE

BENLYSTA is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of patients 5 years of age and older with:

- Active systemic lupus erythematosus (SLE) who are receiving standard therapy; (1)
- Active lupus nephritis who are receiving standard therapy. (1)

Limitations of Use:

The efficacy of BENLYSTA has not been evaluated in patients with severe active central nervous system lupus. Use of BENLYSTA is not recommended in this situation. (1)

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for complete preparation and administration information. (2.1, 2.2, 2.3)
- Intravenous dosage for active SLE or lupus nephritis:
  - 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.
  - Reconstitute, dilute, and administer as an intravenous infusion over a period of 1 hour. (2.2)
  - Consider prophylactic premedication for infusion reactions and hypersensitivity reactions. (2.1, 2.2)
- Subcutaneous dosage for active SLE or lupus nephritis: (2.3)

Indication	Adults (Autoinjector or Prefilled Syringe)	Pediatric Patients 5 Years of Age and Older (Weight-Based Dosing) (Autoinjector Only)[a]
Active SLE	200 mg once weekly	• ≥40 kg: 200 mg once weekly • 15 kg to less than 40 kg: 200 mg once **every 2 weeks**
Active Lupus Nephritis	400 mg[b] once weekly for 4 doses, followed by 200 mg once weekly	• ≥40 kg: 400 mg[b] once weekly for 4 doses, followed by 200 mg once weekly • 15 kg to less than 40 kg: 200 mg once weekly for 4 doses, followed by 200 mg once **every 2 weeks**

[a] Prefilled syringe has not been studied in children less than 18 years of age.
[b] The 400-mg dose requires administration of two 200-mg injections.

A Generalized Pediatric SLE Development Workflow

From adult data generation through pediatric regulatory approval

Adult E-R Foundation	Pediatric Strategy & Design	PK Scaling & Dose Selection	Pediatric Efficacy & Safety
Adult Ph2/Ph3	Pre-Ph3 / EOP2	Early Ph3	Ph3 Concurrent
Adult PK/PD characterization	PIP/PSP agreement with FDA/EMA FDA/EMA	PK-guided dose prediction	cSLE endpoints: SLEDAI-2K, BILAG BILAG
E-R modeling & dose selection	Pediatric SLE trial based on extrapolation	Exposure matching: target adult conc. conc.	Long-term safety: growth, immunogenicity
Pediatric extrapolation assessment	Age-appropriate formulation development	Single-dose / PK assessment study (≥5y)	Regulatory Submission
Large studies (~ 1500+)	***In silico***	**Age cohort (~ n= 6-12)**	**Randomized; reduced size (n~100)**

Reducing Burden on Children and Families

MIDD delivers substantial societal and ethical benefits:

Fewer Children in Trials

Reducing the number of children required in clinical studies

Optimized Dose Selection

Identifying the right dose before study initiation

Limit Unnecessary Exposure

Avoiding exposure to ineffective or harmful doses

Sparse Sampling

Supporting minimal blood draws through model-based strategies

Faster Access

Accelerating children's access to innovative therapies

Without quantitative approaches: dense repeated sampling, large enrollment, and prolonged timelines

Critical Role of MIDD for Emerging New Therapies

Current SLE Pipeline Mechanisms (Precedented in Adults)

- Anifrolumab — Type I IFN receptor
- Obinutuzumab — CD20
- CD19-directed CAR-T cell therapies
- Dual-targeting B-cell approaches
- Cell therapies & immune-reset strategies

Key Questions for Pediatric MIDD

- What concentrations should be targeted in children? children?
- How do developmental changes influence pharmacokinetics?
- Can biomarkers bridge efficacy from adults to children?
- How much pediatric efficacy data are required?

Quantitative ER analyses can substantially reduce uncertainty and support efficient development

Looking Beyond Exposure Matching

MIDD approaches are increasingly integrating advanced modeling

Disease Progression Models

- Disease progression models
- Biomarker response models

Quantitative Systems Pharmacology

- B-cell and plasma-cell dynamics
- Interferon pathway activity
- Autoantibody production
- Complement biology

Real-World & Digital Integration

- Real-world data integration
- Digital biomarkers
- Remote monitoring

Vision

A future in which we can simulate how a new treatment alters the immune system of a child before a pediatric program is initiated.

Thank You

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