Quantitative Assessment of Exposure/Response Similarity in Rheumatoid Arthritis (RA) and Juvenile Idiopathic Arthritis (JIA)
INTRODUCTION

• Conducting studies in the pediatric population is challenging.
• Appropriate pharmacokinetic and pharmacodynamic studies may facilitate pediatric drug development by supporting partial extrapolation, dose optimization, and product labeling.
• Frequently, extrapolation of adult PK is required to inform pediatric dosing and study design.

Allometry

Physiologically Based PK

FDA PEDIATRIC DECISION TREE

Pediatric Study Planning & Extrapolation Algorithm

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

- No to either
- Yes to both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

- No
- Yes

Is the drug (or active metabolite) concentration measurable\(c,d\) and predictive of clinical response?

- No
- Yes

Is there a PD measurement that can be used to predict efficacy in children?

- No
- Yes

"Full extrapolation"\(f\)

Conduct:
(1) Adequate PK study to select dose(s) to achieve similar exposure as adults\(g\).
(2) Safety trials\(g\) at the identified dose(s).

"No extrapolation"\(f\)

Conduct:
(1) Adequate dose-ranging studies in children to establish dosing\(e\).
(2) Safety\(g\) and efficacy\(g\) trials at the identified dose(s) in children.

"Partial extrapolation"\(f\)

Conduct:
(1) Adequate dose-ranging study in children to select dose(s) that achieve the target PD effect\(e\).
(2) Safety trials at the identified dose(s).
### SUMMARY OF APPROACHES TO EXTRAPOLATION

#### TABLE 1 Summary of Approaches to Use of Extrapolation of Efficacy From Adult Population to Pediatric Population

<table>
<thead>
<tr>
<th>Extrapolation of Efficacy From Adult Data</th>
<th>Assumptions Made to Extrapolate Efficacy</th>
<th>Purposes of Pediatric Studies</th>
<th>Supportive Evidence Requested From Pediatric Studies</th>
<th>Products for Which WRIs Issued, n/N (%)</th>
<th>New or Expanded Pediatric Indication Achieved, n/N (%)</th>
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<tbody>
<tr>
<td>No extrapolation</td>
<td>Disease/condition and/or response to intervention are not similar.</td>
<td>Demonstration of efficacy and assessment of safety.</td>
<td>Two adequate, well-controlled, efficacy and safety trials plus pharmacokinetic data. For oncology products only, sequential approach starting with phase 1/2. Do not proceed if no evidence of response.</td>
<td>19/166 (11)</td>
<td>7/19 (37)</td>
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<td>Partial extrapolation</td>
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<td>10/166 (6)</td>
<td>3/10 (30)</td>
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<td>20/166 (12)</td>
<td>15/20 (75)</td>
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<td>Disease/condition and/or response to intervention are similar and there is a high degree of certainty about the strength of assumptions. Dose assumed to be the same (e.g., topical application).</td>
<td>Exposure data to confirm age-appropriate dose and assessment of safety.</td>
<td>Pharmacokinetic and safety data.</td>
<td>10/166 (6)</td>
<td>9/10 (90)</td>
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<td>Assessment of safety.</td>
<td>Safety data only.</td>
<td>14/166 (8)</td>
<td>6/14 (43)</td>
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CLINICAL PHARMACOLOGY MODELING & SIMULATION
KEY APPLICATIONS FOR PEDIATRIC EXTRAPOLATION

- **Optimize Dose And Regimen**
- **Optimize Trial Design**
- **Evaluate Intrinsic Factors**
- **Understanding of Disease in Pediatrics**

**Dose Selection**

**Trial Simulation**

**Covariate Analysis**

**Systems Biology**

Application to Optimize Regulatory Decision Making for Pediatric Plans
PLATFORM APPROACH TO IMPACT REGULATORY STRATEGY: STANDARDIZED APPROACH FOR PEDIATRIC STUDY PLANS

Application: Exploratory analysis to support PIP/PSP discussions
- Established Ph 1 adult and Japanese PK covered older adolescents
- Guided team to apply for adolescent waiver

Application: Pediatric dose selection discussions
- Guided age group and dose selection of Ph 1 bridging PK study
- Adult SKUs (70 to 140 mg) predicted to cover potential pediatric dose range

Demographic Model
- Regulatory feedback
- Sub-populations
- Additional demographic data

Computational Tool
S-PLUS code integrates demographic model and PK to provide best practice for pediatric simulations based on a large database

Study & Protocol Design

PIP/PSP Strategy

Data

Model

PK (drug attributes)

S-PLUS Code

Refinement

S-PLUS Code

Amgen Proprietary—For Internal Use Only
CASE STUDY:
ENBREL® (ETANERCEPT)

• A dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 TNF receptor linked to the Fc portion of human IgG1
• It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kD
• Etanercept is produced by recombinant DNA technology

Ig = immunoglobulin; TNF = tumor necrosis factor.
ROLE OF TNF IN THE PATHOGENESIS OF ARTHROPATHIES

• Plays a role in the inflammatory processes, resulting in joint pathology of
  – Rheumatoid arthritis (RA)
  – Polyarticular juvenile idiopathic arthritis
  – Psoriatic arthritis

TNF-ALPHA PLAYS A ROLE IN RA

Induction of inflammatory cytokines. Adhesion molecule expression

Stimulates synovial fibroblasts, osteoclasts, and chondrocytes

Release of tissue-destroying matrix metalloproteinases

Stimulates osteoclast development

Bone degradation

ENBREL® (ETANERCEPT): PHARMACOKINETICS

- Rheumatoid Arthritis 50 mg Weekly
  - Cmax 2.4 mcg/mL, half life 102 +/-30 hours
  - PK parameters were not different between men and women and did not vary with age in adult patients
  - Pharmacokinetics were not altered by concomitant MTA in RA patients
  - No formal renal or hepatic studies conducted
## COMPARISON OF ADULT RA AND JIA
### A CASE FOR EXTRAPOLATION?

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<th>RA</th>
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| **Clinical Profile** | Significant heterogeneity  
• 7 disease subtypes  
• Significant variation in developmental stage across age range | Heterogeneous, clinically similar |
| **PK/PD relationship** | Association of age and response not well characterized  
Not established across a dose range | Established, concentration dependent across a dose range |
| **Trial Design** | Withdrawal/Flare Design | Traditional Induction Trial |
| **Outcome Measure** | JIA 30,50,70 score | ACR 20, 50,70 score |
| **Prevalence** | Rare Disease  
70-100,000 active and inactive (CDC) | ~ 4.7 million |

**Leverage Enbrel PK/PD from Adults with RA to Inform Treatment in JIA**
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Clinical Strategy for Enbrel® (etanercept) JIA
Partial Extrapolation

ENBREL®(ETANERCEPT) CASE STUDY:
STEPS IN EXTRAPOLATION IN JIA POPULATION

Integrate
- Integrate prior clinical data on etanercept using a population PK model
- Understand assumptions of the model such as similar disease progression across populations

Extrapolate
- Make adjustments to model to account for potential differences in pediatric subjects
- Extrapolate PK and conduct clinical trial simulations
- Optimize design of pediatric trial

Validate
- Conduct clinical trial to validate predictions
- Confirm dosing in pediatrics
- Propose interchangeability across regimen based on trial simulations
**ENBREL® (ETANERCEPT) CASE STUDY**

**ADULT POPULATION PKPD ANALYSIS**

- **Population PK Model**
  - 1 Compartment with 1st order abs.
  - Covariates of sex and race on CL/F and standardized body weight on CL/F and V/F

- **Population PKPD Model**
  - Cumulative AUC as exposure variable related with binary ACR clinical outcome variable

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**Adult Model Based PKPD Analyses are the 1st step to Support the Pediatric Extrapolation Strategy**

Lee et al, CPT, 73, 2003
### ENBREL® (ETANERCEPT) CASE STUDY: STEPS IN EXTRAPOLATION IN JIA POPULATION

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  • Extrapolate PK and conduct clinical trial simulations  
  • Optimize design of pediatric trial  
    • Propose mg/kg dosing in pediatrics | • Conduct clinical trial to validate predictions  
  • Confirm dosing in pediatrics  
  • Propose interchangeability across regimen based on trial simulations |
**ENBREL® (ETANERCEPT) IN MODERATELY TO SEVERELY ACTIVE POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS (JIA)**

**ENBREL is indicated for reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ages 2 and older.**

<table>
<thead>
<tr>
<th>Study Name (Patient Type)</th>
<th>Etanercept (ETN) Therapy</th>
<th>Journal Citation</th>
</tr>
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</table>

*Above referenced study is included in the Enbrel® (etanercept) Prescribing Information. It is not listed with a study number.*

STUDY DESIGN

• Objective
  – To evaluate the efficacy and safety profile of ETN in children (4–17 years) with polyarticular JIA who did not tolerate or had an inadequate response to MTX

• Endpoints
  – Primary: The number of patients developing disease flare in the double-blind phase
  – Others: Changes of individual measures of disease activity

STUDY DESIGN (CONT’D)

- 69 children with moderately to severely active polyarticular JIA with a variety of onset types were evaluated
- Patients were refractory to or intolerant to MTX
- Stable dose of a single nonsteroidal anti-inflammatory drug (NSAID) and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum) were allowed
- Two-part trial
  - Part 1: All patients received ETN 0.4 mg/kg (maximum 25 mg per dose) subcutaneously (SC) twice weekly
  - Part 2: At day 90, the 51 responders were randomized to continue ETN or receive placebo (PBO) for 4 months and assessed for disease flare
Part 1
Open-Label
Months 1–3

Part 2
Double-Blind
Months 4–7

Ongoing Open-Label Extension (OLE)
Months 8–96

Responders
Randomized

ETN (n = 69)

PBO (n = 26)

ETN (n = 25)

ETN (n = 58*)

Dose: ETN 0.4 mg/kg SC twice weekly (maximum 25 mg/dose)

*Includes 8 nonresponders from part 1 and 25 patients from each arm in part 2.

After 1 year of the extension, the use and doses of corticosteroids, NSAIDs, and pain medications could be adjusted and MTX could be added.

ENDPOINTS

• Primary
  – Patients with disease flare in part 2 (double-blind portion) of the study defined as
    • ≥ 30% worsening in 3 of 6 JIA core set criteria* and a minimum of 2 active joints
    • ≥ 30% improvement in no more than 1 of 6 JIA core set criteria*

• Other
  – Definition of response (part 1)
    • JIA definition of improvement (JIA 30 response)
      – ≥ 30% improvement in at least 3 of 6 JIA core set criteria,* and
      – ≥ 30% worsening in no more than 1 of the 6 JIA core set criteria*
    • JIA 50 and 70 responses†
    • Improvement in the individual components of the JIA core set criteria
  • Safety

*Active joint count, number of joints with limitation of motion, patient/parent global assessment, physician global assessment, functional assessment (Childhood Health Assessment Questionnaire), and erythrocyte sedimentation rate. Number of joints with limitation of motion was accompanied by pain and/or tenderness.
†JIA 50 and 70 responses were defined by a 50% or 70% improvement, respectively, in at least 3 of the 6 response criteria with no more than 1 criterion worsening by more than 30%.

JIA STUDY: BASELINE PATIENT DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Subject Disposition (n = 69)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>62</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>75</td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>10.5 (4–17)</td>
</tr>
<tr>
<td>Mean JIA disease duration in years</td>
<td>5.9</td>
</tr>
<tr>
<td>MTX at washout (%)</td>
<td>72</td>
</tr>
<tr>
<td>Concomitant therapy (%) at start of washout period*</td>
<td></td>
</tr>
<tr>
<td>• NSAIDs</td>
<td>96</td>
</tr>
<tr>
<td>• Corticosteroids</td>
<td>36</td>
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- From study onset through year 1 of the extension, prednisone dose had to remain stable (0.2 mg/kg/d or 10 mg/d maximum). After year 1 of the extension, doses of corticosteroids, NSAIDs, and pain medications could be adjusted and MTX could be added (10–20 mg/m²/wk)
  - ENBREL is not approved for use in patients with pediatric plaque psoriasis

OPEN-LABEL: CLINICAL RESPONSE

- 51 of 69 (74%) patients demonstrated a clinical response in part 1 (open-label phase) and entered part 2 (double-blind phase)
DOUBLE-BLIND: DISEASE FLARE

Percentage of Patients Experiencing Flare

- **PBO (n = 26)**
  - 77%
  - Median Time to Flare: 28 days

- **ETN (n = 25)**
  - 24%
  - Median Time to Flare: ≥ 116 days

*P = 0.007

*6 of 25 patients

*20 of 26 patients
DOUBLE-BLIND: CLINICAL RESPONSE*

*At the end of the 7-month study (3-month open-label and 4-month double-blind).

†P < 0.01 ETN vs PBO.

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Initial efficacy study dose was at 0.4 mg/kg twice weekly.

Simulation study at 0.8 mg/kg once weekly:
- Widely overlapping concentration profiles at steady-state.

Yim, et al, JCP 45, 2005
CLINICAL PHARMACOLOGY, MODELING AND SIMULATION APPLYING DIVERSE TECHNOLOGIES TO SERVE A UNIFIED PURPOSE

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“Advancing our Understanding of Biology to Advance Clinical Medicine”
ACKNOWLEDGEMENTS

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