Use of extrapolation in small clinical trials: Infliximab for pediatric ulcerative colitis

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Learning Objectives

1. Recognize when extrapolation is appropriate.
2. List advantages and limitations of extrapolation.
3. Understand how extrapolation was applied in a small pediatric trial through an example.
Legislation on Extrapolation of Efficacy

“Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another.”

[21 CFR 314.55(a); 21 CFR 601.27(a)]
Extrapolation is based on three evidence-based assumptions.

1) The **course of the disease** is sufficiently similar between adults and children.

2) The **response to treatment** is sufficiently similar between adults and children.

3) Adults and children have a sufficiently similar **exposure-response relationship**.
Pediatric Study Decision Algorithm

- Is it reasonable to assume that children, when compared to adults, have a similar: (a) disease progression? (b) response to intervention?
  - No
  - Yes to both

- Is it reasonable to assume a similar exposure-response (ER) in children when compared to adults?
  - No
  - Yes

- Is there a PD measurement that can predict efficacy in children?
  - No
  - Yes

- Conduct PK studies to establish dose, then pediatric efficacy and safety trials
  - “No Extrapolation”

- Conduct PK/PD studies to establish an ER in children for the PD measurement, conduct PK studies to achieve target concentrations based on ER, then safety trials at the correct dose
  - “Partial Extrapolation”

- Conduct PK studies to achieve drug levels similar to adults, then safety trials at the correct dose
  - “Full Extrapolation”

No
No
No
Yes
Yes
"Partial Extrapolation"
Advantages of Extrapolation

• Reduce the number and complexities of pediatric trials needed to achieve pediatric labeling.
• Obtain trial results more quickly to increase access to efficacious medications.
• Limit exposure of children to unnecessary studies.
• Better utilize limited resources.
Limitations of Extrapolation

• Extrapolation only applies to efficacy.
• Dose cannot be extrapolated.
  – Absorption, distribution, metabolism and elimination often differ in children based on developmental differences.
  – Need PK and exposure-response (ER) relationships.
• Safety cannot be extrapolated.
  – Adverse effects can be different in children.
An example of how extrapolation was applied in a pediatric registration trial:

*Infliximab Pediatric UC Trial*
Infliximab (REMICADE)

- Chimeric IgG1\(\kappa\) monoclonal antibody to human tumor necrosis factor-alpha (TNF-\(\alpha\))
- Also approved for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.
- Approved for pediatric UC in 2011.
Pathogenesis of inflammatory bowel disease (IBD) is thought to be similar between adults and children.

- Exposure of a genetically predisposed host to environmentally modifying factor(s), resulting in immunologically mediated damage against the bowel.
- Major subtypes: Crohn’s disease (CD) and ulcerative colitis (UC).
- Shared genetic risk variants between adults and children.
<table>
<thead>
<tr>
<th></th>
<th>Adult UC</th>
<th>Pediatric UC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Male:female ratio 1:1 in adults &amp; children</td>
<td></td>
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<tr>
<td><strong>Disease Location</strong></td>
<td>Left-sided/proctitis predominant</td>
<td>Pancolitis in 80-90% at presentation</td>
</tr>
<tr>
<td><strong>Disease phenotype</strong></td>
<td>Colectomy rate @ 10 yrs: 20%</td>
<td>Colectomy rate @ 10 yrs: &gt;40%</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>Similar presenting symptoms (e.g., rectal bleeding, diarrhea, abdominal pain) and extra-intestinal manifestations. Children tend to have higher disease severity and growth impairment only seen in children.</td>
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<tr>
<td>Treatment:</td>
<td>Adult UC</td>
<td>Pediatric UC</td>
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<tr>
<td>--------------------------</td>
<td>----------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1° induction agent</td>
<td>1° induction agent (taper over 2 mo)</td>
</tr>
<tr>
<td>5-ASA</td>
<td>High dose induction; mostly maintenance</td>
<td>Mostly maintenance for mild/mod disease</td>
</tr>
<tr>
<td>Immuno-modulators</td>
<td>Maintenance agent for mod/severe disease</td>
<td></td>
</tr>
<tr>
<td>Biologics</td>
<td>Induction and maintenance, but currently</td>
<td></td>
</tr>
<tr>
<td></td>
<td>reserved mostly for immunomodulator failures.</td>
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Assessment of extrapolation

• The review team and the Advisory Committee considered extrapolation of efficacy appropriate in pediatric UC.

• Hence, pediatric studies in UC did not need to be designed as adequate and well-controlled clinical efficacy trials.
Assessment of extrapolation

- It was not clear whether a similar exposure-response relationship in children and adults could be assumed.
- Determined that partial extrapolation was most appropriate based on available information.
- Dosing and safety still needed to be established.
Infliximab Pediatric UC Study Design

INDUCTION PHASE

Open-label Single arm
5 mg/kg IV at Weeks 0, 2, 6 (N=60)

Week 8

Responders Randomized 1:1

Q8W Group: Open-label 5 mg/kg IV every 8 weeks (N=22)

Q12W Group: Open-label 5 mg/kg IV every 12 weeks (N=23)

MAINTENANCE PHASE*

*Step-up therapy was allowed during maintenance phase in patients losing response.
Patient Disposition

INDUCTION

N= 60

Treatment Failure
N=16

Q8w Group
N=22

Step-up
N=9

No step-up
N=13

Remission at Wk 54
N=4

Remission at Wk 54
N=8

Q12w Group
N=23

Step-up
N=14

No step-up
N=9

Remission at Wk 54
N=5

Remission at Wk 54
N=4

Induction response at Wk 8
44/60 (73%) vs. adults 69%
Post-hoc analysis revealed similar exposure-response relationship between adults and children during induction phase
Median concentration and clinical response rate at Week 8 (induction phase) were similar between adult and pediatric UC trials.

<table>
<thead>
<tr>
<th></th>
<th>Pediatric UC (5mg/kg)</th>
<th>Adult UC (5mg/kg)</th>
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</thead>
<tbody>
<tr>
<td>Number of Treated</td>
<td>60</td>
<td>121</td>
</tr>
<tr>
<td>Responder</td>
<td>44</td>
<td>83</td>
</tr>
<tr>
<td>Response Rate</td>
<td>73%</td>
<td>69%</td>
</tr>
<tr>
<td>Median (90% CI) Concentration at Week 8 (µg/mL)</td>
<td>29 (12 ~ 48)</td>
<td>33 (7 ~ 64)</td>
</tr>
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</table>
Limited data to evaluate the maintenance phase

• Few pediatric patients with both PK and clinical response (N=9) or clinical remission (N=17) data at week 54.

• Clinical observations that were supportive of the maintenance dose:
  - Fewer pediatric patients required step-up therapy or discontinued treatment in the 5 mg/kg q8w group.
  - At the 5 mg/kg q8w dose, the observed clinical remission rate at Wk 54 similar between adults (42/121, 35%) and pediatric patients (8/21, 38%).
Limited data to evaluate the maintenance phase

- AC meeting was convened to discuss the application.
  - 9 of 15 voted that there are adequate pediatric data to support the maintenance dose.
  - Committee members who voted “no” (6 of 15) stated that the proposed dose may not be high enough to maintain clinical remission.
Lessons learned

• Early and careful planning is particularly important when designing a small clinical trial.
• In the absence of a placebo or comparator arm, it is critical to determine early whether the exposure-response relationship is similar between adults and children.
• A dose-ranging study would have been helpful to better define appropriate induction and maintenance doses.
Conclusions (1)

- When the course of the disease and the response to therapy are sufficiently similar between adults and children, consider extrapolation of efficacy from adequate and well-controlled adult trials.
Conclusions (2)

• Dosing and safety cannot be extrapolated.

• Plan early and conduct PK studies to determine whether the exposure-response relationship is similar between adults and children to further guide study design.
Challenge Questions

1. All of the following are required to allow extrapolation of efficacy from adult data in pediatric drug development except:
   a) Disease pathogenesis is similar between adults and pediatric patients
   b) Duration of disease at the time of enrollment into the trials is similar between adults and pediatric patients
   c) Effects of the drug are similar between adults and pediatric patients
   d) All of the above are required to allow extrapolation
Challenge Questions

2. All of the following are potential advantages of using extrapolation in pediatric drug development except:
   a) Reduce the number and complexities of pediatric trials needed to achieve pediatric labeling
   b) Limit exposure of children to unnecessary studies
   c) Better utilize limited resources
   d) Eliminate the need to study dosing in pediatric patients
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