Dose Regimen Selection for Biologics in IBD

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Overview

• Introduction
  – Conventional Approach
  – Approved Products & Mechanism of Action

• Experience in Dose Regimen Selection for Adults
  – Summary of Lessons Learned

• Experience in Dose Regimen Selection for Pediatrics
  – Summary of Lessons Learned

• Concluding Remarks
Conventional Dose Selection Strategy in Drug Development Programs

**Phases of Drug Development**

- **Phase 1**
  - FIH, MD
- **Phase 2**
  - Proof of Concept
  - Dose ranging
- **Phase 2**
  - Pivotal Trials / Extension Trials
- **Phase 3**
  - Efficacy
  - Supplementary

**Information**

- Clinical response (PD, efficacy, safety)
- Dose-response
- Exposure
  - PK-PD Modeling
- Exposure-response (E-R) relationship

**Impact**

*Learn and confirm*

**Dose selections**

**Learn and confirm**

**Dosing recommendation for labeling**

**EMA IBD workshop**

06/29/2015
Mechanism of Action for IBD Treatments

Approval in USA

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>2006*</td>
<td>2011*</td>
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<tr>
<td>2007</td>
<td>2012</td>
<td></td>
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<tr>
<td>2008</td>
<td>2013</td>
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<tr>
<td>2014*</td>
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* Pediatric use

Etanercept was ineffective in CD.

Mechanism of Action for IBD Treatments

Approval in USA

<table>
<thead>
<tr>
<th>CD</th>
<th>UC</th>
</tr>
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<tbody>
<tr>
<td>2008</td>
<td>--</td>
</tr>
<tr>
<td>2014</td>
<td>2014</td>
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</tbody>
</table>

Dose Selection: Common Practice in IBD (when CD or UC is the 1st indication)

- IBD was the first indication
  - CD for infliximab & certolizumab
  - CD + UC for vedolizumab

- Development program
  - Phase 1 single and multiple ascending dose trial(s)
  - Phase 2 proof of concept / dose ranging trials (induction)
  - Phase 3 confirmatory trials (induction + maintenance)

<table>
<thead>
<tr>
<th></th>
<th>Phase 2 (Induction)</th>
<th>D-R / E-R used to select dose</th>
<th>Phase 3 # of regimens</th>
<th>Phase 3 D-R ; E-R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab CD</strong></td>
<td>4 dose levels IV</td>
<td>[Max effect] @ mid dose</td>
<td>Induction: 2-3</td>
<td>No ; NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 2</td>
<td>[Max effect] @ mid dose</td>
</tr>
<tr>
<td><strong>Certolizumab CD</strong></td>
<td>3 dose levels, IV &amp; SC</td>
<td>Yes, [Max effect] @ top dose</td>
<td>Induction: 1</td>
<td>NA ; Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 1</td>
<td>NA ; NA</td>
</tr>
<tr>
<td><strong>Vedolizumab CD</strong></td>
<td>---</td>
<td>---</td>
<td>Induction: 1</td>
<td>NA ; No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 2</td>
<td>No ; No [Max effect] @ low dose</td>
</tr>
<tr>
<td><strong>Vedolizumab UC</strong></td>
<td>3 dose levels, IV</td>
<td>Yes, max PD by RO @ top dose; No, response</td>
<td>Induction: 1</td>
<td>NA ; Yes-W6, No-W14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 2</td>
<td>No ; No [Max effect] @ low dose</td>
</tr>
</tbody>
</table>
Dose Selection: Common Practice in IBD (For 1st IBD indication, non-IBD approved)

- **Independent dose-ranging study** when efficacy has been demonstrated in non-IBD indications

- Case example 1: adalimumab CD program
  - Phase 2/3 dose ranging for induction: 3 regimens
  - Phase 2/3 dose ranging for maintenance: 2 regimens
  - E-R observed for induction, but not maintenance.
  - Only the highest induction regimen statistically better than placebo.

- Case example 2: golimumab UC program
  - Phase 2 dose ranging for induction: 3 regimens
  - Phase 2/3 evaluated 2 induction regimens and 2 maintenance regimens
  - Approved lower induction regimen + higher maintenance regimen
  - E-R was considered supportive only as a result of inconsistency between E-R and D-R, and/or other confounding factors in study design.
Dose Selection: Common Practice in IBD (when one IBD indication was approved)

- **Direct-to-phase 3 approach** when efficacy has been demonstrated in one IBD indication;
- Leveraging prior knowledge + limited dose ranging in phase 3
- Example 1: infliximab UC program
  - Studied 2 induction & 2 maintenance regimens
  - Results showed maximum efficacy achieved at the approved dose (low tested dose) for CD. → approval at the same dose for UC and CD.
- Example 2: adalimumab UC program
  - Studies evaluated 2 induction regimens and the approved maintenance regimen for CD
  - Efficacy results was suboptimal even with the high induction dose.
  - E-R for induction phase suggested a higher dose may improve efficacy.
  - PMR to evaluate a higher induction regimen, study ongoing.
Lessons Learned in Adult IBD

• Dose-ranging studies have almost always been done separately for CD and UC.

• Potential risk of suboptimal dose/regimen if the highest dose performed the best and the E-R curves suggest increasing dose may increase efficacy.
  – e.g., certolizumab & adalimumab CD data showing E-R for induction phase

• A dose range showing a full range of dose/exposure-response curve (e.g., exhibiting a plateau) is the most helpful.
  – Infliximab and vedolizumab for CD and UC achieved maximum effect at a dose below the highest dose studied.
Lessons Learned in Adult IBD

• Extrapolation of dose regimen from CD to UC and vice versa may not be appropriate.
  – Multiple products have the same dose regimen approved for both CD and UC, which can be interpreted as “dose extrapolation from UC to CD, and vice versa, may be reasonable.” (True or False?)
  – However, adalimumab has an ongoing PMR study to explore higher induction doses in UC.

• Products with the same pharmacological targets can perform differently.
  – Etanercept differs from other anti-TNFα, shown ineffective in CD. (Sandborn et al. Gastroenterology 2001)
Experience with Pediatric IBD

- Two products approved for pediatric use: infliximab (UC & CD), adalimumab (CD)
- Body weight (BW) was primary consideration in dose selection
- Overall, limited dose-ranging
- Infliximab
  - Same weight-based dosing (5 mg/kg) as for adults
  - Same induction regimen (W0, 2, 6)
  - Two maintenance dosing frequencies studied in phase 3: q8w & q12w
- Adalimumab
  - Same fixed dose as in adults for peds with high BW (160, 80, 40 mg)
  - Induction dose: High vs. Low BW (160/80 vs. 80/40 mg)
  - Two maintenance doses by BW studied at one dosing frequency in phase 3: 40 or 20 mg for high BW and 20 or 10 mg for low BW.
- Both allowed dose escalation (higher dose or frequency) for inadequate response
Infliximab -- Induction of Response in Pediatric and Adult UC Patients

Similar Median Concentration and Response Rate in Pediatrics and Adults

<table>
<thead>
<tr>
<th>WEEK 8 Data (Induction Phase)</th>
<th>T72 Pediatric UC (5 mg/kg)</th>
<th>ACT1 Adult UC (5 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number 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 (µg/mL)</td>
<td>29 (12 ~ 48)</td>
<td>33 (7 ~ 64)</td>
</tr>
</tbody>
</table>

- Pediatric Trial (T72) – 5 mg/kg (N=55, 5 patients withdrew before week 8)
- Adult Trial (ACT1) – 5 mg/kg (N=114) & 10 mg/kg (N=108)
- Mean response from T72 and ACT1

Exposure-Response Do Not Appear different

- Pediatric Trial (T72) – 5 mg/kg (N=55, 5 patients withdrew before week 8)
- Adult Trial (ACT1) – 5 mg/kg (N=114) & 10 mg/kg (N=108)

06/29/2015
Source – CCFA 2012 podium presentation
Adalimumab in Pediatric and adult CD Patients – Induction and Maintenance

- $C_{\text{trough}}$ were similar in pediatrics and in adults.
- Response rates in pediatrics were in similar range as adults.
- However, E-R were inconsistent between pediatrics and adults.
  - Induction E-R: pediatrics (x), adults (√)
  - Maintenance E-R: pediatrics (√), adults (x)

<table>
<thead>
<tr>
<th>Population (N)</th>
<th>Dose (mg)</th>
<th>W4 $C_{\text{trough}}$ (µg/mL)</th>
<th>Week 4 Remission</th>
<th>Dose (mg)</th>
<th>N</th>
<th>W26 $C_{\text{trough}}$ (µg/mL)</th>
<th>Week 26 Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 kg (N=54)</td>
<td>80/40</td>
<td>10.57 ± 6.00</td>
<td>13/54 (24.1%)</td>
<td>20 eow</td>
<td>20</td>
<td>7.57 ± 3.62</td>
<td>8/20 (40.0%)</td>
</tr>
<tr>
<td>≥ 40 kg (N=113)</td>
<td>160/80</td>
<td>14.97 ± 6.94</td>
<td>31/113 (27.4%)</td>
<td>40 eow</td>
<td>47</td>
<td>10.7 ± 4.60</td>
<td>23/47 (48.9%)</td>
</tr>
<tr>
<td>Adults (M02-403)(N=76)</td>
<td>160/80</td>
<td>12.61 ± 5.25</td>
<td>27/76 (35.5%)</td>
<td>40 eow</td>
<td>94</td>
<td>6.81 ± 4.32</td>
<td>54/94 (57.4%)</td>
</tr>
<tr>
<td>Adults (M04-691)(N=159)</td>
<td>160/80</td>
<td>12.63 ± 6.04</td>
<td>34/159 (21.4%)</td>
<td>40 eow</td>
<td>260</td>
<td>NA</td>
<td>87/260 (33.5%)</td>
</tr>
</tbody>
</table>

Concentration reported as Mean±SD; eow = every other week

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EMA IBD workshop
Lessons Learned in Pediatric IBD

• Dose-ranging in pediatric population has been limited; therefore, understanding of exposure-response (E-R) in pediatric patients is limited.

• The exposure and response rate in pediatrics and adults do not appear different for infliximab in UC and adalimumab in CD.

• However, E-R relationship is not consistent between pediatric and adult patients.

• Other potential confounding issues, e.g., differences in endpoints, with/without placebo control.

• Given the uncertainty in E-R, whether exposure matching approach is appropriate for selecting dose in pediatric patients remains unclear.
Concluding Remarks

- Phase 2 dose-ranging is essential to facilitate dose selection.
- Exploring an adequately wide dose range covering minimal effect to plateau of maximal effect is most helpful.
- Evaluating multiple dose regimens in Phase 3 to allow robust dose-ranging and confirmation of efficacy is very useful.
- Even with a 2\textsuperscript{nd}, 3\textsuperscript{rd}… in class for the same molecular target, dose ranging is essential as products may not perform alike, due to the complexity of MOA.
- New molecular entities with new target(s) may challenge current understanding. e.g., Early study of a 2\textsuperscript{nd} integrin inhibitor showed bell-shape dose-response curve, so does a MMP inhibitor.
- The appropriateness of matching pediatric exposure to that of the adults remains unclear without established similarity in E-R.
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  – Hae-Young Ahn, Ph.D.
  – Dennis Bashaw, Pharm.D.

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  – Lin Zhou, Ph.D.
  – Lanyan Fang*, Ph.D.

• Division of Pharmacometrics
  – Nitin Mehrotra, Ph.D
  – Jee Eun Lee, Ph.D.

* past member
Thank you
Resources

- Adalimumab for UC - CP review, resubmission
- Adalimumab for CD SBA package
- Adalimumab for CD peds – CP review, DDW poster
- Certolizumab for CD – CP review
- Golimumab for UC – CP review
- Infliximab for CD – CP review, clinical review
- Infliximab for UC – CP review
- Infliximab for CD peds – CP review
- Infliximab for UC peds – CP review, addendum, CCFA
- Vedolizumab for CD and UC – CP review, Addendum
- Anti-TNFα development program summary in slides