IDeaL – a multi-center prospective Infliximab Dose to Level pharmacokinetic study during induction in pediatric Crohn’s disease

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Objective: • Infliximab (IFX) is an effective therapy for Crohn's disease (CD).
• model the pharmacokinetics (PK) and to use the individual clearance (CL) estimates to explore relationships between PK and factors associated with clinical remission in children with CD during induction.

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Funding:
WCHRI Capacity grant
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Study Design

• Aged 2 to 17 years of age, known diagnosis of Crohn’s Disease
• IFX initiated as clinically indicated
• Endoscopy/imaging last 6 months
• Paris classification/Simple endoscopic Score (SES-CD).
• Immunomodulators allowed

Inclusion Criteria

• Past exposure to anti-TNF therapy

Exclusion Criteria

• Baseline data collected including SES-CD and **weighted Pediatric CD Activity index (wPCDAI)**.
• IFX dose prescribed - 5-10 mg/kg.
• Fecal calprotectin (FCP), CBC-dif., Albumin (ALB), ESR and CRP collected at each infusion.
• NONlinear Mixed Effects Modeling (NONMEM ver 7.3 Icon PLC) was used to develop a pharmacokinetic model.
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35 Biologic Naïve Pediatric CD Patients

**Induction**
- IFX 1
  - W0
  - Trough
  - Peak
- IFX 2
  - W2
  - Trough
  - Peak
- IFX 3
  - W6
  - Trough
  - Anti-IFX Ab
  - Peak

**Week 10 & 12**
- Optional trough at weeks 10 and 12

**Maintenance**
- IFX 4
  - Trough
  - Anti-IFX Ab
- IFX 5
  - Trough
  - Anti-IFX Ab
Results

Median weighted PCDAI at IFX infusions #1, #2, #3, #4, and #5 for all patients

83% clinical remission wPCDAI < 12.5

Median doses at IFX infusions #1, #2, #3, #4, and #5 for all patients

<table>
<thead>
<tr>
<th>Dose #</th>
<th>Median dose given (mg/kg)</th>
<th>IQR</th>
<th>Median Interval between doses (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.315</td>
<td>(5.6725 - 7.14)</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>6.25</td>
<td>(5.36 - 6.96)</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>5.71</td>
<td>(5.285 - 6.67)</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>(5.26 - 7.14)</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>6.25</td>
<td>(5.305 - 7.375)</td>
<td>42</td>
</tr>
</tbody>
</table>
Trough Levels between those in Remission vs. Non-Responders

- IFX#2_IFX trough Result (microg/mL)
- IFX#3_IFX trough Result (microg/mL)
- Week10_IFX trough Result (microg/mL)
- Week12_IFX trough Result (microg/mL)
- IFX#5_IFX trough Result (microg/mL)
- IFX#4_IFX trough Result (microg/mL)

Remission: N=29
Non-responders: N=6

*No responders in cohort with a wPCDAI drop of >17.5
IFX CL was marked varied between subjects and improved during follow-up. CL has a nonlinear correlation with weight where CL/kg is higher in those with weight ≤ 30 kg compare to those > 30 kg (p=0.005). <30kg (0.011L/day/kg) and >30kg (0.007L/day/kg)

Single covariate analysis: Alb was negative and FCP, CRP, SES-CD & wPCDAI were positive correlated with IFX CL.

Back elimination only **low Alb and high CRP** were important predictors of high IFX CL.
• 80% of patients were dose optimized.
• 83% went into clinical remission
• All ATI levels were negative.
• During induction, IFX CL is variable and affected by factors including weight, albumen, disease activity and endoscopic severity.
• Under dosing is likely in lower weight bracket, due to higher drug CL/kg using current dosing by weight.
• This study suggests that IFX dosing in children should use a PK model (Dashboard), which takes into account individual patient factors as well as CL.