Improved Prediction of Infliximab Clearance Using Erythrocyte Sedimentation Rate and Anti-infliximab Antibody in Pediatric Patients with Inflammatory Bowel Disease

Ye Xiong\textsuperscript{1)}, Laura Bauman\textsuperscript{2)}, Tomoyuki Mizuno\textsuperscript{1)}, Tsuyoshi Fukuda\textsuperscript{1)}, Min Dong\textsuperscript{1)}, Michael Rosen\textsuperscript{2)}, Alexander A. Vinks\textsuperscript{1)}

Divisions of 1) Clinical Pharmacology, 2) Gastroenterology, Cincinnati Children’s Hospital Medical Center
Inflammatory Bowel Disease in Pediatrics

• Inflammatory bowel disease (IBD) is consisted of Crohn’s disease and ulcerative colitis.

• Affecting ~1.4 million people in North America, pediatric onset accounts for ~ 20% of overall IBD population.

• Pro-inflammatory cytokine TNF-α localized in bowel induce tissue damage in IBD patients.

Goal of treatment: prevent bowel damage

Pariente et al. Inflamm Bowel Dis. 2011
Infliximab Treatment in Pediatric IBD

✓ Infliximab (Remicade®) is anti-TNFα antibody, a mainstay choice in treating moderate to severe IBD.
✓ Widely used in pediatric patients (35-55%)
✓ Patients on infliximab for up to 7 years with great efficacy and safety.

Loss of response (~40% of patients) is associated with failure to maintain target trough concentrations.

Identify influential patient- and disease-related factors that can lead to better prediction of the variability and allows optimization of the dosing strategy.
METHODS

Clinical data review
Retrospectively evaluate dose and infliximab target attainment

Model development
n=135, covariate effect on clearance e.g. biomarkers, patient factors

Model validation
n=94, predictive performance in new patients, compare with literature model

Individualize Dose
Dose prediction with model, or in combination with feedback
Large Variability in Infliximab Trough Concentrations

Infliximab Treatment
The median dose in current practice is:
Amount: 8.5 mg/kg (3.6-14.9)
Interval: 7.3 weeks (1.4-15.3)
n=136 (maintenance)

- 74% were outside of target $C_{\text{trough}}$ range
- 42% did not reach the target $C_{\text{trough}}$

Target range: Vaughn et al. *Inflamm Bowel Dis*. 2014
Patient Characteristics at 1st IFX C_{trough} Record

• 135 patients for model development
• 80% of patients were diagnosed with Crohn’s
• 40% of patients were females
• Anti-infliximab antibody (ATI) was detected in 66% patients
• A broad spectrum of laboratory values were available for covariate analysis: albumin (ALB), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hematocrit, platelets, etc
Refine Population PK Model with Pediatric Data from Clinical Practice

Stepwise covariate analysis

- Weight
- + ALB
- + ATI level
- + ESR

Between subject variability reduces by 26%

Model: Adapted from existing model (Fasanmade 2011) of pediatric cohort, to explicitly examine disease markers or factors that influence PK behavior of infliximab
Covariate Effect on Clearance

\[ CL_{\text{ind}} = CL_{\text{pop}} \times (\text{WT}/65)^{0.7} \times (\text{ALB}/3.5)^{-1.1} \times 1.18^{\text{ATI level}} \times (\text{ESR}/9)^{0.11} \]

*Additional informative covariates were identified that further explain the variability*
Individualized Dosing Strategy - Proactive vs Reactive

Case: 16 yo
WT: 69.5 kg
ALB: 3.5 g/dL
ATI: 36 (level 1)
ESR: 29 mm/h
(at 1st IFX measurement)

Current practice: Dose adjustment driven by symptoms and trough concentration

Model-predicted dose that can attain target: 10q7.5w

Not effective dose intensification for 4 years
SUMMARY

• High body weight, erythrocyte sedimentation rate, anti-infliximab antibody level, and low albumin values were associated with increased infliximab clearance.

• The extended covariate model has potential to proactively individualize dosing regimen.

NEXT STEP
• Build individualizing application and incorporate into EHR
• Evaluate the proactive dosing strategy in comparison to current strategy
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Division of Gastroenterology
Michael Rosen, MD
Laura Bauman, MD
Phillip Minar, MD

Division of Clinical Pharmacology
Alexander A Vinks, PharmD, PhD
Tsuyoshi Fukuda, PhD
Min Dong, PhD
Tomoyuki Mizuno, PhD
Chie Emoto, PhD
David Hann, PhD
Brooks McPhail, PhD
Kana Mizuno, PhD
Rajiv Balyan, PhD
Holly Ward
# Patient Characteristics at 1\textsuperscript{st} IFX C\textsubscript{trough} Record

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (SD or IQR)</th>
<th>N=135</th>
<th>% Crohn’s Disease</th>
<th>80.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% female</td>
<td>39.7%</td>
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<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (SD or IQR)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14.5 (3.8)</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>55.9 (22.3)</td>
</tr>
<tr>
<td>Infliximab Level* (mg/L)</td>
<td>4.8 (1.9-11.3)</td>
</tr>
<tr>
<td>ATI Level* (ng/mL)</td>
<td>22 (22.0-48.5)</td>
</tr>
<tr>
<td>% Positive ATI (&gt;22 ng/mL)</td>
<td>66.2</td>
</tr>
<tr>
<td>Infusion Number</td>
<td>7.2 (5.2)</td>
</tr>
<tr>
<td>Hematocrit (gm/dL)*</td>
<td>38.9 (36.3-41.6)</td>
</tr>
<tr>
<td>Platelets (k/mcL)</td>
<td>304.4 (109.1)</td>
</tr>
<tr>
<td>WBC (k/mcL)</td>
<td>7.4 (2.8)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>15.5 (14.9)</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.6 (1.6)</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
<td>3.6 (0.5)</td>
</tr>
<tr>
<td>AST (u/L)</td>
<td>25.4 (21.6)</td>
</tr>
<tr>
<td>ALT (u/L)</td>
<td>26.6 (17.0)</td>
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<tr>
<td>Total Bilirubin (mg/dL)</td>
<td>0.37 (0.2)</td>
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</tbody>
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Presented as median and SD (or IQR for non-central distributed parameters)