Infliximab Dosing Strategies and Predicted Trough Exposure in Children with Crohn’s Disease

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Disclosures: NONE

Background

• Infliximab is a chimeric monoclonal antibody against tumor necrosis factor alpha

• Mainstay treatment of children with Crohn’s

• Standard infliximab dosing in children
  – Induction: 5 mg/kg at 0, 2, and 6 weeks
  – Maintenance doses of 5 mg/kg every 8 weeks

• Dosing regimen is based on the original randomized controlled studies

• Treatment failure is common with up to 63% of children with Crohn’s Disease experiencing loss of response by 54 weeks

Background

• Increasing evidence suggests treatment failure may be due in part to low infliximab exposures

• Infliximab trough concentrations < 3 μg/ml are associated with worse clinical outcomes

• Dose optimization including dose escalation based on trough concentration monitoring has proved beneficial

• Trough concentrations achieved after standard infliximab dosing are not known less known

• large variation in the pharmacokinetics of infliximab in children

• one-size fits all approach may be inadequate
Hypothesis & Background

• **Hypothesis:** Standard dosing is inadequate and does not consistently achieve trough levels >3 μg/ml

• **Aim 1:** To evaluate the predicted infliximab trough concentrations in children with Crohn’s disease during maintenance therapy

• **Aim 2:** Determine the percentage of patients achieving target trough concentration >3 μg/ml

Methods

• **Data Source:** Population pharmacokinetic model developed from 112 children and 580 adults was implemented in the non-linear mixed effects modeling software NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD)

Pharmacokinetic Model – Data Source

• Two-compartment model with first-order elimination was used to describe infliximab pharmacokinetics

• Clearance (CL) was predicted:
  – weight (WT, kg)
  – serum albumin (ALB, mg/dl)
  – presence of antibodies to infliximab (ATI; yes/no)
  – concomitant immunomodulation therapy (IMM; yes/no)

• Central and peripheral volume of distribution (Vc and Vp) were predicted by weight.

• Inter-compartmental clearance (Q) was constant.
Our Monte Carlo Simulation

- Using the infliximab population pharmacokinetic model, Monte Carlo methods were applied
  - Simulates the pharmacokinetic profiles of children with Crohn's Disease

- Constructed an analytic tree to evaluate infliximab maintenance dosing strategies of 5, 7.5, and 10 mg/kg at dosing intervals of every 4, 6, and 8 weeks for 'hypothetical' children that differed by age, weight, albumin level, and concomitant immunodulation therapy status
  - Statistical analyses and figure productions were performed using STATA 13 (StataCorp LP, College Station, TX)

Model Inputs

Table 1. Model inputs for Monte Carlo simulations.

| Infliximab Maintenance Regimen | Dose: 5, 7.5 or 10 mg/kg | Interval: Every 4, 6, or 8 wk |
| Age | 6, 10, or 14 years |
| Weight | CDC 50% weight-for-age (ref) |
| Albumin | 3, 4, or 5 g/dL |
| Concomitant immunomodulation | Yes or No |
| Infliximab antibodies | Assumed not present |

Our Monte Carlo Simulation

- For a given Monte Carlo simulation (n=1000), the maintenance dosing regimen and patient type (i.e. age, weight, albumin, and concomitant immunodulator status) were fixed.

  Simulations were repeated for each possible combination in the analytic tree
Results

- The base case of a 10 year old with Crohn’s Disease receiving concomitant immunomodulator therapy.
- At standard infliximab maintenance dosing (5 mg/kg every 8 weeks), infliximab exposure is highly dependent on albumin level.

Table 1. Percentage of children with Crohn’s Disease on concomitant immunomodulator therapy reached to achieve target infliximab trough concentrations at week 12/14 of maintenance therapy by albumin and dosing regimen.

<table>
<thead>
<tr>
<th>Albumin</th>
<th>5 mg/kg</th>
<th>7.5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/dl</td>
<td>50-90%</td>
<td>70-90%</td>
<td>90-90%</td>
</tr>
<tr>
<td>4 mg/dl</td>
<td>50-80%</td>
<td>70-80%</td>
<td>90-90%</td>
</tr>
<tr>
<td>5 mg/dl</td>
<td>50-70%</td>
<td>70-70%</td>
<td>90-90%</td>
</tr>
</tbody>
</table>

A: Steady state dosing regimen has failed to achieve target in 10% of children.

B: Steady state dosing regimen has failed to achieve target in 10% of children.
Conclusions

- Standard infliximab maintenance dosing of 5mg/kg dosed every 8 weeks is predicted to frequently result in trough concentrations < 3 μg/ml in children with Crohn's Disease and albumin ≤ 4 g/dL.
- Likely improved clinical response in those with infliximab trough concentrations > 3 μg/ml.
- Higher infliximab maintenance dosing regimens are likely warranted in children with Crohn’s Disease and albumin ≤ 4 g/dL.

Discussion

- Role for therapeutic drug monitoring
- Personalized dosing strategies
- Pragmatic ways to optimize cost-effectiveness
- Future studies using optimized dosing in pediatric IBD
Thank You
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Questions?
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