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

KT Park, M.D., M.S.
Assistant Professor
Co-Director,
Stanford Children's Inflammatory Bowel Disease Center

Disclosures: NONE

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

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 61% 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

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

4

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)


Clinical Therapeutics

Volume 33, Issue 7, July 2011, Pages 946–964

Pharmacokinetics, bioavailability, & bioequivalence

Pharmacokinetic Properties of Infliximab in Children and Adults with Crohn's Disease: A Retrospective Analysis of Data from 2 Phase III Clinical Trials

Adedigbo A. Fasanmade, PhD, Omoniyi J. Adedokun, MS, Marion Blank, PhD, Honghui Zhou, PhD, Hugh M. Davis, PhD

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

5

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.

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

6

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)

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

7

Model Inputs

Table 1. Model inputs for Monte Carlos 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

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

8

Our Monte Carlo Simulation

- For a given Monte Carlos 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

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

9

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

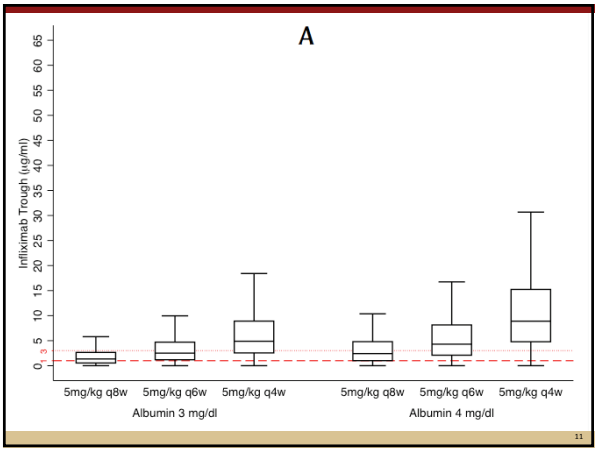
Table 2. Percentage of children with Crohn's Disease on concomitant immunomodulator therapy predicted to achieve target infliximab trough concentrations at week 12/14 of maintenance therapy by albumin and dosing regimen.

Trough Target	Albumin (g/dL)	Maintenance Dosing Regimen: 5 mg/kg q 8 wk	5 mg/kg q 6 wk	5 mg/kg q 4 wk	7.5 mg/kg q 8 wk	7.5 mg/kg q 6 wk	7.5 mg/kg q 4 wk	10 mg/kg q 8 wk	10 mg/kg q 6 wk	10 mg/kg q 4 wk
>1 ug/ml	3	59	79	95	70	86	98	76	91	99
	4	75	91	98	84	96	99	88	98	100
	5	86	95	100	90	97	100	93	99	100
>3 ug/ml	3	21	43	69	35	59	82	46	69	89
	4	41	64	88	57	77	94	65	84	97
	5	62	79	96	74	87	98	80	92	99

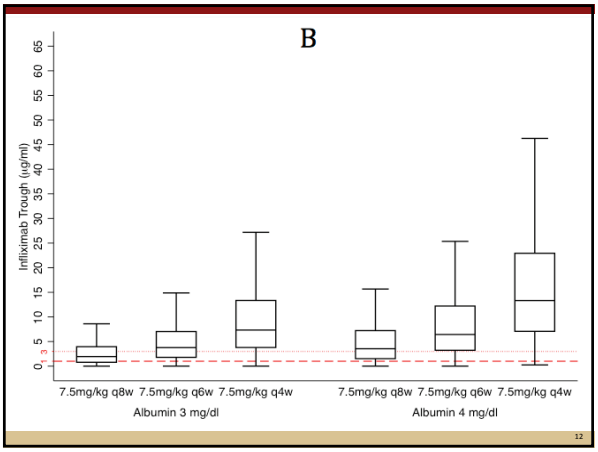
* Shading notes dosing regimens that failed to achieve target in >20% of children.

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

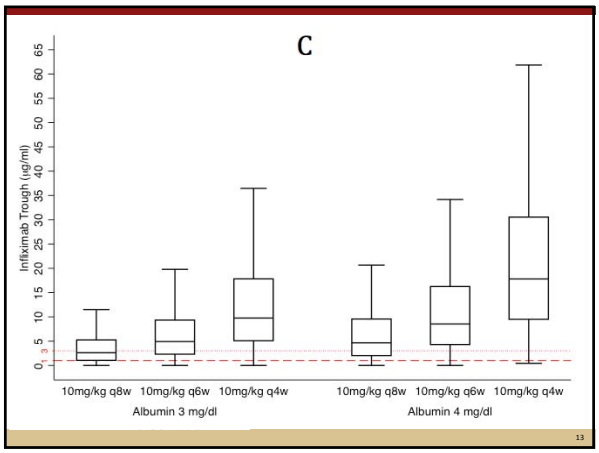
10



11



12



Conclusions

Stanford MEDICINE

- 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

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

14

Discussion

Stanford MEDICINE

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

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

15

Stanford MEDICINE

Thank You

First Author: Adam Frymoyer, MD, MS
Co-Author: Travis Piester, MD

Questions?

ktpark@stanford.edu

Stanford Children's Health | Lucile Packard Children's Hospital Stanford