

## Principal Investigator

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## General Information

### Key Personnel (in addition to PI):

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**First Name:** Adam

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**Are external grants or funds being used to support this research?:** No external grants or funds are being used to support this research.

**How did you learn about the YODA Project?:** Colleague

## Conflict of Interest

[http://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_2018kt.pdf](http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2018kt.pdf)

[http://yoda.yale.edu/system/files/yoda\\_ci\\_signed\\_adam.pdf](http://yoda.yale.edu/system/files/yoda_ci_signed_adam.pdf)

[http://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestor\\_melody.pdf](http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestor_melody.pdf)

## Certification

**Certification:** All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

**Associated Trial(s):**

1. [NCT00207675 - A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF a Chimeric Monoclonal Antibody \(Infliximab, REMICADE\) in Pediatric Subjects With Moderate to Severe CROHN'S Disease](#)

**What type of data are you looking for?:** Individual Participant-Level Data, which includes Full CSR and all supporting documentation

## Research Proposal

### Project Title

Early Infliximab Drug Exposure and Outcomes in Children with Crohn's Disease

#### Narrative Summary:

Crohn's disease (CD) is a chronic inflammatory condition involving the small bowel and colon. In children, infliximab - a monoclonal antibody - is first line treatment for those with moderate to severe CD. Current dosing of infliximab in children applies a 'one-size-fits-all' approach, yet low infliximab drug exposures are frequent, and loss of response and therapy failure remain a clinical challenge. This proposal will exam the importance of early drug exposure during initiation of treatment, and the ability to predict the pharmacokinetics of infliximab in patients with the goal of providing an individualized dosing framework for infliximab in children.

#### Scientific Abstract:

**Background** - Current dosing of infliximab in children applies a 'one-size-fits-all' approach, yet low infliximab drug exposures are frequent, and loss of response and therapy failure remain a clinical challenge.

**Objective** - To exam (a) whether a population pharmacokinetic (PK) model can predict IFX exposures in children with CD and (b) whether IFX exposures during induction dosing predict treatment response.

**Study Design** – Retrospective cohort study of patients who were previously enrolled in a clinical trial examining infliximab efficacy in children with CD.

**Participants** - Children ages 6 through 17 years with moderate to severe Crohn's disease who received infliximab therapy and had subsequent drug level testing.

**Main Outcome Measure(s)** – The main outcomes measures are IFX drug concentrations and the clinical response over the 54 week treatment period.

**Statistical Analysis** – Drug concentration predicted by the PK model will be compared to the actual measure IFX drug concentrations. Standard measures of bias and precision will be reported. The relationship of week 2 and week 6 IFX concentration and clinical response/remission will be compared including the ability for early FX concentration to discriminate between patients with and without clinical response/remission using receiver operating characteristic (ROC) curve analyses.

#### Brief Project Background and Statement of Project Significance:

Our recent work utilizing a population pharmacokinetic (PK) model developed from the data of the landmark REACH trial in pediatric Crohn's disease (CD) demonstrated the current 'one-size-fits-all' approach to infliximab (IFX) maintenance dosing in children with inflammatory bowel disease (5 mg/kg IV q8 wks) is predicted to produce highly variable exposures across patients.(1) In addition, standard maintenance dosing frequently results in low trough concentrations during (i.e. <3 ?g/ml) that are associated with poor treatment response. We have since validated the model in a small cohort of 34 children with CD who prospectively underwent therapeutic drug monitoring during maintenance dosing.(2) Our model performed well, predicting IFX trough concentrations within  $\pm 1.0$  ?g/ml of actual measured concentrations for 88% of measurements. In addition, we demonstrated the predicted infliximab dosing strategy needed to achieve a trough concentration >3 ?g/ml in the cohort was quite heterogeneous and ranged from the standard dosing of 5 mg/kg every 8 weeks up to 5 mg/kg every 4 weeks. Taken together our work demonstrates individualized infliximab dosing strategies in children with IBD will be critical to consistently achieve concentrations associated with optimal outcomes, and there is a great opportunity for population pharmacokinetic models to help guide infliximab dose selection in children with CD (i.e. model-based

dosing).

Our proposal's overarching goal is to establish a standardized framework for personalized dosing of IFX in pediatric CD patients. At the core of this framework is the need for a robust and validated PK model of IFX in CD patients. We have encouraging results as described above in a small cohort of CD patients receiving IFX during maintenance dosing. However, the question remains whether drug exposures during induction phase are just as or even more important in treatment response. In this application, we propose to exam (a) whether a population PK model can predict IFX exposures during induction dosing and later dose needs during maintenance dosing and (b) whether IFX exposures during induction dosing predict treatment response. This work is highly significant in that understanding the desired IFX exposures and how to achieve these target exposures across all patients are critical to maximizing the therapeutic benefit of IFX in children with CD.

### **Specific Aims of the Project:**

- 1) To evaluate the predictive performance of a previously published IFX population pharmacokinetic model in children with CD during induction dosing (i.e. drug concentration at week 6).
- 2) To evaluate the predictive performance of a previously published IFX population pharmacokinetic model in children with CD during maintenance dosing (i.e. drug concentration at week 42).
- 3) To examine the relationship between IFX exposure during induction (week 2 and week 6 drug concentrations) and response (as measured by clinical remission and clinical response at week 10, 30, and, 54.)

### **What is the purpose of the analysis being proposed? Please select all that apply.**

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations  
Confirm or validate previously conducted research on treatment effectiveness

### **Research Methods**

#### **Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

The study population will consist of individuals enrolled in the above clinical trial with a history of Crohn's disease. As per the original trial Inclusion/Exclusion Criteria include pediatric subjects ages 6 through 17 years with moderate to severe Crohn's disease (defined as PCDAI > 30 points at baseline); active disease despite adequate current treatment with an immunomodulator (ie, azathioprine [AZA], 6 mercaptopurine [6-MP], or methotrexate [MTX]); and infliximab-naïve.

#### **Main Outcome Measure and how it will be categorized/defined for your study:**

For Aim 1, the main outcome measures are the bias and precision of the PK model which is calculated using the predicted and observed IFX concentrations at week 6 by:

Prediction error (i.e. bias)= ((Predicted – Observed)/Observed) x 100

Absolute prediction error (i.e. precision)= (|(Predicted – Observed)/Observed|) x 100

For Aim 2, the main outcome measures are bias and precision of the PK model using the predicted and observed IFX concentrations at week 42 as calculated as in Aim 1.

For Aim 3, the main outcome measures are clinical response (yes/no based on decrease from baseline in the Pediatric Crohn's Disease Activity Index (PCDAI) score >15 points; total score <30) and clinical remission (yes/no PCDAI score <10 point) as defined in the original study at Week 10, 30, and 54. We will also exam change in PCDAI from baseline (continuous) at each time point.

#### **Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

For Aim 1 and Aim 2, the predictors that will be used in the PK model include weight (continuous), serum albumin (continuous), immunomodulator use (yes/no), and presence of antibodies to infliximab (yes/no). In addition, IFX dose amount and time from start of study in days are required for PK predictions. For Aim 3, the main predictors will be week 2 and week 6 IFX concentrations (both continuous).

#### **Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

For Aim 3, we will measure several covariates of interest related to CD severity and the likelihood of response, allowing us to potentially adjust for them in our analysis such as age ESR (continuous), duration of disease (continuous), and sex (binary).

**Statistical Analysis Plan:**

AIM 1 and 2 – For each patient, an individual Bayesian concentration prediction at week 6 will be simulated using the population pharmacokinetic model. The individual Bayesian prediction is based on a maximum a posteriori estimation (MAP) method calculated using a patient's dose history, clinical characteristics, and week 2 IFX concentration. Similarly, an individual Bayesian concentration prediction at week 42 will be predicted using (a) both week 2 and week 6 concentrations and (b) only week 6 concentration. The bias and precision of the model for predicting the week 6 and week 42 concentrations will be calculated as described above. The 95% confidence interval of the median prediction error and median absolute prediction error will be estimated using a bootstrap re-sampling procedure of 1000 replication datasets. The percentage of predicted concentrations within  $\pm 1$   $\mu\text{g/ml}$  of the observed concentration will also be calculated.

AIM 3 - Median (IQR) week 2 and week 6 IFX concentration will be compared between patients with and without clinical response/remission at week 10, 30, and, 54 using the Mann–Whitney U test. Receiver operating characteristic (ROC) curve analyses including area under the ROC curve (AUC) will be constructed for week 2 and week 6 IFX concentration in terms of predicting clinical clinical response/remission at week 10, 30, and 54. Optimal cut-off values for the week 2 and week 6 IFX concentration to discriminate between patients with and without clinical response/remission will be determined by the ROC curves. The sensitivity, specificity, and positive and negative predictive values (PPV, NPV) of the cut-off value will be calculated. Using the  $\chi^2$  test, the proportion of patients achieving clinical response will be compared between the patients who reached the optimal cut-off IFX concentration at week 2 and week 6 and those who did not.

**Project Timeline:**

Upon receipt of the data, we anticipate starting the project immediately. During the first two months, we would assess the quality of the received data and continuity between variable definitions where necessary. We will then begin analyzing the data, with plan to complete the analysis within the next 3-4 months. We will then draft the manuscript and abstract for this work, and anticipate first submission 3-4 months for this step. Once completed, we will report our results to YODA and submit our work. We estimate that from receipt of data, the project will take an estimated 8-10 months to manuscript submission. Based on this outline, assuming a data receipt date of 03/01/2018, we would complete data quality analysis by 05/01/2018, complete analysis by 09/01/2018, and complete the manuscript by 01/01/2019.

**Dissemination Plan:**

We plan on submitting this research in both abstract form and manuscript form. We would plan to present this data at a national meeting such as the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting or Advances in Inflammatory Bowel Diseases: Crohn's & Colitis Foundation's Clinical and Research Conference. We will submit our manuscript to a leading peer-reviewed journal in the field of gastroenterology (i.e. *J Pediatr Gastroenterol Nutr.*, *Inflammatory Bowel Diseases*, etc.).

**Bibliography:**

1. Frymoyer A, Piester TL, Park KT. Infliximab Dosing Strategies and Predicted Trough Exposure in Children With Crohn Disease. *J Pediatr Gastroenterol Nutr.* 2016 May;62(5):723–7.
2. Frymoyer A, Hoekman DR, Piester TL, de Meij TG, Hummel TZ, Benninga MA, et al. Application of Population Pharmacokinetic Modeling for Individualized Infliximab Dosing Strategies in Crohn Disease. *J Pediatr Gastroenterol Nutr.* 2017 Dec;65(6):639–45.