Principal Investigator

First Name: Adam
Last Name: Cheifetz
Degree: MD
Primary Affiliation: Beth Israel Deaconess Medical Center
E-mail: acheifet@bidmc.harvard.edu
Phone number: (617) 667-2135
Address: 330 Brookline Ave

City: Boston
State or Province: MA
Zip or Postal Code: 02215
Country: United States

General Information

Key Personnel (in addition to PI):
First Name: Konstantinos
Last name: Papamichail
Degree: MD, PhD
Primary Affiliation: Beth Israel Deaconess Medical Center
SCOPUS ID:

First Name: Niels
Last name: Vande Casteele
Degree: PharmD, PhD
Primary Affiliation: UC San Diego
SCOPUS ID:

First Name: Zhongya
Last name: Wang
Degree: MS
Primary Affiliation: Robarts Clinical Trials
SCOPUS ID:

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

https://yoda.yale.edu/system/files/coi_asc.pdf
https://yoda.yale.edu/system/files/coi_kp.pdf
https://yoda.yale.edu/system/files/niels_yoda_project_coi_form_for_data_requestors_2019_signed.pdf
https://yoda.yale.edu/system/files/zhongya_yoda_project_coi_form_for_data_requestors_2019_signed.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

1. NCT00207675 - C0168T47 - 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

Defining a therapeutic drug window for infliximab induction therapy in pediatric patients with moderate-to-severe Crohn's disease

Narrative Summary:

Two pivotal randomized-controlled trials clearly showed high clinical response/remission rates after induction infliximab treatment in pediatric patients with inflammatory bowel disease (IBD). Serum infliximab concentrations have been related to favorable therapeutic outcomes in IBD, such as clinical, biochemical and endoscopic response. Nevertheless, there are limited data on the therapeutic window and the role of therapeutic drug monitoring during induction infliximab therapy in pediatric patients with IBD. The aim of the study is to investigate the association between serum infliximab concentrations and clinical response or remission in patients with moderate-to-severe Crohn's disease.

Scientific Abstract:

Background: Infliximab is an effective treatment for Crohn's disease (CD). Recent exposure-response relationship studies have revealed a positive correlation between high serum infliximab concentration and favorable therapeutic outcomes, although there are limited data regarding induction therapy and pediatric patients with CD.
Objective: To define the therapeutic window for adequate serum infliximab concentration associated with clinical response and remission following induction therapy in pediatric patients with moderate-to-severe CD.
Study Design: Post-hoc analysis of the REACH randomized controlled trial.
Participants: Patients with moderate-to-severe CD who received infliximab induction therapy (5mg/Kg at weeks 0, 2 and 6) (n=112).
Main outcome measure(s): Association between infliximab concentration at weeks 2, 6 and 10 with primary non-response (defined as lack of clinical response) or clinical remission assessed at week 10.
Statistical Analysis: Descriptive statistics will be provided with medians and interquartile range for continuous variables and frequency and percentage for categorical variables. A receiver operating characteristic analysis will be performed for infliximab concentrations to trace thresholds associated with outcomes of interest. Infliximab concentrations will be compared between groups with the Mann-Whitney U and Kruskal Wallis test, as appropriate. Univariate and multivariate analyses will be performed to identify variables associated with outcomes of interest.

Brief Project Background and Statement of Project Significance:

Two pivotal randomized-controlled trials clearly showed high clinical response/remission rates after induction infliximab treatment in pediatric patients with inflammatory bowel disease (IBD). [1, 2] Serum infliximab concentrations have been related to favorable therapeutic outcomes in IBD, such as clinical, biochemical and endoscopic response. [3-7] Nevertheless, there are limited data on the therapeutic window and the role of therapeutic drug monitoring during induction infliximab therapy in pediatric patients with IBD. As pharmacological treatment options in pediatric patients with IBD remain limited, emphasis has to be given to rational decision-making and optimization of therapies utilizing a therapeutic drug monitoring (TDM)-based therapeutic approach. This project by defining the adequate drug concentration for better therapeutic outcomes can be the first step for the application of reactive and proactive TDM towards a more personalized infliximab therapy in pediatric patients

with moderate-to-severe CD. This could potentially improve care and reduce the substantial social and economic burden to the community by preventing future CD-related hospitalizations and surgeries.

Specific Aims of the Project:

Specific Aim 1:
To investigate the association between serum infliximab concentration at weeks 2, 6 and 10 with clinical remission at week 10.

Specific Aim 2:
To investigate the association between serum infliximab concentration at weeks 2, 6 and 10 with primary non-response at week 10.

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

Research Methods

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

Post-hoc analysis of the REACH RCT regarding patients who received induction infliximab therapy (n=112). [1]

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

• Main outcome measures of interest include:
1. Clinical remission, defined as a pediatric Crohn's disease activity index (PCDAI)?10 at week 10.
2. Primary non-response, defined as lack of clinical response (decrease from baseline to week 10 in the total PCDAI score of at least 15 points and a total PCDAI score of no more than 30 points at week 10).
• Secondary outcome measures of interest include:
1. Change from baseline in quality of life based on the IMPACT III Questionnaire score at week 10. (The IMPACT III scores range from 35 to 175, with higher scores indicating better quality of life).
2. Change from baseline of the erythrocyte sedimentation rate (ESR) at week 10.

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

Main predictor/independent variables associated with outcomes of interest include:
• Serum infliximab concentrations at weeks 2, 6 and 10 associated with outcomes of interest.

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

Other variables associated with outcomes of interest include:
• gender
• race
• involved GI area
• age
• concomitant corticosteroids at baseline
• concomitant immunomodulators (thiopurines/methotrexate) at baseline
• disease duration
• weight
• height
• PCDAI at baseline
• ESR at baseline

Statistical Analysis Plan:

Descriptive statistics will be provided with medians and interquartile range (IQR) for continuous variables and

frequency and percentage for categorical variables. A receiver operating characteristic (ROC) analysis will be performed for infliximab concentrations to trace thresholds associated with outcomes of interest. Optimal thresholds will be chosen by using the Youden index, which maximizes the sum of the specificity (SP) and sensitivity (SN) of the ROC curve. SN, SP, positive predictive value, and negative predictive value will be also calculated. Infliximab concentrations at weeks 2, 6 and 10 will be compared between groups with the Mann-Whitney U test. Serum infliximab concentrations will be categorized also into quartiles. Rates of clinical remission and primary non-response at week 10 will be compared across infliximab serum concentration quartiles with the chi-square test (linear-by-linear association). The Kruskal-Wallis and the chi-square test will be used to compare continuous or discrete variables, respectively, across quartile groups. Univariate and multivariate logistic regression analyses will be performed to identify variables independently associated with outcomes of interest. The results will be expressed as odds ratio (OR) with 95% confidence intervals, followed by the corresponding P-value. Results will be considered statistically significant when P<0.05.

Software Used:

STATA

Project Timeline:

It is estimated that it will take 6-7 months to review the appropriate data. Statistical analyses will take another 2-3 months, while manuscript preparation will take approximately another 1-2 months. Consequently, the whole project will be completed in 9-12 months.

Dissemination Plan:

Presentation of the results to national and international medical congresses including Digestive Disease Week (DDW), Advances in IBD (AIBD), American College of Gastroenterology (ACG), European Crohn's and Colitis Organization (ECCO) and publication of the data in a high impact medical journal such as the American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, or the Journal of Crohn's and Colitis.

Bibliography:

1. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007;132:863-73.
2. Hyams J, Damaraju L, Blank M, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10:391-9.
3. Adedokun OJ, Xu Z, Padgett L, et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. Inflamm Bowel Dis 2013;19:2753-62.
4. Papamichael K, Rakowsky S, Rivera C, et al. association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic, and histologic remission in Crohn's disease. Inflamm Bowel Dis 2018;24:2266-2271
5. Papamichael K, Rakowsky S, Rivera C, et al. Infliximab trough concentrations during maintenance therapy are associated with endoscopic and histologic healing in ulcerative colitis. Aliment Pharmacol Ther. 2018 Feb;47(4):478-484.
6. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology 2014;147:1296-1307.
7. Singh N, Rosenthal CJ, Melmed GY, et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2014;20(10):1708-13.