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General Information

Key Personnel (in addition to PI): **First Name:** Gary
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Primary Affiliation: University of Pennsylvania

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

 [yoda_final_grl.pdf](#)

 [scott_coi.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): [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](#)

[NCT00094458 - Multicenter, Randomized, Double-Blind, Active Controlled Trial Comparing REMICADE® \(infliximab\) and REMICADE plus Azathioprine to Azathioprine in the Treatment of Patients with Crohn's Disease Naive to both Immunomodulators and Biologic](#)

[NCT00207662 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody \(Infliximab, Remicade\) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease](#)

[NCT00207766 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric](#)

[Monoclonal Antibody \(Infliximab, Remicade\) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease](#)

[NCT00004941 - A Placebo-controlled, Repeated-dose Study of Anti-TNF Chimeric Monoclonal Antibody \(cA2\) in the Treatment of Patients with Enterocutaneous Fistulae as a Complication of Crohn's Disease](#)

[NCT00269854 - A Placebo-Controlled, Dose-Ranging Study Followed by a Placebo-Controlled, Repeated-Dose Extension of Anti-TNF Chimeric Monoclonal Antibody \(cA2\) in the Treatment of Patients With Active Crohn's Disease](#)

[Efficacy and safety of retreatment with anti-tumor necrosis factor antibody \(infliximab\) to maintain remission in 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

The impact of anti-TNF drug levels on rates of fistula healing in individuals with Crohn's Disease

Narrative Summary:

Crohn's disease (CD) is a chronic inflammatory condition involving the small bowel and colon. A significant and common complication of this disorder is the formation of fistulas, or abnormal connections from the bowel to other bowel segments, skin, or other organs. Fistula affect up to 40% of individuals with CD. While anti-Tumor necrosis factor-alpha (anti-TNF) drugs have demonstrated efficacy in both non-fistulizing and fistulizing disease, limited population sizes in individual clinical trials have inhibited analyses to assess what factors may predict fistula healing, particularly regarding drug levels. We aim to assess the impact of anti-TNF drug levels on fistula healing in CD.

Scientific Abstract:

Background: The incidence of Crohn's disease (CD) is increasing. A common complication of CD is fistulizing disease, affecting up to 40% of individuals. While anti-Tumor necrosis factor- (anti-TNF) drugs have demonstrated efficacy in both non-fistulizing and fistulizing disease, limited population sizes in individual clinical trials have inhibited analyses to assess what factors may predict fistula response.

Objective: To assess the impact of anti-TNF drug levels on fistula healing in CD.

Study design: Retrospective cohort study of individuals with fistulizing CD from clinical trials of anti-TNF agents.

Participants: Individuals with CD with known fistula enrolled in clinical trials of anti-TNF agents who received therapy and had subsequent drug level testing.

Main Outcome Measure(s): The primary dependent variable will be a >50% reduction in drainage from fistula measured by week 14 of the study. Additional outcomes will include > 50% reduction at 1 year and complete cessation and closure of fistula.

Statistical analysis: Baseline covariates will be compared using descriptive statistics. We will then use logistic regression to adjust for multiple covariates, assessing the impact of drug levels >5ug/mL versus <5ug/ml. We will first employ univariate analysis, including all individual covariates with a p-value >0.10 in a final combined model. Backwards elimination will then be utilized to remove variables that do not significantly impact the OR by >10%. We will also conduct a propensity score analysis adjusting for factors predictive of a drug level <5ug/ml.

Brief Project Background and Statement of Project Significance:

The incidence of Crohn's disease (CD) is increasing worldwide(1). Unlike the other forms of inflammatory bowel disease, the inflammation in CD is transmural, significantly increasing the risk of penetrating and stenosing phenomena such as stricture, abscesses and fistula. Enteric fistula are a particularly troublesome and common complication, affecting up to 43% of patients with CD, and are responsible for a significant amount of morbidity and patient distress. Previous therapies such as antibiotics and immunomodulators to eliminate these tracts have demonstrated marginal efficacy in case series and small randomized controlled trials(2,3).

Infliximab, a chimeric IgG1 antibody against tumor necrosis factor- α (TNF- α) has demonstrated efficacy in both inducing and maintaining remission in CD in several large randomized controlled trials(4,5). In addition, several subgroup analyses and additional studies have demonstrated the efficacy of infliximab in the treatment of fistulizing and perianal CD(6-9).

One such trial was the ACCENT-II trial, which assessed the efficacy of infliximab in 306 adult patients with at least

one draining abdominal or perianal fistula⁶. The primary outcome assessed was the time to loss of response in those who initially had a response to infliximab, with a total of 54 weeks of follow-up time. Infliximab demonstrated a significantly increased time to loss of response (40 weeks vs 14 weeks, $p < 0.001$) and a significantly greater number of individuals still with response at 54 weeks (46% vs 23%, $p = 0.001$).

While these data demonstrated that infliximab had significant efficacy in the management of fistulizing disease, a proportion of patients had a loss of response (LOR), which was defined not only as recrudescence of fistula activity, but also any worsening of luminal CD or need for changes in CD therapy. On multivariate analyses, no variables were associated with increased rate of response or relapse, however.

Due to unavailability of routine drug level testing at the time, IFX levels were not assessed in the ACCENT-II trial. However, there is growing evidence that these levels are important indicators of response in those with luminal CD. We hypothesize that serum trough infliximab levels, as well as infliximab antibody levels are key variables in predicting who will respond and subsequently lose response to infliximab with fistulizing CD.

Therefore, we aim to specifically address the impact of infliximab levels on fistulizing Crohn's disease and rates of closure and healing. To assess these aims, we will employ pooled data previously collected in the scope of clinical trials involving infliximab to assess this impact and currently available via the Yale Open Data Access Project. This will provide the largest collection of patients with fistulizing Crohn's disease receiving infliximab studied to date. The results of this study will provide the most conclusive information available regarding the impact of anti-TNF levels on the impact of fistula healing, greatly impacting patient care.

Specific Aims of the Project:

Specific Aim 1: To assess the correlation of high infliximab serum trough levels with a decrease in fistula drainage greater than 50%.

Hypothesis 1: Elevated infliximab levels above are associated with improved fistula response, evidenced by a decrease in drainage by >50%

Specific Aim 2: To assess the impact of factors associated with reduced drug levels on subsequent fistula healing, employing propensity score analysis.

Hypothesis 2: Clinical factors that are associated with lower infliximab serum drug levels are also predictive of lower rates of fistula healing in Crohn's disease

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 that confirms or validates 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:

To achieve our stated aims of assessing the impact of infliximab serum drug levels on initial response of fistula and on subsequent maintenance of fistula response and remission, we will perform a retrospective cohort study using data previously from multiple clinical trials involving infliximab in Crohn's as previously selected. The study population will consist of individuals enrolled in the above clinical trials with a history of Crohn's disease, known to be complicated by 1 or more draining perianal or enterocutaneous fistula for more than 3 months, as well as women with rectovaginal fistula accompanied by at least one Enterovaginal fistula. As was allowed in the above studies, we will allow for seton use, concomitant medication use such as steroids, immunomodulators, 5-ASAs, and antibiotics. We will exclude those with other penetrating and fibrosing complications such as abscess, stricture or surgery when such data is available.

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

The primary dependent variable will be a >50% reduction in drainage from fistula measured by week 14 of the study. This will be structured as a binary variable. Secondary outcomes will include > 50% reduction at 1 year and complete cessation and closure of fistula. These will also be structured as binary variables in secondary analyses. As these are standardized outcomes used in clinical trials, we are confident that they have been recorded within the context of the original clinical trials.

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

The primary independent variable will be trough infliximab level. We will perform an initial analysis dichotomizing the exposure as being present or not present on assay (i.e. drug level is detectable versus non-detectable). We will then perform a secondary analysis structuring the exposure as an ordinal variable, where 0=undetectable, 1=<5ug/mL, and 2=>5ug/mL to assess for dose-response employing ordinal logistic regression. This cut-off was selected as it is commonly employed in clinical practice.

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

We will measure several covariates of interest related to CD severity and the likelihood of response, allowing us to adjust for them in our analysis. We will assess the number of fistula as a categorical variable (1 or >1), level of CD disease activity in the bowel as per Crohn's Disease Activity Index (CDAI), whether there was clinical response to infliximab (defined as CDAI reduction of at least 70 points or >25%), duration of disease (continuous variable), steroid use (categorical), immunomodulator use (categorical), antibiotic use (categorical), seton use (categorical), tobacco use (categorical), presence of antibodies to IFX(categorical), concentration of antibodies (continuous), and need for IFX dose escalation (categorical). We will also assess several demographic factors, such as age (categorical), sex (binary), and race (categorical).

Statistical Analysis Plan:

We will assess baseline covariates among those with IFX levels >5ug/mL compared to those with <5ug/mL, using Fisher's exact test and chi2 test where appropriate. We will then perform univariate analysis using logistic regression assessing the relationship between our covariates and the primary outcomes. We will then construct a multivariate model including those baseline characteristics with a p-value >0.10 in the univariate analysis, along with our exposure of interest and specific variables of clinical interest. These variables, which will be forced into the model will include number of fistula, disease activity, clinical response, use of immunomodulators, and dose escalation. We will then perform backwards elimination, removing non-significant variables that are not among the group of clinically significant variables or do not modify the OR of the primary exposure of interest >10%. We will assess for interaction between immunomodulator use and the primary exposure, as there is known interaction between these variables. We will also assess for interaction between dose escalation and IFX levels.

In a secondary analysis, we will conduct a propensity score analysis looking at factors that may directly impact the drug level (treatment), and adjust for these in comparison to likelihood of fistula healing. We will also conduct sensitivity analysis examining our cut-off for drug levels and the relationship with fistula healing. We will also perform an exploratory analysis looking at the impact of the concentration of antibodies to infliximab.

Project Timeline:

Upon receipt of the data, we anticipate starting the project immediately. During the first month, 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 1-2 months. We will then draft the manuscript and abstract for this work, and anticipate 2 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 6-7 months to manuscript submission.

Based on this outline, assuming a data receipt date of 12/1/2016, we would complete data quality analysis by 2/1/2017, complete analysis by 4/1/2016, and complete the manuscript by 6/1/2016.

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 Digestive Diseases Week or the annual American College of Gastroenterology annual scientific meeting. We will submit our manuscript to Gastroenterology, the preeminent journal in the field of gastroenterology.

Bibliography:

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