Principal Investigator

First Name: Siddharth
Last Name: Singh
Degree: MD, MS
Primary Affiliation: Divison of Gastroenterology, University of California San Diego
E-mail: sis040@ucsd.edu
Phone number: 3102957103
Address: 9500 Gilman Drive

City: La Jolla
State or Province: CA
Zip or Postal Code: 92093
Country: United States

General Information

Key Personnel (in addition to PI):
First Name: James
Last name: Proudfoot
Degree: MD
Primary Affiliation: University of California San Diego
SCOPUS ID: 57038204000

First Name: Parambir
Last name: Dulai
Degree: MD
Primary Affiliation: University of California San Diego
SCOPUS ID: 53463435600

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?: Scientific Publication

Conflict of Interest

http://yoda.yale.edu/system/files/coi_singhs_0.pdf
http://yoda.yale.edu/system/files/coi_proudfoot_0.pdf
http://yoda.yale.edu/system/files/coi_dulai_ps_0.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. 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
2. 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
3. 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
4. NCT00771667 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With T
5. NCT01369329 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed
6. NCT01369342 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease (UNITI-2)
7. NCT01369355 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects With Moderately to Severely Active 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

Treatment outcomes with biologics in moderate-severely active Crohn’s disease stratified by ileal vs. colonic disease location

Narrative Summary:

Crohn's disease (CD) is phenotypically classified by disease location (ileal or colonic). CD patients with ileal disease location are at a higher risk for disease related complications (strictures, fistulae, surgery). Post-hoc analyses of certolizumab clinical trial data and observational data in clinical practice have suggested that a differential response to biologics may exist between CD patients with ileal involvement versus those with isolated colonic disease. We will evaluate the impact of disease location on clinical outcomes in biologic-treated patients with moderate-severe CD, through analyses of late stage trials of infliximab and ustekinumab in CD.

Scientific Abstract:

Background: Ileal disease location is an independent predictor of disease related complications in Crohn’s disease (CD). The impact of ileal involvement on response to various biologics is yet to be quantified.
Objective: To evaluate the impact of ileal disease involvement on biologic-treated patients with moderate-severe CD.
Study Design: Individual participant level pooled analysis of RCTs of infliximab (IFX) and ustekinumab (UST) in patients with CD
Participants: Patients enrolled in phase III RCTs of IFX or UST in moderate-severe CD, receiving active therapy with biologic agents
Main Outcome Measures: Clinical remission/response and endoscopic remission
Statistical Analysis: We will pool data of patients in active agent arms (IFX/UST separately) to analyze outcomes, stratified by ileal disease involvement, using logistic regression analysis. Multivariate regression analysis will be performed after adjusting for confounding variables including age, sex, smoking status, baseline disease activity, concomitant corticosteroids, concomitant immunomodulators.

Brief Project Background and Statement of Project Significance:

Ileal disease involvement is observed in 70-80% of patients, and ileal involvement has consistently been observed

to be associated with an increased risk for hospitalization, stricturing and penetrating disease complications, need for immunosuppressive therapy, surgical resection, and post-operative recurrence.(1-3) Biologic therapy is initiated in moderate-severe CD in an effort to offset the risk for disease related complications through the achievement of disease remission (clinical and endoscopic). Post-hoc analyses of certolizumab clinical trial data and observational data in clinical practice have suggested that a differential response to biologics may exist between CD patients with ileal involvement versus those with isolated colonic disease,(4, 5) however, it is unclear if this is seen with other biologic agents and what the overall magnitude of impact is for ileal disease location on response to therapy. Understanding this would be informative when determining disease-monitoring strategies, the use of early combined immunosuppression, and potentially choice of biologic agent.
The overall objective of this proposal is to understand whether ileal disease involvement in patients treated with biologic therapy impacts clinical outcomes such as achieving clinical and/or endoscopic remission. Our central hypothesis is that moderate-severe CD patients with ileal disease involvement will be less likely to achieve clinical and/or endoscopic remission with biologics as compared to those with isolated colonic involvement, but the magnitude of impact may vary across biologics. The long-term goal of our program is to promote personalization of biologics and disease monitoring in CD. The significance of this work lies in systematically informing the impact of ileal disease location on response to biologic therapy. The information generated through this study would be invaluable to inform both science and patient care. From a scientific perspective, if we find evidence of differential response rates across biologics in CD patients with ileal disease location, it may help to better inform biologic selection in these patients and could potentially advance our understanding of IBD pathophysiology and merit evaluation of potential mechanisms as to why a differential response was observed (for example, impact on pharmacokinetics of biologic therapy, etc.). From a clinical perspective, information generated from this study on treatment response to biologic therapy, will be generalizable and directly applicable to patient care, informing clinical guidelines and offering potential for promoting personalized therapy in patients with IBD.

Specific Aims of the Project:

Specific aim #1: To compare CD disease activity and outcomes in patients with or without ileal disease involvement, in post-hoc analysis of phase III RCTs of IFX and UST in CD.
Hypothesis: As compared to patients without ileal involvement (isolated colonic CD), patients with ileal disease involvement will be less likely to achieve clinical or endoscopic remission after adjusting for confounding variables including age, sex, smoking status, baseline disease activity, concomitant corticosteroids and/or immunosuppressive agents.

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:

Data sources:
• Trials of ustekinumab in CD (NCT00771667, NCT01369329, NCT01369342, NCT01369355)
• Trial of infliximab in CD (NCT00207662, NCT00207766, NCT00094458)
Inclusion criteria:
• Patients (adults or pediatric) with moderate-severe CD
• Treated with infliximab or ustekinumab or placebo for induction and/or maintenance
• Reported presence or absence of ileal involvement at study enrollment or baseline. For studies not reporting baseline presence or absence of ileal involvement, historic ileal involvement will be used as it has been observed that disease location does not change over time in CD patients.
Exclusion criteria
• Patients lost to follow-up or did not participate in trial after randomization (without receiving any dose of the medication)

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

• Primary outcome – clinical remission (Crohn's disease activity index [CDAI]<150 for adults; pediatric CDAI<10 for children; complete fistula closure at 2 consecutive visits, for fistulizing CD) after induction (4-12 weeks) or after maintenance therapy (week 24-60)

• Secondary outcomes – clinical response (decrease in CDAI by 100 [clinical response [CR]100] or 70 points [CR70] from baseline for adults; decrease in pediatric CDAI to 11-30, for children; reduction in number of draining fistulae by 50% from baseline, for fistulizing CD); biochemical remission (C-reactive protein [CRP] <0.5mg/dl), to be assessed only in patients with elevated CRP at baseline; endoscopic remission (resolution of ulceration)

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

Main predictor/independent variable will be presence or absence of ileal disease location

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

Key confounding variables of interest in our study are:
o Biochemical measures of disease severity – baseline CRP as a categorical variable (<0.5mg/dl or ?0.5mg/dl), fecal calprotectin (where available, <150mcg/g vs. ?150mcg/g)
o Co-interventions – concomitant use of immunsuppressves like azathioprine, 6-mercaptopurine or methotrexate (yes vs. no), concomitant use of steroids (yes vs. no)
o Factors known to modify pharmacokinetics of biologics – baseline albumin as a categorical variable (<3.5g/dl vs. ?3.5g/dl), sex (males vs. females)
o Trials of induction and maintenance therapy will be analyzed separately

Statistical Analysis Plan:

Descriptive analysis: We will report proportions to present distribution of demographic, clinical and biochemical characteristics of participants stratified by ileal disease involvement, and calculate differences between groups using chi-square tests.
Univariate analysis: To assess how ileal disease involvement may modify response to biologic therapy, we will pool data from active agent arms of all included trials. In this, we will estimate whether ileal disease involvement influences response to therapy by comparing proportion of patients achieving primary and secondary outcomes by ileal disease involvement versus no involvement; IFX and UST trials will be analyzed separately.
Multivariable analysis: To evaluate the impact of ileal disease involvement use independently on response to therapy in IBD, we will perform logistic regression analysis after adjusting for confounding variables including age, sex, smoking status, baseline disease activity, concomitant corticosteroids, concomitant immunosuppressive.

Project Timeline:

o Project start date: September 15, 2018
o Analysis completion date: October 15, 2018
o Manuscript drafted: November 10, 2018
o Manuscript submitted for publication: November 30, 2018
o Date results reported back to YODA: November 30, 2018

Dissemination Plan:

We anticipate generation of one manuscript from this project on the impact of ileal disease involvement on treatment outcome. The target audience would be clinical gastroenterologists. Potentially suitable journals for this manuscript would be: American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, Inflammatory Bowel Diseases.

Bibliography:

1. de Barros KSC, Flores C, Harlacher L, Francesconi CFM. Evolution of Clinical Behavior in Crohn's Disease: Factors Associated with Complicated Disease and Surgery. Dig Dis Sci. 2017;62(9):2481-8.
2. Ouaz A, Fekih M, Labidi A, Ben Mustapha N, Serghini M, Zouiten L, et al. Changes of Crohn's disease phenotype over time. Tunis Med. 2016;94(6):167-70.
3. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol. 2010;105(2):289-97.
4. Subramanian S, Ekbom A, Rhodes JM. Recent advances in clinical practice: a systematic review of isolated colonic Crohn's disease: the third IBD? Gut. 2017;66(2):362-81.

5. Sandborn WJ, Schreiber S, Feagan BG, Rutgeerts P, Younes ZH, Bloomfield R, et al. Certolizumab pegol for active Crohn's disease: a placebo-controlled, randomized trial. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2011;9(8):670-8 e3.