

Principal Investigator

First Name: Siddharth

Last Name: Singh

Degree: MD, MS

Primary Affiliation: Division 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: Siddharth

Last name: Singh

Degree: MD, MS

Primary Affiliation: University of California San Diego

SCOPUS ID: 37066442700

First Name: Vipul

Last name: Jairath

Degree: MD, PhD

Primary Affiliation: Western University, London, Ontario

SCOPUS ID: 16679040000

First Name: James

Last name: Proudfoot

Degree: MS

Primary Affiliation: University of California San Diego

SCOPUS ID: 57038204000

First Name: Leonard

Last name: Guizzetti

Degree: PhD

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?: Scientific Publication

Conflict of Interest

http://yoda.yale.edu/system/files/coi - 5-asa_in_moderate-severe_cd - singhs.pdf

http://yoda.yale.edu/system/files/coi - 5-asa_in_moderate-severe_cd - proudfoot_j.pdf

http://yoda.yale.edu/system/files/coi - 5-asa_in_moderate-severe_cd - jairathvp.pdf

<http://yoda.yale.edu/system/files/coi - 2018-3126 - guizzetil.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-TNFα 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

Concomitant 5-ASA in Biologic-Treated Patients with Moderate-Severe Crohn's Disease: A Post-Hoc Analysis of RCTs

Narrative Summary:

5-aminosalicylates (5-ASA) are the most commonly prescribed drug class in patients with Crohn's disease (CD) worldwide, despite uncertainty for their benefit. A significant proportion of patients with moderate-severe disease treated with biologics, are still continued on 5-ASA though there is very limited evidence of any incremental clinical benefit of continuing 5-ASA. This practice may impose significant economic burden. We will evaluate the impact of continued 5-ASA use on clinical outcomes in biologic-treated patients with moderate-severe CD, through analyses of late stage trials of infliximab and ustekinumab. This will be directly relevant to clinical practice.

Scientific Abstract:

Background: Approximately 50% patients with Crohn's disease (CD) are treated with 5-ASA as their index therapy, despite limited evidence supporting efficacy. About 20% patients with CD escalate to biologic therapy for moderate-severe disease typically after failure of 5-ASA, but a significant proportion of these patients are still continued on 5-ASA without clear clinical or biological rationale.

Objective: To evaluate the impact of concomitant 5-ASA use 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 concomitant use of 5-ASA, 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:

5-ASAs are the most frequently prescribed drug class for patients with CD, despite uncertainty for their benefit. In population-based cohort studies, approximately 40-60% patients with CD received 5-ASA. Approximately 50-60% patients with CD require corticosteroids for acute flare, and in steroid-dependent patients, treatment is escalated to immunomodulators and/or biologic agents. In contemporary cohorts, biologic are used in 20% patients with CD. In clinical practice, a significant proportion of these patients who have escalated to biologic therapy are still continued on 5-ASA, without any evidence supporting incremental benefit of continuing 5-ASA. For example, in clinical trials of moderate-severe CD, we calculated 45-49% patients continued to receive 5-ASA. This imposes significant economic burden, in excess of CAN\$32 million annually based on a modeling study, and is inconsistent with principles of value-based care.

The overall objective of this proposal is to understand whether continued use of 5-ASA in patients treated with concomitant biologic therapy improves clinical outcomes such as achieving clinical and/or endoscopic remission. Our central hypothesis is that concomitant use of 5-ASA is not associated with any clinical benefit in biologic-treated patients with moderate-severe CD. The long-term goal of our program is to promote value-based care in CD. The significance of this work lies in systematically informing the role of concomitant 5-ASA use in patients who have failed 5-ASA and escalated to biologic therapy. The information generated through this study would be invaluable to inform both science, patient care and treatment guidelines. From a scientific perspective, if we find evidence of additional benefit to continuing 5-ASA in these refractory patients, it will advance understanding of IBD pathophysiology and merit evaluation of potential mechanisms as to why it may be beneficial (for example, impact on pharmacokinetics of biologic therapy, etc.). This study will also inform the design of an international, randomized, withdrawal study of 5-ASA in CD (Stopping Aminosalicylate Therapy in Inactive Crohn's Disease (STATIC), NCT03261206). 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 value-based in patients with IBD.

Specific Aims of the Project:

Specific aim #1: To compare CD disease activity and outcomes in patients who are concomitantly on 5-ASA vs. not on 5-ASA, in post-hoc analysis of phase III RCTs of IFX and UST in CD.

Hypothesis: As compared to patients not on 5-ASA, concomitant use of 5-ASA will not be associated with improvement in rates of achieving clinical or endoscopic response or 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:

- 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 concomitant use or non-use of 5-ASA at time of screening or first study-related visit

Exclusion criteria

- Lack of information on use of 5-ASA at time of screening or first study-related visit
- 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 (CDAI<150 for adults; PCDAI<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 [CR100] or 70 points [CR70] from baseline for adults; decrease in PCDAI to 11-30, for children; reduction in number of draining fistulae by 50% from baseline, for fistulizing CD); biochemical remission (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 concomitant use vs. non-use of 5-ASA.

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 C-reactive protein 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 immunosuppressives like azathioprine, 6-mercaptopurine or methotrexate (yes vs. no), concomitant use of steroids (yes vs. no)
- o Factors known to modify pharmacokinetics of anti-TNF therapy – baseline albumin as a categorical variable (<3.5g/dl vs. ?3.5g/dl), sex (males vs. females)
- o All analysis will be stratified by age group of participants (adults vs. children); 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 concomitant use of 5-ASA or not, and calculate differences between groups using chi-square tests.

Univariate analysis: To assess how concomitant use of 5-ASA may modify response to biologic therapy, we will pool data from active agent arms of all included trials. In this, we will estimate whether concomitant 5-ASA influences response to therapy by comparing proportion of patients achieving primary and secondary outcomes by baseline use vs. non-use of 5-ASA; IFX and UST trials will be analyzed separately.

Multivariable analysis: To evaluate the impact of concomitant 5-ASA 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:

Once study is approved and data access provided (assuming by May 2018), our key milestones dates are:

- o Project start date: June 1, 2018
- o Analysis completion date: August 30, 2018
- o Manuscript drafted: October 30, 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 concomitant 5-ASA use 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. Peyrin-Biroulet L1, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol.* 2010 Feb;105(2):289-97.
2. Targownik LE, Tennakoon A, Leung S, Lix LM, Singh H, Bernstein CN. Temporal Trends in Initiation of Therapy With Tumor Necrosis Factor Antagonists for Patients With Inflammatory Bowel Disease: A Population-based Analysis. *Clin Gastroenterol Hepatol.* 2017 Jul;15(7):1061-1070