Principal Investigator

First Name: Vipul
Last Name: Jairath
Degree: MB ChB, PhD
Primary Affiliation: The University of Western Ontario
E-mail: tran.nguyen@lhsc.on.ca
Phone number:
Address:

City: London
State or Province: Ontario
Zip or Postal Code: N6A 3K7
Country: Canada

General Information

Key Personnel (in addition to PI):
First Name: Guangyong
Last name: Zou
Degree: MSc, PhD
Primary Affiliation: Western University
SCOPUS ID: 0000-0001-5773-4185

First Name: Siddharth
Last name: Singh
Degree: MBBS, MS
Primary Affiliation: University of California San Diego
SCOPUS ID:

First Name: Dhruv
Last name: Ahuja
Degree: MBCHB
Primary Affiliation: Indira Ghandi Hospital
SCOPUS ID:

First Name: Meagan
Last name: Archer
Degree: MSc, BSc
Primary Affiliation: Lawson Health Research Institute
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?: Data Holder (Company)

Conflict of Interest

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. NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
2. NCT00096655 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
3. NCT00487539 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis
4. 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
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 or Are Intolerant to TNF Antagonist Therapy (UNITI-1)
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. NCT00488774 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Intravenously, in Subjects With Moderately to Severely Active Ulcerative Colitis

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

**Research Proposal**

**Project Title**

Impact of concomitant baseline medication on efficacy of biologics and small molecules for Inflammatory Bowel Disease

**Narrative Summary:**

Patients with IBD may be on a variety of different medications to help manage their condition, thus it is important to understand whether the medications a patient is currently taking at the start of a trial modifies the efficacy of the new drug being studied. The aims of the study are to assess whether the use of concomitant steroids, aminosalicylates, immunosuppressants (azathioprine, methotrexate), protein pump inhibitors (PPI), antidepressants, or opioid use at baseline in patients with IBD, impacts the efficacy of the investigational drug. By identifying the impact of these medications used at baseline, it may help improve the design of future studies and guide treatment decisions.

**Scientific Abstract:**
Background: IBD is a common disease, with 6.8 million people around the world who suffer from it (Global Burden of Disease Inflammatory Bowel Disease Collaborators, 2020). There is currently no cure for IBD, however there are several types of medications that can be used to treat the disease including aminosalicylates, corticosteroids, immunomodulators, antibiotics, biologic therapies and small molecule drugs. Patients with IBD may be on a variety of different medications to help manage their condition, therefore it is important to understand whether the medications a patient is currently taking at the start of a trial modifies the efficacy of the new drug being studied.

Objective: The primary objective of this study is to assess whether the efficacy of the investigational drug in IBD induction clinical trials differs according to concomitant baseline use of steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants, or opioids.

Study Design: This study is an analysis of individual participant data (IPD) from IBD clinical trials to assess whether the clinical response and remission rates differ for those taking steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants, or opioids at baseline, compared to those not taking steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants, or opioids at baseline.

Participants: UC and CD patients

Main Outcome Measures: The main outcome measure will be clinical response/remission. The secondary outcome measures include: Endoscopic response/remission, histologic response/remission, C-reactive protein (CRP) levels (median, IQR), change in CRP levels, fecal calprotectin (FCP) levels (median, IQR), and change in FCP levels.

Statistical Analysis: Statistical analyses will be performed using a complete-case analysis. Individual level data using the modified Poisson regression will be used to quantify modification of new drug effects by baseline medications on the risk ratio scale (Zou 2004). Study-specific estimates and the 95% two-sided confidence intervals will be obtained for outcomes of interest (clinical, histologic, and endoscopic remission and response).

Brief Project Background and Statement of Project Significance:

Inflammatory bowel disease (IBD) is a condition that causes chronic inflammation to the gastrointestinal (GI) tract. The two types of IBD include ulcerative colitis (UC) and Crohn’s Disease (CD). In UC, inflammation occurs in the colon and rectum, mainly affecting the inner lining of the colon. For CD, inflammation occurs in any part of the GI tract from mouth to anus, affecting multiple layers of the small intestinal and colon. IBD is a common disease, with 6.8 million people around the world who suffer from it (Global Burden of Disease Inflammatory Bowel Disease Collaborators, 2020). There is currently no cure for IBD, however there are several types of medications that can be used to treat the disease including aminosalicylates, corticosteroids, immunomodulators, antibiotics, biologic therapies and small molecule drugs.

Given that patients with IBD may be on a variety of different medications to help manage their condition, it is important to understand whether the medications a patient is currently taking at the start of a trial modifies the efficacy of the new drug being studied (Feuerstein et al., 2020; Bressler et al., 2015). For example, we would be interested in whether the new drug is more or less effective for patients on steroids at the start of a study, compared to patients not on steroids. This is important to establish as the results could influence how we interpret the results of clinical trials and how clinicians use treatments in routine practice, such as prescribing the drug to most effective groups of patients. The results will also guide the design of future clinical trials. Published clinical trials usually do not present effect modification of new drug by baseline medications. Such results can only be obtained through access to patient level data from clinical trials.

In this study, we want to specifically look at whether the use of concomitant steroids, aminosalicylates, immunosuppressants (azathioprine, methotrexate), protein pump inhibitors (PPI), antidepressants, or opioid use at baseline in patients with IBD, impacts the efficacy of the investigational drug (Lu et al., 2021; Macer et al., 2017; Niccum et al., 2021). By identifying the impact of these medications used at baseline, it may help improve the design of future studies as well as help guide treatment decisions for patients with IBD.

Specific Aims of the Project:

The primary objective of this study is to assess whether the efficacy of the investigational drug in
IBD induction clinical trials differs according to concomitant baseline use of steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants, or opioids.

Research Methods

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

This study is an analysis of individual participant data (IPD) from IBD clinical trials to assess whether the response and remission (clinical, endoscopic, and histologic) rates differ for those taking steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants, or opioids at baseline, compared to those not taking steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants, or opioids at baseline. Induction phases of pivotal phase 3 IBD (UC and CD) trials will be identified and IPD (e.g., baseline demographics, disease and clinical characteristics, concomitant medications) will be obtained.

The data from the Yoda Platform will be combined with the studies from the Vivli platform. Please see the rest of the studies that we will be including in the analysis below:

NCT01224171
NCT00552058
NCT00783692
NCT01465763
NCT01458951
NCT00385736
NCT00783718
NCT00408629

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The main outcome measure will be clinical response/remission. Clinical response (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no). Clinical remission at the primary endpoint visit (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no). The secondary outcome measures include: Endoscopic response/remission, histologic response/remission, C-reactive protein (CRP) levels (median, IQR), change in CRP levels, and fecal calprotectin (FCP) levels (median, IQR).

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

The main predictor/independent variable include the concomitant baseline use of steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants, or opioids.

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

The following will be reported for the baseline (Week 0) and primary endpoint assessment visits for the induction period:

UC Trials:
1. Mayo Clinic Score (MCS) (median, IQR)
2. Each sub-component of the MCS (median, IQR)
3. Change in the total MCS score and change in each sub-component of the MCS
4. Geboes Score (median, IQR)
5. Change in Geboes Score
6. Robarts Histopathology Index (RHI) score (calculated from Geboes subscores, if available) (median, IQR)
   Change in RHI score
CD Trials:
1. Crohn’s Disease Activity Index (CDAI) (mean, standard deviation (SD), median, IQR)
2. Each sub-component of the CDAI, if available
3. Change in the total CDAI from baseline and change in each component of the CDAI
4. 2-item patient-reported outcome (PRO2), if stool frequency (SF) and abdominal pain (AP) subscores of the CDAI are available (median, IQR)
5. Change in PRO2 scores
6. Simple Endoscopic Score for Crohn’s Disease (SES-CD)/ Crohn’s Disease Endoscopic Index of Severity (CDEIS) (median, IQR)
7. Each sub-component of the SES-CD/CDEIS, per segment
8. Change in total SES-CD/CDEIS score and change in each component of the SESCD/CDEIS
9. GHAS and change in GHAS (median, IQR)

Statistical Analysis Plan:

Appropriate descriptive statistics will be presented for demographic and baseline characteristics for both the entire study sample and according to each study treatment arm (active or placebo) across baseline medications (yes/no).
In order to assess our primary outcome (clinical response/remission), we will analyze individual level data using the modified Poisson regression to quantify modification of new drug effects by disease distribution on the risk ratio scale (Zou 2004). Study-specific estimates and the 95% two-sided confidence intervals will be obtained for outcomes of interest (clinical remission and response). To obtain overall estimates and 95% confidence intervals of all studies, we will apply the extended modified Poisson regression model (Zou et al., 2013) with studies being considered as clusters. The same analysis will be performed for the other secondary binary outcomes, including endoscopic and histologic response/remission.
For the secondary outcomes including the CRP and FCP levels and change in the CRP and FCP levels from baseline (Week 0) to primary endpoint assessment, log-transformed endpoint CRP and FCP will be analyzed using regression model with independent variables including baseline CRP/FCP and treatment indicators, as well as other patients’ characteristics as appropriate.
The additional endpoints for UC trials include: the baseline (Week 0) and primary endpoint assessment visits for the MCS, each subcomponent of the MCS, change in the total MCS score and change in each subcomponent of the MCS, Geboes score, change in the Geboes score, RHI score, and change in the RHI score. The additional endpoints for CD trials include: the baseline (Week 0) and primary endpoint assessment visits for the CDAI, each subcomponent of the CDAI, change in the total CDAI score, PRO2 score, change in the PRO2 score, SES-CD score, CDEIS score, total, colonic, and ileal Global Histologic Disease Activity Score (GHAS), and change in the total, colonic, and ileal GHAS. To assess the additional endpoints for the UC and CD trials, appropriate regression methods for continuous data will be used. All analyses will be adjusted for other patient characteristics including age, sex, and disease duration. Results will be reported in terms of treatment effects (mean differences in scores) for patients used baseline medications and those did not use baseline medications, as well as difference in treatment effects between the two groups. Two-sided 95% confidence intervals and associated p-values will be presented.
Each model will have independent variables including drug, baseline medication, and their interaction. The focus of this project is the coefficient estimation for the interaction term.

Project Timeline:
Project start date: September 1, 2022
Analysis completion date: December 1, 2022
Abstract and manuscript drafted: February 1, 2023
Submission to journal: April 1, 2023

Dissemination Plan:
We anticipate that the analysis will result in a manuscript in a specialty gastrointestinal or Inflammatory Bowel Disease journal such as: Alimentary Pharmacology & Therapeutics, Gut, Gastroenterology, Clinical Gastroenterology and Hepatology, or Journal of Cohn’s and Colitis. We also anticipate the sharing of the resulting information through presentation at relevant international conferences (e.g., Digestive Disease Week (DDW), and the European Crohn’s and Colitis Organization Congress (ECCO)).

The results from this study will have several stakeholders. The immediate target audience are clinicians treating patients with IBD and those involved in designing clinical trials (primarily researchers, investigators, and industry).

Bibliography: