

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: Guanyong
Last name: Zou
Degree: PhD
Primary Affiliation: Department of Epidemiology and Biostatistics, Robarts Research Institute, Schulich School of Medicine & Dentistry, University of Western Ontario
SCOPUS ID: 0000-0001-5773-4185

First Name: Tran
Last name: Nguyen
Degree: MSc
Primary Affiliation: Lawson Health Research Institute
SCOPUS ID: 0000-0002-2640-7269

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 Gandhi 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

https://yoda.yale.edu/wp-content/uploads/2019/05/nguyen_tran_coi.pdf

https://yoda.yale.edu/wp-content/uploads/2019/11/singh_sidd_coi.pdf

https://yoda.yale.edu/wp-content/uploads/2014/10/jairath_vip_coi.pdf

https://yoda.yale.edu/wp-content/uploads/2019/12/zou_gy_coi.pdf

<https://yoda.yale.edu/wp-content/uploads/2021/08/COI-form-MA.pdf>

<https://yoda.yale.edu/wp-content/uploads/2020/08/Dhruv-YODA-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

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. [NCT00488631 - A Phase 3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects With Moderately to Severely Active Ulcerative Colitis](#)
5. [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

Efficacy of medical therapies for ulcerative colitis according to disease distribution: An individual patient data meta-analysis of RCTs

Narrative Summary:

Ulcerative colitis (UC) can be categorized according to its location as either left-sided colitis where the continuous inflammation affects mainly the left side of the body, in comparison to extensive colitis where the inflammation affects the entire colon. Differing distribution of disease may present with differing burden of symptoms and a differential response to treatment, neither of which have been well studied. In this study, we want to look at whether the disease distribution of patients enrolled in clinical trials of moderate to severe UC, impacts the treatment effects of the trial intervention.

Scientific Abstract:

Background: Inflammatory bowel disease (IBD) is a common condition that causes chronic inflammation to the gastrointestinal (GI) tract, impacting 6.8 million people around the world (Global Burden of Disease Inflammatory Bowel Disease Collaborators, 2020). The two types of IBD include ulcerative colitis (UC) and Crohn's Disease (CD). In UC, inflammation occurs in the colon and rectum, typically only affecting the outer layer of the colon. The inflamed areas are continuous and starts at the rectum, spreading proximally into the colon. UC can be categorized according to its location as either left-sided colitis where the continuous inflammation affects mainly the left side of the body, in comparison to extensive colitis where the inflammation affects the entire colon.

Objective: The primary objective of this study is to assess whether the treatment effect of the intervention differs according to the disease distribution (left-sided vs. extensive disease) in induction and maintenance trials with moderate to severe UC patients. The secondary objectives of this study is to examine the impact on the individual symptoms of stool frequency and rectal bleeding.

Study Design: This study is an individual participant data (IPD) meta-analysis to assess whether the clinical response and remission rates differ for UC patients with left-sided colitis compared to UC patients with extensive colitis. Recently published pivotal phase 3 UC trials were identified. IPD (e.g., baseline demographics, disease and clinical characteristics, concomitant medications) will be obtained for induction and maintenance trials.

Participants: UC patients

Main Outcome Measure(s): Clinical response and remission are the main outcome measures. The secondary outcome measures include: endoscopic response/remission, histologic response/remission, individual symptoms of rectal frequency, individual symptoms of stool bleeding, 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 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.

Brief Project Background and Statement of Project Significance:

Inflammatory bowel disease (IBD) is a common condition that causes chronic inflammation to the gastrointestinal (GI) tract, impacting 6.8 million people around the world (Global Burden of Disease Inflammatory Bowel Disease Collaborators, 2020). The two types of IBD include ulcerative colitis (UC) and Crohn's Disease (CD). In CD, inflammation occurs in any part of the GI tract, affecting multiple layers of the colon. The inflamed areas are not continuous and may appear next to areas with healthy tissue. In UC, inflammation occurs in the colon and rectum, typically only affecting the outer layer of the colon. The inflamed areas are continuous and starts at the rectum, spreading proximally into the colon.

UC can be categorized according to its location as either left-sided colitis where the continuous inflammation affects mainly the left side of the body, in comparison to extensive colitis where the inflammation affects the entire colon. Previous studies have shown that disease in UC patients in only the rectum and sigmoid colon is found in 30%-50% of patients, left-sided colitis found in 20%-30%, and pancolitis found in approximately 20% (Ordas et al., 2012). The Montreal classification categorizes disease distribution in UC by extent of disease as follows: (E1) Ulcerative proctitis; (E2) Left sided UC (distal to splenic flexure); (E3) Extensive (proximal to splenic flexure) (Satsangi et al., 2006). Differing distribution of disease may present with differing burden of symptoms and a differential response to treatment, neither of which have been well studied. For example, patients with more distal disease could be more likely to experience bleeding and urgency. Given that patients with UC have different disease distributions, it is important to assess whether disease distribution impacts the efficacy of the new drug being studied. However, when clinical trials are performed to assess the efficacy of a medication, there are no restrictions on disease distribution as an entry criteria, apart from the exclusion of patients with isolated proctitis.

In this study, we want to look at whether the disease distribution of patients enrolled in clinical trials of moderate to severe UC, impacts the treatment effects of the trial intervention. We are specifically interested in whether the treatment effect varies by patients with left sided colitis, compared to patients with extensive colitis. By identifying the impact of disease distribution on treatment efficacy, it may help improve the design of future clinical trials as any differential effect may result in

stratification of patients by disease distribution. It may also help to inform treatment recommendations for patients depending upon their disease distribution.

Specific Aims of the Project:

The primary objective of this study is to assess whether the treatment effect of the intervention differs according to the disease distribution (left-sided vs. extensive disease) in induction and maintenance trials with moderate to severe UC patients, based on the rates of clinical response and remission. The secondary objectives of this study is to examine the impact on the individual symptoms of stool frequency and rectal bleeding, determine the rates of endoscopic and histologic response/remission, assess the C-Reactive protein (CRP) levels (median, IQR) from baseline (Week 0) and primary endpoint assessment, change in CRP levels from baseline (Week 0) and primary endpoint assessment, assess the fecal calprotectin (FCP) levels (median, IQR) from baseline (Week 0) and primary endpoint assessment, and assess the change in FCP levels from baseline (Week 0) and primary endpoint assessment.

Research Methods

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

This study is an individual participant data (IPD) meta-analysis to assess whether the clinical response and remission rates differ for UC patients with left-sided colitis compared to UC patients with extensive colitis. Recently published pivotal phase 3 UC trials were identified. IPD (e.g., baseline demographics, disease and clinical characteristics, concomitant medications) will be obtained for induction and maintenance trials.

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

NCT01465763
NCT01458951
NCT00385736
NCT02611830
NCT01458574
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, individual symptoms of rectal frequency, individual symptoms of stool bleeding, C-Reactive protein (CRP) levels (median, IQR), change in CRP levels, fecal calprotectin (FCP) levels (median, IQR), and change in FCP levels.

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

The main predictor/independent variable is the disease distribution (left-sided vs. extensive disease).

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

Other variables of interest that will be used in your analysis:

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

- Mayo Clinical Score (MCS) (median, interquartile range (IQR))
- Each subcomponent of the MCS (median, IQR)
- Change in the total MCS score and change in each subcomponent of the MCS
- Geboes score (median, IQR)
- Change in Geboes score
- Roberts Histopathology Index (RHI) score (calculated from Geboes subscores, if available) (median, IQR)
- Change in RHI score

Please see the attached data extraction form for additional variables of interest.

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 different disease distributions (extensive disease vs. left sided disease).

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 individual symptoms of rectal frequency and stool bleeding, the regression model for counts will be used, while binary data will be analyzed using the modified Poisson regression. To handle the potential over-dispersion of the data, negative binomial regression models will be used and the results will be presented in terms of rate ratios and 95% confidence intervals. In order to assess both 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.

Lastly, to assess the additional endpoints including 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, linear regression models will be used with covariates including baseline outcomes, treatment groups and other characteristics as appropriate.

Each model will have independent variables including drug, disease distribution, and their interaction. The focus of this project is the coefficient estimation for the interaction term. Primary estimates will be the ratio of treatment effects on left-sided colitis to that of extensive colitis.

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 Crohn'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:

1. Ords, I., Eckmann, L., Talamini, M., Baumgart, D. C., & Sandborn, W. J. (2012). Ulcerative colitis. *Lancet (London, England)*, 380(9853), 1606-1619. [https://doi.org/10.1016/S0140-6736\(12\)60150-0](https://doi.org/10.1016/S0140-6736(12)60150-0)
2. Global Burden of Disease 2017 Inflammatory Bowel Disease Collaborators. (2020). The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Gastroenterology & Hepatology*, 5(1), 17-30. [https://doi.org/10.1016/S2468-1253\(19\)30333-4](https://doi.org/10.1016/S2468-1253(19)30333-4)
3. Satsangi, J., Silverberg, M. S., Vermeire, S., & Colombel, J. F. (2006). The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*, 55(6), 749-753. <https://doi.org/10.1136/gut.2005.082909>
4. Zou G. (2004). A modified poisson regression approach to prospective studies with binary data. *American journal of epidemiology*, 159(7), 702-706. <https://doi.org/10.1093/aje/kwh090>
5. Zou, G. Y., & Donner, A. (2013). Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Statistical methods in medical research*, 22(6), 661-670. <https://doi.org/10.1177/0962280211427759>