Principal Investigator

First Name: Vipul
Last Name: Jairath
Degree: MB ChB, PhD
Primary Affiliation: The University of Western Ontario
E-mail: dhruv8196@gmail.com
State or Province: Ontario
Country: Canada

General Information

Key Personnel (other than PI):
First Name: Guangyong
Last name: Zou
Degree: MSc, PhD
Primary Affiliation: Western University
SCOPUS ID: 0000-0001-5773-4185
Requires Data Access? No

First Name: Siddharth
Last name: Singh
Degree: MBBS, MS
Primary Affiliation: University of California San Diego
SCOPUS ID:
Requires Data Access? No

First Name: Dhruv
Last name: Ahuja
Degree: MBCHB
Primary Affiliation: Indira Gandhi Hospital
SCOPUS ID:
Requires Data Access? Yes

First Name: Meagan
Last name: Archer
Degree: MSc, BSc
Primary Affiliation: Lawson Health Research Institute
SCOPUS ID:
Requires Data Access? No

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 - C0168T37 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
2. NCT00096655 - C0168T46 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
3. NCT00487539 - C0524T17 - 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 - C0168T21 - 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 - CNTO1275CRD3001 - 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 - CNTO1275CRD3002 - 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 - C0524T16 - 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, statins, meds for diabetes & BP, protein pump inhibitors (PPI), antidepressants, or opioid use at baseline in IBD patients, 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 chronic lifelong disease. In the last decade, several highly efficacious. therapeutic options have emerged. Patients with IBD may be on a variety of different medications to help manage their condition, therefore it is important to understand whether other medications a patient is taking at the start of a trial modifies the efficacy of the new drugs being studied.
Objective: The primary objective is to assess whether the efficacy and safety of the investigational drug in IBD induction clinical trials differs according to concomitant baseline use of different drugs which a patient might be taking for non-IBD indication.
Study Design: This is a pooled analysis of multiple trials studying the advanced therapies in IBD.
Participants: UC and CD patients
Main Outcome Measures: The main outcome will be clinical remission. The secondary outcome measures include: endoscopic response/remission, infections and serious adverse events.
Statistical Analysis: Individual level data using the modified Poisson regression will be used to quantify drug effect modification 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 and safety of the investigational drug in IBD induction clinical trials differs according to concomitant baseline use of steroids, antibiotics, aminosalicylates, statins and other lipid lowering drugs, drugs for diabetes, anti-hypertensives, immunosuppressants, PPIs, antidepressants, or opioids.

The secondary objective of the study is to assess the impact of different races and ethnicities on efficacy and safety of investigational drugs in IBD induction trials.

Study Design:

Meta-analysis (analysis of multiple trials together)

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

New research question to examine treatment safety

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research on clinical trial methods

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) and safety (infections or serious adverse events) rates differ for those taking steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants, statins or other lipid lowering drugs, medications for diabetes, anti-hypertensives or opioids at baseline, compared to those not taking steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants, statins or other lipid lowering drugs, medications for diabetes, anti-hypertensives 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.
Similar approach will be applied to assess the impact of races and ethnicities.
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 efficacy 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, remission based on patient reported outcomes, histologic response/remission, C-reactive protein (CRP) levels (median, IQR), change in CRP levels, and fecal calprotectin (FCP) levels (median, IQR).

The main safety outcome will be infections and serious adverse events. The infections occuring during induction period will be dichotomized into a binary response (yes/no). The serious adverse events (as defined in the trial) occuring during induction period will be dichotomized into a binary response (yes/no).

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

1. The main predictor/independent variable include the concomitant baseline use of steroids, aminosalicylates, immunosuppressants, PPIs, antidepressants , opioids, antibiotics, statins and other lipid lowering drugs, medications for diabetes or anti-hypertensives.
2. The other independent variable includes different races and ethnicities with white as reference (Blacks vs Whites, Asians vs Whites, Hispanics vs non-Hispanic whites).

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, endoscopic remission/improvement, infections and serious adverse events). 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.

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, each subcomponent of the SES-CD/CDEIS score, change in the SES-CD/CDEIS, change in each of the sub-component of the SES-CD/CDEIS, 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.

Software Used:

RStudio

Project Timeline:

Project start date: August 1, 2024
Analysis completion date: December 1, 2024
Abstract and manuscript drafted: February 1, 2025
Submission to journal: April 1, 2025

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. 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
2. Feuerstein, J. D., Isaacs, K. L., Schneider, Y., Siddique, S. M., Falck-Ytter, Y., Singh, S., & AGA Institute Clinical Guidelines Committee (2020). AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology, 158(5), 1450?1461. https://doi.org/10.1053/j.gastro.2020.01.006
3. Bressler, B., Marshall, J. K., Bernstein, C. N., Bitton, A., Jones, J., Leontiadis, G. I., Panaccione, R., Steinhart, A. H., Tse, F., Feagan, B., & Toronto Ulcerative Colitis Consensus Group (2015). Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology, 148(5), 1035?1058.e3. https://doi.org/10.1053/j.gastro.2015.03.001
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
6. Lu, T. X., Dapas, M., Lin, E., Peters, T., & Sakuraba, A. (2021). The influence of proton pump

inhibitor therapy on the outcome of infliximab therapy in inflammatory bowel disease: a patient-level meta-analysis of randomised controlled studies. Gut, 70(11), 2076?2084. https://doi-org.proxy1.lib.uwo.ca/10.1136/gutjnl-2020-321609
7. Macer, B. J., Prady, S. L., & Mikocka-Walus, A. (2017). Antidepressants in Inflammatory Bowel Disease: A Systematic Review. Inflammatory bowel diseases, 23(4), 534?550. https://doi.org/10.1097/MIB.0000000000001059
8. Niccum, B., Moninuola, O., Miller, K., & Khalili, H. (2021). Opioid Use Among Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association, 19(5), 895?907.e4. https://doi.org/10.1016/j.cgh.2020.08.041

9. Nguyen GC, LaVeist TA, Harris ML, Wang MH, Datta LW, Brant SR. Racial disparities in utilization of specialist care and medications in inflammatory bowel disease. Am J Gastroenterol. 2010 Oct;105(10):2202-8. doi: 10.1038/ajg.2010.202. Epub 2010 May 18. PMID: 20485281; PMCID: PMC3170037.

10. Liu JJ, Abraham BP, Adamson P, Barnes EL, Brister KA, Damas OM, Glover SC, Hooks K, Ingram A, Kaplan GG, Loftus EV, McGovern DPB, Narain-Blackwell M, Odufalu FD, Quezada S, Reeves V, Shen B, Stappenbeck TS, Ward L. The Current State of Care for Black and Hispanic Inflammatory Bowel Disease Patients. Inflamm Bowel Dis. 2023 Feb 1;29(2):297-307. doi: 10.1093/ibd/izac124. PMID: 35816130; PMCID: PMC10210746.

11. Asotibe JC, Akuna E, Williams D, Busari OA, Edigin E, Achebe I, Asotibe BM, Trick W, Mishra S. Racial differences in the outcomes of IBD hospitalizations: a national population-based study. Int J Colorectal Dis. 2022 Jan;37(1):221-229. doi: 10.1007/s00384-021-04052-z. Epub 2021 Oct 25. PMID: 34694440.

12. Ore AS, Vigna C, Fabrizio A, Messaris E. Evaluation of Racial/Ethnic Disparities in the Surgical Management of Inflammatory Bowel Disease. J Gastrointest Surg. 2022 Dec;26(12):2559-2568. doi: 10.1007/s11605-022-05483-x. Epub 2022 Oct 17. PMID: 36253503.

13. Anita Afzali, Raymond K. Cross, Racial and Ethnic Minorities with Inflammatory Bowel Disease in the United States: A Systematic Review of Disease Characteristics and Differences, Inflammatory Bowel Diseases, Volume 22, Issue 8, 1 August 2016, Pages 2023–2040, https://doi.org/10.1097/MIB.0000000000000835

14. Lewis JD, Parlett LE, Jonsson Funk ML, Brensinger C, Pate V, Wu Q, Dawwas GK, Weiss A, Constant BD, McCauley M, Haynes K, Yang JY, Schaubel DE, Hurtado-Lorenzo A, Kappelman MD. Incidence, Prevalence, and Racial and Ethnic Distribution of Inflammatory Bowel Disease in the United States. Gastroenterology. 2023 Nov;165(5):1197-1205.e2. doi: 10.1053/j.gastro.2023.07.003. Epub 2023 Jul 20. PMID: 37481117; PMCID: PMC10592313.

15. Barnes EL, Loftus EV Jr, Kappelman MD. Effects of Race and Ethnicity on Diagnosis and Management of Inflammatory Bowel Diseases. Gastroenterology. 2021 Feb;160(3):677-689. doi: 10.1053/j.gastro.2020.08.064. Epub 2020 Oct 21. PMID: 33098884.

16. Hashash JG, Mourad FH, Odah T, Farraye FA, Kroner P, Stocchi L. Ethnic Variation Trends in the Use of Ileal Pouch-Anal Anastomosis in Patients With Ulcerative Colitis. Crohns Colitis 360. 2023 Nov 16;5(4):otad072. doi: 10.1093/crocol/otad072. PMID: 38034883; PMCID: PMC10686008.

17. Montgomery SR Jr, Butler PD, Wirtalla CJ, Collier KT, Hoffman RL, Aarons CB, Damrauer SM, Kelz RR. Racial disparities in surgical outcomes of patients with Inflammatory Bowel Disease. Am J Surg. 2018 Jun;215(6):1046-1050. doi: 10.1016/j.amjsurg.2018.05.011. Epub 2018 May 12. PMID: 29803499; PMCID: PMC7764563.

Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2024/07/YODA-narrative-summary-1.docx