Principal Investigator

First Name: Neeraj
Last Name: Narula
Degree: MD, MPH, FRCPC
Primary Affiliation: Hamilton Health Sciences
E-mail: emchulee@gmail.com
Phone number: 9055212100
Address:

City: Hamilton
State or Province: Ontario
Zip or Postal Code: L8S 4L8
Country: Canada

General Information

Key Personnel (in addition to PI):
First Name: Emily
Last name: Wong
Degree: BHSc
Primary Affiliation: Hamilton Health Sciences
SCOPUS ID:

First Name: Neeraj
Last name: Narula
Degree: MD, MPH, FRCPC
Primary Affiliation: Hamilton Health Sciences
SCOPUS ID:

First Name: Shruthi
Last name: Sundararaman
Degree: BA / BS / BSc
Primary Affiliation:
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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_coi_-_narula_5.pdf
https://yoda.yale.edu/system/files/yoda_coi_-_wong_4.pdf
https://yoda.yale.edu/system/files/coi_form_ss_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

1. NCT02407236 - CNTO1275UCO3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy 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

Patient-reported Symptoms, Endoscopic, and Histologic Predictors of Endoscopic Improvement in Ulcerative Colitis

Narrative Summary:

In clinical trials of ulcerative colitis, symptom-based indices were previously used to measure response to treatment. However, symptoms lack specificity for true disease activity and does not accurately reflect inflammatory burden. Despite the disconnect between symptoms and endoscopic disease activity, symptoms are important for approval of novel therapies. In contrast, endoscopic and histologic measures of disease activity lack formal validation in the setting of regulatory approval for therapies. Therefore, clinical trials use definitions of remission that combine both symptoms, endoscopy and/or histology. The purpose of this study is to develop a predictive model for one year outcomes.

Scientific Abstract:

Background
In clinical trials of ulcerative colitis, symptom-based indices were previously used to measure response to treatment. However, symptoms lack specificity for true disease activity and does not accurately reflect inflammatory burden. Despite the disconnect between symptoms and endoscopic disease activity, symptoms are important for approval of novel therapies. In contrast, endoscopic and histologic measures of disease activity lack formal validation in the setting of regulatory approval for therapies. Therefore, clinical trials use definitions of remission that combine both symptoms, endoscopy and/or histology.
Objective
The purpose of this study is to develop a predictive model for one year endoscopic improvement (EI) and/or histo-endoscopic mucosal improvement (HEMI) in ulcerative colitis (UC).

Study Design
Several scoring indices were used in UNIFI to assess endoscopic disease severity, including the Mayo endoscopic subscore and the UCEIS. The Geboes score was used to assess histologic disease severity, with histologic healing defined as <5% neutrophils in the epithelium and no crypt destruction, erosions, ulcerations or granulations. Therefore, this proposal aims to evaluate baseline and/or week 8 endoscopic parameters (as defined by the UCEIS) and histologic parameters (as defined by the Geboes score) to develop a predictive model for one year EI and/or HEMI.
Participants
Data from participants with baseline patient-reported symptoms (as defined by the Mayo score), endoscopy and histology, with confirmed mucosal ulcerations at baseline, will be included.
Main Outcome Measure(s)
EI will be defined as Mayo endoscopic score < 2 and HEMI defined as EI and <5% of neutrophilic infiltrate of crypts, no crypt destruction, erosions, ulcerations, or granulations, as assessed by the Geboes score.
Statistical Analysis
Data will be randomly split into a 70% training cohort and 30% testing cohort. The training cohort will be used to perform multivariate logistic regression in which all parameters of the UCEIS and Geboes score will be considered

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }

and evaluated for their association with one year EI or HEMI. Odds ratios and respective 95% confidence intervals will be reported.

Brief Project Background and Statement of Project Significance:

Endoscopic assessment of ulcerative colitis (UC) is integral to evaluate disease severity and the efficacy of therapeutic interventions in UC. Several scoring systems have been developed, including the Mayo endoscopic score, which is widely used in clinical trials and routine practice. Endoscopic improvement (EI), commonly defined as Mayo endoscopic score of 0 or 1, is an established predictor for long-term outcomes and is an important treatment target for UC.1 However, interobserver variation in endoscopic assessments of UC severity cannot be fully mitigated, which may impact trial outcomes.2 The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was developed on the basis of a proper validation process and may be more sensitive to change. It encompasses three descriptors with three or four levels of severity scored on a Likert scale (mucosal vascular pattern score of 0: normal, 1: patchy obliteration, 2: obliterated; bleeding score of 0: none, 1: mucosal 2: luminal mild, 3: luminal moderate or severe; erosions/ulcers score of 0: none, 1: erosions, 2: superficial ulcer, 3: deep ulcer), with a total score that ranges from 0 to 8.3 The initial publication detailing the UCEIS varies slightly (the lowest severity is assigned a score of 1), with a total score that ranges from 3 to 11.4 The UCEIS is a validated index, explaining 86% of the variance in the overall assessment of endoscopic disease severity.3
Beyond EI, studies evaluating the associations between histologic activity and outcomes in UC have suggested additional benefit for attaining histologic remission.5 Various histologic scoring tools and indices have been developed, including the Geboes score, the Robarts histopathology index, and the Nancy histological index. However, variation between observers largely limits the adoption of histologic remission as an independent treatment target, which is reflected by recent STRIDE consensus statements.6 Endpoints such as histo-endoscopic mucosal improvement (HEMI), often defined as EI and <5% of neutrophilic infiltrate of crypts, no crypt destruction, erosions, ulcerations, or granulations, seek to combine the prognostic value of histologic and endoscopic disease severity.7 However, correlations between endoscopic and histologic disease activity in UC are inconsistent and may be attributed to differences in protocols, histologic indices and definitions of histologic remission.8,9 Recently, a post-hoc analysis of baseline histologic predictors for week 52 EI has suggested changes in epithelial neutrophil involvement from baseline to week 14 had the best performance for predicting week 52 EI and was the only histologic predictor associated with increased odds of week 52 EI and HEMI on multivariate analyses.10
Despite the disconnect between symptoms and endoscopic disease activity, symptoms in UC remain important for approval of novel therapies. In contrast, endoscopic and histologic measures of disease activity lack formal validation in the setting of regulatory approval for therapies in UC. Therefore, clinical trials now adopt definitions of remission that combine both symptoms and endoscopy and/or histology.12

Specific Aims of the Project:

Despite advances in endoscopic and histologic scoring systems for UC, there is a need to develop models that consider a combination of baseline and/or week 8 patient-reported symptoms, endoscopic and histologic markers of disease severity to predict long-term outcomes. The purpose of this study is to develop a predictive model for one year EI and/or HEMI in UC.

What is the purpose of the analysis being proposed? Please select all that apply.

Research on clinical prediction or risk prediction

Research Methods

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

Data from participants with baseline patient-reported symptoms (as defined by the Mayo score), endoscopy and histology, with confirmed mucosal ulcerations at baseline, will be included.

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

EI will be defined as Mayo endoscopic score < 2 and HEMI defined as EI and <5% of neutrophilic infiltrate of

crypts, no crypt destruction, erosions, ulcerations, or granulations, as assessed by the Geboes score. Outcomes will be evalauted at one year.

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

The main predictors of this study include baseline and week 8 patient-reported symptoms, endoscopic and histologic markers of disease severity, including the Geboes score (including all histologic sub-scores if available), UCEIS (including all sub-scores), Mayo score (including all four sub-scores if available), Robart's histopathology index

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

Other variables such as age, sex, treatment allocation, concomitant immunomodulator use, concomitant corticosteroid use, disease duration, smoking status, prior biologic exposure, and disease location will be used for descriptive statistics to describe the study population. Continuous variables will be represented as means/standard deviations (or medians/interquartile ranges) and categorical variables will be represented as proportions and percentages.

Statistical Analysis Plan:

Data from participants with baseline patient-reported symptoms (as defined by the Mayo score), endoscopy and histology, with confirmed mucosal ulcerations at baseline, will be included. Data will be randomly split into a 70% training cohort and 30% testing cohort. The training cohort will be used to perform multivariate logistic regression in which all parameters of the UCEIS and Geboes score will be considered and evaluated for their association with one year EI or HEMI. Odds ratios and respective 95% confidence intervals will be reported. Performance of the model will be assessed on its discrimination (using the area under the receiver operator curve, sensitivity, and specificity, positive predictive value, negative predictive value, and F1-score), predictive error (using Nagelkerke's R-squared) and calibration (using the Hosmer-Lemeshow goodness-of-fit test). Area under the curve results will be considered excellent for values ? 0.9, good for values between 0.8-0.9, fair for values between 0.7-0.8, poor for values 0.6-0.7, and very poor for values < 0.6. Model validation will be conducted on the testing cohort. Other variables of interest, such as treatment allocation, prior biologic exposure, age, smoking status, concomitant corticosteroid use, concomitant immunomodulator use, and sex will be considered for inclusion in the model. Variables with a p<0.15 on univariate analysis will be included in the multivariate model. Variables with a p < 0.05 on backward stepwise selection will be included in the final predictive model. To specifically evaluate the impact of treatment (ustekinumab or placebo) on the predictive model, two separate models stratified by treatment will be developed and compared to the main model.
Software Used:
STATA
Project Timeline:

Start date - June 2022
Analysis completion date - August 2022
Manuscript draft - November 2022
Submitted for publication - December 2022

Dissemination Plan:

Results arising from this study may be through presentations and abstracts to target audiences. These may be submitted to relevant conferences such as Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organisation. A manuscript may also be submitted for publication. The YODA Project will be acknowledged in all study products, which will be shared at the time of submission.

Bibliography:

1. D'haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007 Feb 1;132(2):763-86.
2. Cooney RM, Warren BF, Altman DG, et al. Outcome measurement in clinical trials for ulcerative colitis: towards standardisation. Trials. 2007 Dec;8(1):1-9.

3. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013 Nov 1;145(5):987-95.
4. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012 Apr 1;61(4):535-42.
5. Yoon H, Jangi S, Dulai PS, et al. Incremental Benefit of Achieving Endoscopic and Histologic Remission in Patients With Ulcerative Colitis: A Systematic Review and Meta-Analysis. Gastroenterology. 2020;159(4):1262-75.e7.
6. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2020.
7. Li K, Strauss R, Marano C, et al. A simplified definition of histologic improvement in ulcerative colitis and its association with disease outcomes up to 30 weeks from initiation of therapy: post hoc analysis of three clinical trials. Journal of Crohn's and Colitis. 2019 Aug 14;13(8):1025-35.
8. Colombel J-F, Keir ME, Scherl A, et al. Discrepancies between patient-reported outcomes, and endoscopic and histological appearance in UC. Gut. 2017;66(12):2063-8.
9. Bryant RV, Winer S, Travis SP, et al. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. Journal of Crohn's & colitis. 2014;8(12):1582-97.
10. Narula N, Wong ECL, Colombel J-F, et al. Early Change in Epithelial Neutrophilic Infiltrate Predicts Long-Term Response to Biologics in Ulcerative Colitis. In preparation.
11. Colombel JF, Keir ME, Scherl A, Zhao R, de Hertogh G, Faubion WA, Lu TT. Discrepancies between patient-reported outcomes, and endoscopic and histological appearance in UC. Gut. 2017 Dec 1;66(12):2063-8.
12. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. American journal of gastroenterology. 2012 Oct 1;107(10):1474-82.

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; } li.menu-973.menu-path-user-login { display: inline-block !important; opacity: 1 !important; width: auto !important; height: auto !important; } #block-nice-menus-2 { display: block; left: 0; margin: 0; } .main-menu#block-nice-menus-2 .nice-menu > li.menuparent a { margin: 0 0 0 1em; }