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General Information

Key Personnel (in addition to PI):

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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_form_-_narula_0.pdf

https://yoda.yale.edu/system/files/yoda_coi_form_-_wong_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. [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 \(UNITI-1\)](#)
2. [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 \(UNITI-2\)](#)

3. [NCT01369355 - CNTO1275CRD3003 - 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

Predictors of Endoscopic Healing in Crohn's Disease: A Post-hoc Analysis of the UNITI and IM-UNITI Trials

Narrative Summary:

Medical therapies in the treatment of Crohn's disease (CD) must be able to effectively heal the mucosa. While mucosal healing (MH) remains an important treatment target, baseline endoscopic predictors of MH have not yet been established. In a recent post-hoc analysis of the SONIC trial (YODA Protocol #2019-3980), it has been demonstrated that deep and large ileal and rectal ulcers at baseline are less likely to achieve MH. This study aims to validate these findings in an external cohort of patients from the UNITI 1, 2 and IM-UNITI trials.

Scientific Abstract:

Background

Achievement of mucosal healing is an important therapeutic target in Crohn's disease (CD).(1) Previous post-hoc analyses of the SONIC trial identified specific baseline endoscopic predictors of endoscopic remission at week 26.

Objectives

This study aims to validate findings from YODA Protocol #2019-3980 with data from the UNITI 1, 2 and IM UNITI trials.

Study Design

The proposed study will be a post-hoc analysis of UNITI 1, 2 and IM UNITI, which were multicentre, randomized, double-blind trials. UNITI 1 and 2 were 8-week induction trials. Patients who responded were re-randomized into the maintenance study. This post-hoc analysis aims to evaluate endoscopic predictors of EH and CR at week 52 (i.e. week 44 maintenance) and validate findings from YODA Protocol #2019-3980.

Participants

Patients with moderate-to-severe CD, defined as CDAI score of 220-450, and failed conventional or anti-TNF therapy were eligible for UNITI.

Outcomes

The primary outcome of the proposed study will be endoscopic remission and MH at week 44. Secondary outcomes include clinical outcomes at week 44 (i.e. clinical remission and corticosteroid-free remission). Subgroup analyses based on remission status, ustekinumab levels, histologic scoring, and other markers of disease activity may also be done.

Statistical Analysis

Multivariate logistic regression will be used to evaluate the association between endoscopic evaluations of disease activity at baseline and achievement of MH and CR. Adjustment for known confounders such as disease duration and treatment allocation will be done.

Brief Project Background and Statement of Project Significance:

Crohn's disease (CD) is a type of inflammatory bowel disease that is characterized by periods of relapse and remission. Unfortunately, progression of disease commonly leads to structuring and penetrating complications, which impairs patient quality of life.(1,3) However, there is a lack of correlation between patient symptoms and disease activity as asymptomatic patients may indeed have progressive disease.(4) Therefore, there is a need to identify objective endoscopic predictors of mucosal healing (MH) and clinical remission (CR). A post-hoc analysis of the SONIC trial (YODA Protocol #2019-3980) identified specific baseline endoscopic predictors of week 26 MH. Patients with large ileal and rectal ulcers at baseline were found to be 69% and 74% less likely to achieve MH

compared to those with smaller ileal and rectal ulcers, respectively. This trend was more pronounced when deep and large ileal and rectal ulcers were compared to superficial and smaller ulcers (ileum: OR 0.10, 95% CI 0.02-0.68, $p=0.02$; rectum: OR 0.12, 0.02-0.82, $p=0.03$). Further, the healing rate in the ileum was found to be significantly lower than the colon.(2)

Specific Aims of the Project:

The proposed study aims to validate findings from YODA Protocol #2019-3980 with patients from UNITI-1 (ClinicalTrials.gov number: NCT01369329), UNITI-2 (ClinicalTrials.gov number: NCT01369342) and IM-UNITI (ClinicalTrials.gov number: NCT01369355). Baseline endoscopic evaluations as measured by Simple Endoscopic Score-CD (SES-CD) will be used. MH will be evaluated at week 52.

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:

A cohort of patients in UNITI were enrolled in the endoscopic sub-study at baseline. Subsequent colonoscopies occurred at week 8 (end of induction) and week 52 (end of week 44 maintenance). Patients who had ulcerations present at baseline colonoscopy will be included in this study.

Inclusion Criteria

Participants must meet all of the following criteria to be eligible for study inclusion(5):

1. \geq 18 years of age
2. CD for a minimum duration of 3 months
3. Moderate-to-severe CD (defined as a Crohn's Disease Activity Index [CDAI] score 220-450)
4. Nonresponse to anti-TNF therapy (UNITI-1) or treatment failure or intolerance to immunomodulators and/or glucocorticoids (UNITI-2)

Exclusion Criteria

Participants who meet any of the following criteria are not eligible for study inclusion (5):

1. Bowel resection within 6 months
2. Received infliximab, adalimumab or certolizumab pegol \geq 8 weeks before receiving study drug
3. Ongoing chronic or recurrent infectious disease
4. Previously received a biologic agent targeting IL-12 or IL-23

Main Outcome Measure and how it will be categorized/defined for your study:

The primary outcome of the proposed study will be endoscopic remission and MH at week 44. Secondary outcomes of interest include clinical outcomes at week 44 (i.e. clinical remission and corticosteroid-free remission). Subgroup analyses based on remission status, ustekinumab levels, histologic scoring, and other objective markers of disease activity may also be done to validate findings. Scores from the SES-CD will be used for the primary outcome (endoscopic remission and mucosal healing). The SES-CD is a simplified scoring system based on four endoscopic parameters: presence and size of ulcers, surface involvement of ulcerations, surface affected by ulcerations and the presence and severity of stenosis.(6) Each of the five ileocolonic segments (rectum, sigmoid/left colon, transverse colon, right colon, and ileum) are scored using this system. Scores from the CDAI will be used for the secondary outcome (clinical remission and corticosteroid-free remission).

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

The main predictor for this study will be the size and extent of ulcerations at baseline. Scores from the SES-CD (as detailed above) will be used to categorize ulcer size and extent of ulceration.

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

your study:

Scores from the CDAI will be used for the secondary outcome (clinical remission and corticosteroid-free remission). Clinical remission is defined as CDAI < 150 and corticosteroid-free remission is defined as absence of corticosteroid use in addition to CDAI < 150.

Statistical Analysis Plan:

Descriptive statistics will be used to summarize baseline characteristics (e.g. disease activity and patient demographics) as well as outcomes among patients with baseline endoscopic disease activity. Dichotomous variables will be presented as proportions or percentages. Continuous variables will be reported as means with standard deviations or medians with interquartile ranges. The Chi-square test will be used to compare the proportion of patients achieving various outcomes among different bowel segments.

Software Used:

STATA

Project Timeline:

Date to Start Project: July – August 2020.

Date to Complete Analysis: August – September 2020.

Date to Draft Manuscript: September – October 2020.

Date to Submit Manuscript: October – November 2020.

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:

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4. Ng, S. C. et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* (2017). doi:10.1016/S0140-6736(17)32448-0
5. Feagan, B. G. et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N. Engl. J. Med.* (2016). doi:10.1056/NEJMoa1602773
6. Daperno, M. et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: The SES-CD. *Gastrointest. Endosc.* (2004). doi:10.1016/S0016-5107(04)01878-4