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General Information

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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_-_narula_2.pdf

https://yoda.yale.edu/system/files/yoda_coi_-_wong_2.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 - CNT01275CRD3003 - 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

Endoscopic Disease Severity and Patient Reported Outcomes in Crohn's Disease

Narrative Summary:

Crohn's disease (CD) is a type of inflammatory bowel disease that is characterized by periods of relapse and remission. Patient-reported outcomes (PROs) in CD include abdominal pain, number of daily soft/liquid stools and general well-being, which are reported as part of the Crohn's Disease Activity Index (CDAI) . However, several studies have identified a disconnect between the CDAI, PROs and objective measures of disease such as endoscopy (3). Recent analyses have suggested that PROs at baseline and after the induction phase of treatment are not associated with one-year ER (4). Further, ulcer size and location at baseline may play a role in the ability to achieve one-year ER (5).

Scientific Abstract:

Background

Common symptoms of Crohn's disease (CD) include abdominal pain, diarrhea and fatigue. Three patient-reported outcomes (PROs) in CD are abdominal pain, number of daily soft stools and general well-being. Several studies have identified a disconnect between PROs and endoscopy (3). Recent post-hoc analyses have suggested PROs at baseline and after induction may not be associated with one-year endoscopic remission (ER) (4). Further, ulcer size and location at baseline may impact one-year ER (5).

Objective

The primary objective of this study is to evaluate whether patients with medium or large ulcers (SES-CD ulcer size subscore 2 or 3) at baseline and at the end of induction phase of treatment impacts one-year ER (SES-CD <3).

Study Design

This is a post-hoc analysis of EXTEND, UNITI-1, UNITI-2 and IM-UNITI.

Participants

For this analysis, participants with baseline and post-induction endoscopic and PRO assessments will be included. Those who crossed over between treatments will be excluded.

Main Outcome Measure(s)

The Simple Endoscopic Score for Crohn's disease (SES-CD) is a scoring system based on four endoscopic parameters (6). The primary outcome is ER at week 52 (SES-CD <3). Secondary outcomes include SES-CD=0 and endoscopic response (SES-CD reduction ?50%).

Statistical Analysis

Multivariate logistic regression will be used to assess the relationship between medium/large ulcers at baseline and post-induction and likelihood of achieving outcomes. Disease duration and treatment allocation are known confounders of ER, which will be adjusted for.

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. CD affects any area of the gastrointestinal tract but is more common in the ileum and colon (1). Symptoms of CD include abdominal pain, diarrhea, fever, fatigue and weight loss, which are considered as part of disease assessment. The Crohn's Disease Activity Index (CDAI) is a tool that combines laboratory values, findings from physical examination, and three patient-reported outcomes (PROs): abdominal pain, number of daily soft/liquid stools and general well-being.

PRO-based endpoints are now required for clinical trials for CD in place of CDAI-based endpoints (2). However, several studies have identified a disconnect between the CDAI, PROs and objective measures of disease such as endoscopy (3). Endoscopic remission (ER) remains an important goal of treatment in CD. Recent post-hoc analyses have suggested that PROs at baseline and after the induction phase of treatment are not associated with one-year ER (4). Further, it has been shown that ulcer size and location at baseline play an integral role in the ability to achieve one-year ER (5). In the context of these findings, there is a need to better understand how ulcer size at baseline and post-induction impact the ability to achieve one-year ER.

The proposed study aims to analyze data from the UNITI-1, UNITI-2, and IM-UNITI trials (provided by the YODA Project) and the EXTEND trial (provided by Vivli).

Multivariate logistic regression will be used to assess the relationship between medium/large ulcers at baseline and post-induction and the likelihood of achieving one-year ER and endoscopic response. Subgroup analyses by PRO2 or PRO3 remission status at the end of induction will be done to evaluate if symptom resolution at the end of induction is associated with one-year ER or response. Disease duration and treatment allocation are known confounders of ER, which will be adjusted for.

Specific Aims of the Project:

The primary objective of this study is to evaluate whether patients with medium or large ulcers (defined as SES-CD ulcer size subscore of 2 or 3) at baseline and at the end of induction phase of treatment impacts the ability to achieve one-year ER (SES-CD < 3), which is the primary outcome. The secondary objectives of this study include assessing alternative definitions of ER (SES-CD of 0) and endoscopic response (SES-CD reduction from baseline of at least 50%), which are the secondary outcomes. Subgroup analyses by PRO2 or PRO3 remission status at the end of induction will be done to assess the likelihood of achieving the primary and secondary outcomes.

We hypothesize that CD patients with medium or large ulcers at baseline with no ulcer size improvement by the end of induction are less likely to achieve one-year ER.

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

Research Methods

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

Data from EXTEND, UNITI-1, UNITI-2 and IM-UNITI are being requested. Data from three time points will be acquired: baseline, end of induction (week 8 in UNITI and week 12 in EXTEND) and week 52.

For this analysis, participants with baseline and post-induction endoscopic and PRO assessments will be included. Those who crossed over between treatments (e.g. adalimumab and placebo, ustekinumab and placebo) will be excluded. Participants will be analyzed on an intention-to-treat basis; as such, participants with missing outcome data will be assumed to not have achieved the outcome of interest.

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

The Simple Endoscopic Score for Crohn's disease (SES-CD) is a simplified scoring system based on four endoscopic parameters: presence/size of ulcers (0=none, 1=small, 2=medium, 3=large), proportion of ulcerated area (0=none, 1=<10%, 2=10-30%, 3=>30%), proportion of affected area (0=unaffected, 1=<50%, 2=50-75%, 3=>75%) and presence/severity of stenosis (0=none, 1=single passable, 2=multiple passable, 3=cannot be passed) (6). Each of the five ileocolonic segments (ileum, ascending colon, transverse colon, descending colon and rectum) are scored using these criteria to provide a total SES-CD score, where ?16 reflects severely active disease, ?7-15 moderately active disease, ?3-6 mildly active disease and <3 inactive disease.

The primary outcome is ER at week 52 (defined as SES-CD < 3). Secondary outcomes include an alternative definition of ER at week 52 (defined as SES-CD of 0) and endoscopic response (defined as SES-CD reduction of

at least 50% from baseline). These definitions were chosen based on commonly used and accepted definitions of ER in clinical trials (7).

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

The independent variable is ulcer size at baseline and post-induction, which is defined by the SES-CD subscore presence/size of ulcers. Medium or large ulcers will be defined as SES-CD presence/size of ulcers subscore 2 or 3. Participants who have medium/large ulcers at baseline and did not have any reduction in size of these ulcers at the end of induction (week 8 in UNITI and week 12 in EXTEND) will be compared to those with medium/large ulcers at baseline with ulcer size improvement at the end of induction for achievement of the defined outcomes.

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

The CDAI includes the three PROs abdominal pain (AP), stool frequency (SF) and general well-being (GWB). AP is scored from a scale of 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe), SF is summed over the last 7 days prior to assessment and GWB is scored from 0 to 4 (0=well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible) and averaged over 7 days.

PRO2 remission is defined as the 7-day average daily SF < 1.5 and AP < 1.0, based on previous studies demonstrating this as the optimal cut-off for CDAI-based remission (8). Similarly, PRO3 remission is defined as the 7-day average daily SF < 1.5, AP < 1.0, and GWB < 1.0. PRO3 response is defined as > 50% improvement in PRO3 score from baseline. These definitions will be used in subgroup analyses to determine if PRO2 and PRO3 remission/response at the end of induction impacts the likelihood of achieving one-year ER and endoscopic response.

Statistical Analysis Plan:

Data from EXTEND, UNITI-1, UNITI-2 and IM-UNITI are being requested. Data from three time points will be acquired: baseline, end of induction (week 8 in UNITI and week 12 in EXTEND) and week 52.

UNITI-1 and UNITI-2 were phase three induction studies with a duration of 8 weeks in which patients were randomized to weight-based ustekinumab, standard dose ustekinumab, or placebo. Patients who responded to induction therapy were re-randomized to placebo or ustekinumab every 8 or 12 weeks in the maintenance phase of the study, IM-UNITI, which continued for an additional 44 weeks for a total study duration of 52 weeks. Participants in the endoscopic substudy underwent colonoscopies at baseline, week 8 (end of induction) and week 52 (one-year).

Participants in EXTEND were treated with adalimumab induction therapy for four weeks and subsequently were randomized to adalimumab every other week or placebo for an additional 48 weeks, for a total study duration of 52 weeks. Endoscopies were performed at baseline, week 12 (end of induction) and week 52 (one-year). In both UNITI and EXTEND, all endoscopies were centrally read.

For this analysis, participants with baseline and post-induction endoscopic and PRO assessments will be included. For the main analysis, a complete case analysis of all participants will be done. In separate sensitivity analyses, those who crossed over between treatments (e.g. adalimumab and placebo, ustekinumab and placebo) will be excluded. Additionally, participants will be analyzed on an intention-to-treat basis; as such, participants with missing outcome data will be assumed to not have achieved the outcome of interest.

Baseline summary statistics of the patient population will be provided. While participants from all trials requested will be grouped for the main analysis, baseline characteristics for each trial population will also be evaluated. A variable that categorizes participants based on trial will be included in the model. Continuous variables will be presented as means and standard deviations and dichotomous variables as proportions/percentages. Logistic regression will be performed to model the relationship between the independent and dependent variables. Unadjusted and adjusted odds ratios, 95% confidence intervals and associated p-values will be provided. To address the issue of multiple hypotheses testing, the threshold for statistical significance will be set to 0.01 instead of the conventional 0.05. Disease duration and treatment allocation are known confounders of endoscopic healing, which will be adjusted for in multivariate logistic regression.

Data from YODA will be transferred to the Vivli secure platform for analysis. Data will be analyzed using Stata,

which is available on the Vivli secure platform.

Software Used:

STATA

Project Timeline:

December 2020 - January 2021: Data analysis

January - February 2021: Drafting and submission of manuscript

Dissemination Plan:

Anticipated products include abstracts, which presented at scientific meetings such as Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organization. A manuscript is expected and will be submitted for consideration at peer-reviewed journals such as American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, Journal of Crohn's and Colitis, and Inflammatory Bowel Diseases. All products resulting from this research project, which may include abstracts, manuscripts, posters, and slide decks will be shared with Vivli at least 30 days prior to the time of submission or public disclosure.

Target audiences include clinicians and researchers with an interest in inflammatory bowel disease.

Bibliography:

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4. Wong ECL, Buffone E, Dulai PS, Marshall JK, Reinisch W, Narula N. End of Induction Patient Reported Outcomes Predict Clinical Remission but not Endoscopic Remission in Crohn's Disease. *Journal of Crohn's and Colitis*.
5. Narula N, Wong EC, Aruljothy A, Dulai PS, Colombel JF, Marshall JK, Ferrante M, Reinisch W. Ileal and Rectal Ulcer Size Affects the Ability to Achieve Endoscopic Remission: A Post hoc Analysis of the SONIC Trial. *The American Journal of Gastroenterology*. 2020 Aug 1;115(8):1236-45.
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7. Vuitton, L., Marteau, P., Sandborn, W. J., Levesque, B. G., Feagan, B., Vermeire, S., ... & Fiorino, G. (2016). IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut*, 65(9), 1447-1455.
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Supplementary Material:

https://yoda.yale.edu/sites/default/files/endoscopic_disease_severity_and_patient_reported_outcomes_in_cd_-_protocol_vivli_approved.docx

https://yoda.yale.edu/sites/default/files/supplementary_appendix_-_yoda_protocol_2020-4529.docx