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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_project_coi_form_for_data_requestors_2019_wong.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_narula.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

The Role of Fecal Calprotectin in Predicting Clinical Remission and Mucosal Healing in Crohn's Disease

Narrative Summary:

Data from phase 4 trials have suggested the use of a fecal calprotectin (FC) threshold of $\geq 250\mu\text{g/g}$ as part of the decision to escalate therapy in Crohn's disease (CD).¹ However, the comparative efficacy of a threshold FC vs. absolute difference in FC from baseline (ΔFC) in achieving mucosal healing (MH) and clinical remission (CR) has not been investigated. The proposed study will obtain data from the UNITI-1 and UNITI-2 trials to evaluate if ΔFC is more likely to predict short-term MH and CR compared to an FC threshold.

Scientific Abstract:

Background and Rationale:

Fecal calprotectin (FC) is a validated biomarker for inflammation in Crohn's disease (CD). However, it is unknown what is the optimal way to use FC in order to monitor patients with CD and to predict who is likely to experience good outcomes.

Objectives:

This study aims to compare ΔFC and a threshold FC in predicting mucosal healing (MH) and clinical remission (CR) in CD patients.

Study Design:

UNITI-1 and UNITI-2 were two multicentre, double-blinded, placebo-controlled trials that randomized patients to ustekinumab or placebo in CD. This study will use data from these studies to determine if using the ΔFC from week 0 to week 6 can predict MH and CR at week 8 and how this compared with using an absolute FC threshold of $250\mu\text{g/g}$.

Participants:

Patients were eligible for UNITI-1 and UNITI-2 if they had moderate-to-severe CD and if they were failing conventional therapies or anti-TNF therapy.

Main Outcome Measure(s):

For this study, the primary outcome measure will be MH at week 8. Secondary outcome measures include CR at week 8. The Simple Endoscopic Score for Crohn's Disease (SES-CD) will be used to evaluate inflammation and the presence of MH at week 8.

Statistical Analysis:

Receiver operating curves (ROC) will be generated to compare the ability of an absolute FC threshold and ΔFC to predict each outcome of interest, MH and CR. The area under the curve (AUC) will be compared between groups to evaluate the model's relative ability to predict MH and CR.

Brief Project Background and Statement of Project Significance:

In inflammatory bowel disease (IBD), endoscopy is the gold standard for evaluating mucosal inflammation [2]. However, several drawbacks to endoscopy exist, including limited access in some regions, and the invasiveness,

cost, and discomfort of the procedure [2,3]. Therefore, there is a need to identify alternatives of comparable accuracy to endoscopy. Serological markers such as C-reactive protein (CRP) have largely been used to assess inflammation in IBD. However, these markers more appropriately reflect systemic inflammatory processes and lack specificity for inflammation in the context of IBD [4]. More recently, fecal calprotectin (FC) has been adopted as a validated novel biomarker for IBD. Several pooled analyses have demonstrated its utility in evaluating disease activity and predicting relapse in IBD [5–7].

CALM (ClinicalTrials.gov number: NCT01235689) was a pivotal multicentre, open-label, phase 3 randomized trial which compared two algorithmic approaches to treatment escalation in CD based on symptoms, CRP, and FC vs. symptoms alone [1]. Findings from the study suggest that treatment escalation on the basis of symptoms and biomarkers with specific thresholds (i.e. FC $\geq 250\mu\text{g/g}$) is a more robust strategy to achieve MH in CD patients. However, it is unclear whether the decision to escalate treatment based on a prespecified FC threshold is the most optimal approach. One alternative is to use \leq FC, which is hypothesized to be more appropriate. As no studies to date have been conducted on this comparison, this question merits further investigation.

Specific Aims of the Project:

This project aims to compare the efficacy of two approaches, \leq FC at week 6 compared to baseline at week 0 and an FC threshold of $<250\mu\text{g/g}$ at week 6, in predicting MH and CR at week 8 in CD patients. We hypothesize that, in CD patients, use of \leq FC at week 6 compared to baseline will have improved sensitivity and specificity for MH and CR at week 8 compared to use of an FC threshold of $<250\mu\text{g/g}$ at week 6.

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:

This study will utilize data from the Yale University Open Data Access (YODA) Project. Participant-level data will be required for the following trials: UNITI-1 (ClinicalTrials.gov number: NCT01369329) and UNITI-2 (ClinicalTrials.gov number: NCT01369342). Both were phase 3, multicentre, placebo-controlled randomized trials. In UNITI-1 and UNITI-2, FC was collected at baseline and week 6 [8]. Therefore, an FC threshold of $250\mu\text{g/g}$ at week 6 will be compared to different \leq FC percentages from baseline (i.e. 50% reduction from baseline, 75% reduction from baseline, etc). Participants must meet all of the following criteria to be eligible for study inclusion [8]: ≥ 18 years of age, CD for at least 3 months, moderate-to-severe CD (defined as a CDAI score 220-450), nonresponse to anti-TNF therapy or treatment failure or intolerance to immunomodulators and/or glucocorticoids. Participants who meet any of the following criteria are not eligible for study inclusion [8]: Bowel resection within 6 months, received infliximab, adalimumab or certolizumab pegol ≥ 8 weeks before receiving study drug, ongoing chronic or recurrent infection, previously received a biologic agent targeting IL-12 or IL-23.

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

In both UNITI trials, patients underwent an endoscopy at baseline and week 8. MH and CR were evaluated at week 8. Thus, for this study, the main outcome measures include MH and CR at week 8. MH is defined as the absence of any mucosal ulceration on endoscopy if ulceration was present on previous endoscopies. CR is defined as a CDAI score of <150 at week 8.

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

The primary outcome of the study is MH, which will be evaluated at week 8. To evaluate MH, endoscopic evaluations will be used at baseline and week 8. The SES-CD was used to evaluate disease activity and inflammation based on endoscopic evaluation. The SES-CD scores the same five ileocolonic segments based on four parameters: presence and size of ulcers, proportion of surface covered by ulcers, proportion of affected surface, and presence and severity of stenosis [9]. Patients are considered to have endoscopic healing of their bowel if their SES-CD score is 2 or less.

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

your study:

CR is another outcome measure of interest for which CDAI scores will be evaluated at week 8. The CDAI is a tool consisting of eight variables used to assess the quality of life of patients with CD [10].

Statistical Analysis Plan:

Baseline data, such as patient demographics and disease characteristics, will be summarized using descriptive statistics. Continuous variables will be reported as means or medians with corresponding standard deviations or interquartile ranges, respectively. Fischer's exact test will be used to compare the proportion of patients who achieve EH and CR in each group.

To compare how well the FC threshold and ?FC can predict the outcomes of interest (i.e. EH and CR), the true positive rate (i.e. sensitivity) will be plotted against the false positive rate (i.e. 1 – specificity) to generate Receiver Operative Characteristic (ROC) curves. The performance of each model will be determined based on the area under the curve (AUC). If the AUC of the ?FC model is greater than that of the FC threshold, the ?FC model is better able to predict the outcome of interest. Patients will be classified dichotomously for each outcome of interest at week 8 (i.e. 0=not achieved, 1=achieved).

Data from the YODA project will be accessed remotely in a secure environment by designated study investigators. Analyses with data provided by the YODA project will be conducted using the software available on the remote platform.

Software Used:

R

Project Timeline:

Date to Start Project: November – December 2019.

Date to Complete Analysis: December 2019 – January 2020.

Date to Draft Manuscript: January – February 2020.

Date to Submit Manuscript: February – March 2020.

Dissemination Plan:

Results from the study may be communicated to target audiences through posters, abstracts, and presentations. These may be submitted to conferences such as Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organisation. Further, a manuscript may be completed and submitted for publication in a relevant peer-reviewed journal. The investigators will acknowledge use of data from the YODA Project on all study products, which will be shared at the time of submission.

Bibliography:

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/protocol_amendment_-_01.29.2020.docx