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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.pdf
https://yoda.yale.edu/system/files/yoda_coi_form_-_wong.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. NCT00094458 - C0168T67 - Multicenter, Randomized, Double-Blind, Active Controlled Trial Comparing REMICADE® (infliximab) and REMICADE plus Azathioprine to Azathioprine in the Treatment of Patients with Crohn's Disease Naive to both Immunomodulators and Biologic Therapy (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease)
2. 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)
3. 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)
4. 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

Impact of Baseline Strictures on Clinical and Endoscopic Outcomes in Crohn’s Disease

Narrative Summary:

Stricture formation is a complication of Crohn’s disease (CD) that may impact patient quality of life and ability to achieve disease improvement as determined by endoscopy. However, to our knowledge, this has not been previously reported. This post-hoc analysis of the SONIC, UNITI 1, UNITI 2 and IM-UNITI trials aims to evaluate whether the presence and type of stricture at baseline impacts the ability to achieve clinical symptom and endoscopic improvement.

Scientific Abstract:

Background:
There is a need to identify endoscopic predictors of long-term clinical and endoscopic remission. A comparison of clinical and endoscopic outcomes among patients with and without strictures have not previously been reported.

Objectives:
This study proposes to evaluate whether the presence and type of stenosis at baseline impacts ability to achieve clinical and endocopic outcomes. Data from patients enrolled in the SONIC, UNITI 1, UNITI 2 and IM-UNITI trials will be used.

Study Design:
This study will be a post-hoc analysis of SONIC, UNITI 1, UNITI 2 and IM-UNITI, which were multicentre, randomized, double-blind trials. SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease; ClinicalTrials.gov, NCT00094458) randomized patients to receive infliximab, azathioprine, or a combination of both therapies. UNITI 1 and 2 were 8-week induction trials and patients who responded were re-randomized into the maintenance study, IM-UNITI. This post-hoc analysis aims to evaluate whether the presence of stenosis at baseline impacts the ability to achieve clinical symptom improvement and endoscopic improvement at week 8, 52 (UNITI) and 26 (SONIC).

Study Population:
Patients were eligible for SONIC, UNITI 1 and 2 if they had moderate-to-severe CD and if they failed conventional therapy.

Main Outcome Measures:
The primary outcome of the proposed study will be clinical remission/response at week 52.

Statistical Analysis:
Descriptive statistics will be used to summarize the proportion of patients achieving clinical and endoscopic outcomes.

Brief Project Background and Statement of Project Significance:

Crohn's disease (CD) is a type of inflammatory bowel disease characterized by periods of remission and relapse.(1) Patients who experience progressive disease may develop complications such as abscess and stricture formation, which may significantly impair patient quality of life.(2) Depending on the location and severity of strictures, further medical treatment and/or surgical intervention may be required.(3) Therefore, it is important to prevent such complications and identify predictors of long-term remission. To our knowledge, the impact of baseline strictures on symptom and endoscopic improvement has not previously been reported.

Specific Aims of the Project:

This study proposes to evaluate whether the presence and type of stricture at baseline impacts clinical symptom improvement and endoscopic improvement with patients from SONIC (ClinicalTrial.gov number: NCT00094458), UNITI-1 (ClinicalTrial.gov number: NCT01369329), UNITI-2 (ClinicalTrial.gov number: NCT01369342) and IM-UNITI (ClinicalTrials.gov number: NCT01369355). We hypothesize that patients with no stenosis at baseline are more likely to achieve clinical symptom improvement compared to those with stenosis at baseline.

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 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:

Inclusion Criteria:

Participants must meet all of the following criteria to be eligible for study inclusion (4):
1. ?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)
5. Corticosteroid-dependent, under consideration for an additional course of corticosteroids, or have no response to mesalamine (? 2.4 g/d) or budesonide (? 6 mg/d) after a minimum of 4 weeks of treatment (SONIC)

Exclusion Criteria:

Participants who meet any of the following criteria are not eligible for study inclusion (4):
1. Bowel resection within 6 months
2. Received infliximab, adalimumab or certolizumab pegol ?8 weeks before receiving study drug (UNITI)
3. Ongoing chronic or recurrent infectious disease
4. Previously received a biologic agent targeting IL-12 or IL-23 (UNITI)

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

The primary outcome of the proposed study will be clinical symptom improvement at week 52, which includes clinical response (decrease in CDAI from baseline of at least 100) and clinical remission (CDAI less than 150). Secondary outcomes of interest include endoscopic improvement and ability to achieve passable stenosis or absence of stenosis at week 8 and 52 (in the UNITI population) and week 26 (in the SONIC population). Subgroups based on treatment group, remission status and disease extent may also be done. Clinical response/remission will be determined by CDAI scores at week 52. The CDAI is comprised of 8 items used to measure CD activity, including weight, sex, number of liquid/soft stools, abdominal pain, general well-being, use of anti-diarrheal drugs, presence of abdominal mass and hematocrit percentage.(5) The total score ranges from 0 to 600, with a higher score indicating more severe disease activity. In this study, CDAI scores at baseline and week 52 will be reported and used to determine if clinical response (decrease in CDAI from baseline of at least 100) and clinical remission (CDAI less than 150) was achieved. Specific items of the CDAI may also be evaluated.

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

The main predictor for the study will be presence and type of stenosis at baseline. Patients will be classified into three groups based on the SES-CD sub-score for stenosis: no stenosis at baseline (score of 0), passable stenosis at baseline (score of 1), and non-passable stenosis at baseline (score of 2). Outcomes among patients with no stenosis at baseline will be compared to those with passable stenosis and separately to those with non-passable stenosis. Outcomes among patients without non-passable stenosis at baseline will be compared to those with non-passable stenosis.

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

Endoscopic remission and mucosal healing will be evaluated using SES-CD scores. The SES-CD is an endoscopic scoring system of disease activity and extent, which is 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) The rectum, sigmoid/left colon, transverse colon, right colon, and ileum are individually scored using this system. Sub-scores from the stenosis parameter of the SES-CD will be used to determine stenosis status. A score of 0 corresponds to no stenosis, a score of 1 to passable stenosis and a score of 2 indicates non-passable stenosis. If more than one stenosis sub-score is present, the highest sub-score will be used for that endoscopic assessment. Patients with and without baseline strictures will be evaluated for presence and type of strictures at week 8 and 52 (in UNITI) and week 26 (in SONIC).

Statistical Analysis Plan:

Descriptive statistics will be used to summarize baseline characteristics (e.g. disease activity and patient demographics) and dichotomous variables will be presented as proportions or percentages. Continuous variables will be reported as means or medians with corresponding standard deviations or interquartile ranges, respectively.

Patients will be classified into three groups based on the SES-CD sub-score for stenosis: no stenosis at baseline (score of 0), passable stenosis at baseline (score of 1), and non-passable stenosis at baseline (score of 2). Outcomes among patients with no stenosis at baseline will be compared to those with passable stenosis and separately to those with non-passable stenosis. Outcomes among patients without non-passable stenosis at baseline will be compared to those with non-passable stenosis.
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:

Analyses from this study may be shared to target audiences through presentations and abstracts. These may be submitted to 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. De Cruz, P., Kamm, M. A., Prideaux, L., Allen, P. B. & Moore, G. Mucosal healing in Crohn's disease: A systematic review. Inflammatory Bowel Diseases (2013). doi:10.1002/ibd.22977

2. Gajendran, M., Loganathan, P., Catinella, A. P. & Hashash, J. G. A comprehensive review and update on Crohn's disease. Disease-a-Month (2018). doi:10.1016/j.disamonth.2017.07.001

3. Chang, C.-W. et al. Intestinal Stricture in Crohn's Disease. Intest. Res. (2015). doi:10.5217/ir.2015.13.1.19

4. Feagan, B. G. et al. Ustekinumab as induction and maintenance therapy for Crohn’s disease. N. Engl. J. Med. (2016). doi:10.1056/NEJMoa1602773

5. Cellier, C. et al. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn’s disease. A prospective multicentre study of 121 cases. The Groupe d’Etudes Therapeutiques des Affections Inflammatoires Digestives. Gut (1994). doi:10.1136/gut.35.2.231

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