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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_4.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_aa_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. 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)

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 Ulcer Size and Extent of Inflammation On Ability To Achieve Endoscopic Healing In Crohn's Disease: A SONIC post hoc Analysis

Narrative Summary:

Endoscopic healing of the bowel has become a goal of treatment for patients with Crohn's disease. Clinical trials conducted in Crohn's disease for new therapies need to demonstrate the ability to heal the mucosa. However, nothing is known about the impact of lesion size and distribution on the ability to achieve endoscopic healing. This study proposes to look at the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease; ClinicalTrials.gov, NCT00094458) database and determine whether patients who have more extensive inflammation at baseline and larger ulcer sizes are less likely to achieve endoscopic healing.

Scientific Abstract:

Background
Current and future medical therapies in Crohn's disease (CD) need to demonstrate efficacy in achieving mucosal healing1. However, there is insufficient information regarding what degree of ulceration and inflammation affects endoscopic healing (EH) and clinical remission (CR).

Objective
This study aims to evaluate the association of baseline mucosal lesions and disease activity with the achievement of EH and CR at week 26.

Study Design
SONIC was a multicentre, randomised, double-blinded trial that randomized patients to infliximab, azathioprine, or combination therapy and evaluated corticosteroid-free CR at week 26. This post hoc analysis will assess the likelihood of achieving EH and CR at week 26 based on baseline endoscopic inflammation present.

Participants
Moderate-to-severe CD patients who are naive to immunomodulators and biologics, and had poor response to conventional therapies were eligible.

Main Outcome Measure(s)
The primary outcome measures will be EH, CR and corticosteroid-free CR at week 26. Baseline mucosal lesion features and inflammation will be assessed using endoscopic scoring systems.

Statistical Analysis
A multivariate logistic regression analysis will be used to examine the relationship between baseline endoscopic extent of disease and ability to achieve week 26 EH and CR. Known confounding factors for achieving endoscopic healing, such as treatment allocation and disease duration, will be adjusted for.

Brief Project Background and Statement of Project Significance:

Crohn's disease is a progressive, relapsing and remitting disease due to chronic transmural inflammation which can lead to complications such as strictures, fistulas, and abscess formation2. Current medical therapies and prospective therapies have adopted a 'treat-to-target' approach with the primary target being an ability to achieve EH, defined as an absence of ulcers on endoscopy1. EH in inflammatory bowel disease has become an important measure of treatment efficacy and a prognostic indicator of long-term adverse outcomes, such as hospitalizations and surgeries 3-5. However, there is currently insufficient information as to what degree of ulceration and

inflammation of mucosal lesions across the different colonic segments and ileum affects EH and CR. This has clinical implications in moderate-to-severe CD as it determines if baseline characteristics and location of mucosal lesions, extent of inflammation are negative predictors of EH and CR.

Specific Aims of the Project:

This study of patients with Crohn's disease from the SONIC trial (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease; ClinicalTrials.gov, NCT00094458) aims to evaluate the association of baseline endoscopic ulcerations (size, depth and location), disease activity, as measured by CD endoscopic index of severity (CDEIS) or Simple Endoscopic Score-CD (SES-CD), with the achievement of EH and CR at week 26.

Our hypothesis is that CD patients who are biologic and immunodulator naïve with baseline larger ulcer sizes and extensive inflammation are less likely to achieve EH and CR, regardless of treatment with either combination therapy, infliximab or azathioprine monotherapy at week 26.

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
Confirm or validate previously conducted research on treatment effectiveness

Research Methods

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

Data Source: Eligibility criteria and the SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease) study design were previously published in the clinical trial(ClinicalTrials.gov number: NCT00094458).

Inclusion Criteria: Patients eligible will be at least 21 years of age and have had CD for least 6 weeks, with moderate-to-severe disease activity (i.e. Crohn's Disease Activity Index [CDAI] score 220-450 points). These patients will be either corticosteroid-dependent, being considered for a second course of systemic corticosteroids within 12 months, or will have had no response to either mesalamine (? 2.4 g/d) or budesonide (? 6 mg/d) after at least 4 weeks of treatment.

Exclusion Criteria: Patients who are ineligible include those with previous treatment to 6-mercaptopurine, methotrexate, or anti-TNF biologic agents. Previous abdominal surgery in the previous 6 months, symptomatic stricture, abscess, short gut, or ostomy. Patients with granulomatous infection, including tuberculosis, active infection with human immunodeficiency virus, hepatitis B or C, or opportunistic infection in the prior 6 months, multiple sclerosis or malignancy were excluded.

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

In SONIC, patients underwent a colonoscopy at baseline prior to randomization to treatment and mucosal ulcerations were detected in 325 patients. At week 26, of patients with mucosal ulcerations on baseline colonoscopy, a repeat colonoscopy was performed to determine EH. One of the main outcome measures will be EH at week 26. EH was defined as the absence of mucosal ulceration at week 26 in patients who had confirmed ulceration at baseline.

Additionally, CR at 26 will be an outcome measure defined as a Crohn's Disease Activity Index (CDAI) score < 1506. Corticosteroid-free CR at week 26 will be measured as well, which is defined as CDAI score <150, budesonide <6mg/day, and no systemic corticosteroids in prior 3 weeks.

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

To establish the baseline mucosal lesion characteristics and extent of inflammation of disease activity, multiple scoring systems derived from endoscopy (Crohn's Disease Endoscopic Index of Severity [CDEIS]7 and Simple Endoscopic Score for Crohn's Disease [SES-CD]8) will be used. Further description of CDEIS and SES-CD will be outlined below in 'other variables of interest.'

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

The CDEIS scores six endoscopic variables [presence of deep ulcers, superficial ulcers, nonulcerated stenosis, and ulcerated stenosis; proportion of ulcerated surfaces; and surface involved by disease] that are assessed in each of five ileocolonic segments [rectum, sigmoid/left colon, transverse colon, right colon, and ileum] 7.

The SES-CD is a simple scoring system based on four endoscopic variables [presence and size of ulcers, proportion of surface covered by ulcers, proportion of affected surface, and presence and severity of stenosis] measured in the same five ileocolonic segments as the CDEIS8.

Statistical Analysis Plan:

Continuous variables will be presented as means (and standard deviations [SD] or as medians and interquartile ranges [IQR]) if the distribution is skewed, and categorical or binary variables will be presented as proportions or percentages. Descriptive statistics will be used to summarize baseline demographics, disease characteristics and outcome parameters of CD patients with baseline mucosal lesions at screening colonoscopy. Proportions of patients achieving EH, CR, and corticosteroid-free CR will be compared between treatments with the use of the Fisher's exact test.

Known baseline disease factors significantly associated with the different composite remission outcomes (i.e. EH, CR, and corticosteroid-free CR) at week 26 such as treatment allocation and disease duration will be included within a multivariate logistic regression analysis to help adjust for potential confounding factors.

Approved investigators will be granted access to participant-level data sets via a remote, secure, password-protected data sharing platform. All work on the data must take place within the secure platform. The platform will be easily accessible to researchers, and ongoing system monitoring and support will be available. Within the platform, researchers will have access to the following analytical tools: Stata, R, RStudio, and Open Office. If needed, researchers will be able to upload additional data sets to the secure platform, if the researcher has the rights/license to do so.
Software Used:
Open Office
Project Timeline:

Anticipated Project Start Date: To be started within the first week of database approval and acquisition in September 2019.

Analysis Completion Date: Research proposal to be finalized with data collection and analysis. Estimated data of completion will be November 2019.

Manuscript Draft Date: Manuscript draft estimated to be completed in December 2019 – January 2020.

Manuscript Submission Date: January – February 2020

Date Results Reported to YODA: March - April 2020

The dissemination of results, which may include but are not limited to abstracts and manuscripts will be reported to the YODA Project at the time of submission.

Dissemination Plan:

Anticipated products include abstracts, which will be published or shared during scientific meetings, including Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organisation. Additionally, a manuscript is expected to be completed for the research project and will be submitted for publication. Potential journals for submission include Clinical Gastroenterology and Hepatology, Journal of Crohn's and Colitis, Inflammatory Bowel Diseases, and Digestive Diseases and Sciences. The dissemination of results, which may include but are not limited to abstracts, manuscripts, preprints, posters, and slide decks will be shared with the YODA Project at the time of submission.

Target audiences include clinicians and researchers interested in the advancement of the inflammatory bowel disease diagnostics and management.

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