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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_1.pdf
https://yoda.yale.edu/system/files/yoda_coi_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)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Patient Reported Outcomes in Crohn's Disease: A Post-hoc Analysis of the SONIC Trial

Narrative Summary:

There is increasing interest in evaluating patient reported outcomes (PROs) as endpoints in clinical trials. In Crohn's disease (CD), abdominal pain (AP) and stool frequency (SF) are two PROs of particular relevance. However, the relevance of PROs and whether severity of PROs has any impact on ability to achieve remission is uncertain. It is also unclear how well PROs correlate to objective measures of disease. Therefore, the role of PROs in CD clinical trials and their correlation to objective measures of disease activity requires further investigation.

Scientific Abstract:

Background and Rationale:
PROs in CD clinical trials are more commonly being used as co-primary endpoints. However, there is a paucity of data to suggest an association between PROs and objective measures of disease activity. The severity of PROs and whether they impact likelihood of achieving remission or endoscopic healing is also uncertain.

Objectives:
The purpose of the proposed study is to evaluate the association between relevant CD PROs and the ability to achieve clinical remission, corticosteroid-free remission, endoscopic remission and mucosal healing (MH) at week 26.

Study Design:
This study will be a post-hoc analysis of SONIC, a multicentre, randomized, double-blind trial. PROs of relevance include abdominal pain (AP) and stool frequency (SF), derived from the Crohn's Disease Activity Index (CDAI). Endoscopic evaluations at baseline and week 26 will also be used.

Study Population:
Patients with moderate-to-severe CD who are immunomodulator and biologic naïve were eligible for study inclusion.

Outcomes:
The primary outcome of the proposed study will be endoscopic remission and MH at week 26. Secondary outcomes of interest include clinical remission and corticosteroid-free remission at week 26. Subgroup analyses based on remission status may also be done.

Statistical Analysis:
To evaluate the relationship between baseline PROs and the outcomes of interest at week 26, multivariate logistic regression will be used and known confounders will be adjusted for.

Brief Project Background and Statement of Project Significance:

CD is a type of inflammatory bowel disease which is frequently associated with symptoms such as AP and severe diarrhea.(1) In clinical trials, PROs have been widely adopted as co-primary outcomes. Use of appropriate PROs in clinical trials have the potential to produce data that is both clinically meaningful and relevant to patients. The CDAI is an index of 8 items used to measure CD activity in clinical trials, including AP severity and liquid SF per day. However, the CDAI has been criticized for its lack of correlation with endoscopic disease activity, leading to the creation of the PRO2 score, which exclusively evaluates two patient-reported symptoms, AP and SF.(2,3) Despite its implementation in CD trials, the correlation between endoscopic disease activity and PROs has been questioned. A recent pooled analysis by Lewis et al. found a modest correlation between PRO2 remission and SF on achieving endoscopic remission or response.(4)

Specific Aims of the Project:

This proposed analysis of data from the SONIC trial aims to assess the association between PROs and endoscopic disease activity. Specifically, we hypothesize that in patients with moderate-to-severe CD, baseline AP and SF does not impact the likelihood of achieving clinical remission, corticosteroid-free remission, endoscopic remission

or mucosal healing 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
Research on clinical trial methods

Research Methods

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

Inclusion Criteria
To be included in the study, participants must meet the following criteria (5):
1) ? 21 years of age.
2) CD duration for at least 6 weeks.
3) Moderate-to-severe disease activity at baseline, defined as a CDAI score 220-450.
4) Corticosteroid-dependent, were considered for a subsequent course of systemic corticosteroids within 12 months, or had no response to either mesalamine (? 2.4 g/d) or budesonide (? 6 mg/d) after ?4 weeks of treatment.

Exclusion Criteria
If participants meet any of the following criteria, they are ineligible for study inclusion (5):
1) Previous treatment to 6-mercaptopurine, methotrexate, or anti-TNF biologic agents
2) Short gut
3) Ostomy
4) Symptomatic stricture
5) Abscess
6) Abdominal surgery in prior 6 months
7) Granulomatous infection including TB
8) Opportunistic infection in prior 6 months
9) Active infection with HIV or hepatitis B or C
10) Multiple sclerosis
11) Cancer

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

The primary outcome measures include endoscopic remission and mucosal healing at week 26. Endoscopic remission is defined as an SES-CD score ? 3 and MH is defined as absence of ulcerations.

To evaluate the primary outcome of this proposed study, data from endoscopic scoring tools, including the Crohn's Disease Endoscopic Index of Severity (CDEIS) and Simple Endoscopic Score for Crohn's Disease (SES-CD), will be used. The CDEIS scores five ileocolonic segments based on six endoscopic parameters: presence of deep ulcers, superficial ulcers, nonulcerated stenosis, ulcerated stenosis, proportion of ulcerated surfaces and surface involved by disease.(9) Similarly, the SES-CD is a simplified scoring system which evaluates 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.(10)

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

This study will obtain data from the Yale University Open Data Access (YODA) Project. Participant-level data will be required from SONIC. SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease; ClinicalTrials.gov, NCT00094458) was a multicenter, double-blind clinical trial which randomized patients with moderate-to-severe CD to receive infliximab, azathioprine, or combination therapy. A baseline CDAI score of 220-450 was required for inclusion and was assessed in 4- and 8-week intervals to the end of study or subject discontinuation, whichever preceded.(5) Therefore, in this proposed study, PROs at baseline and subsequently thereafter will be analyzed. In SONIC, ileocolonoscopy was performed at baseline and subsequently at week 26 if mucosal ulcerations were identified at baseline.(5) Thus, endoscopic outcomes at week 26 will be analyzed and may be compared to baseline findings.

Independent variables of interest include PROs found in the CDAI, including AP (mild=1, moderate=2 and severe=3) and SF, which will be analyzed categorically. Based on ongoing CD trials and published literature, severe SF was determined to be >3 per day.(4,6,7)

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

Clinical remission and corticosteroid-free remission are additional outcomes of interest which will be assessed. CDAI scores will be evaluated to determine if remission was achieved. Clinical remission is defined as a CDAI score < 150.(8) Corticosteroid-free remission is defined as remission achievement without use of corticosteroids for disease management in the previous 3 weeks and budesonide <6mg/day. Subgroup analyses based on PRO2 remission achievement (defined as daily AP ?1 and SF ?3) (6,7) and disease location may also be done.

Statistical Analysis Plan:

Relevant baseline data will be collected and summarized using descriptive statistics. Continuous variables will be reported as means and standard deviations or medians and interquartile ranges. Categorical variables will be presented as proportions or percentages. Covariates known to confound the relationship between the independent and dependent variables will be adjusted for using multivariable logistic regression, including treatment allocation (i.e. infliximab, azathioprine or combination), disease duration, presence of strictures at baseline and concomitant corticosteroid use. All covariates will be analyzed categorically with the exception of disease duration, which will be continuous. Subgroup analyses by remission status and disease location may also be done to assess the impact on the relationship between baseline PROs and week 26 remission and MH.
Software Used:
Open Office
Project Timeline:

Date to Start Project: March – April 2020.
Date to Complete Analysis: April – May 2020.
Date to Draft Manuscript: May – June 2020.
Date to Submit Manuscript: June – July 2020.

Dissemination Plan:

Study results may be shared with target audiences through poster presentations and abstracts. 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. In all study products, the YODA Project will be acknowledged as the source of study data. The investigators will share abstracts, manuscripts, etc. at the time of submission.

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