Principal Investigator

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General Information

Key Personnel (in addition to PI): **First Name:** Jean-Frederic
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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

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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

Associated Trial(s): NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
NCT00096655 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
NCT00537316 - Efficacy & Safety of Infliximab Monotherapy Vs Combination Therapy Vs AZA Monotherapy in Ulcerative Colitis (Part 1) Maintenance Vs Intermittent Therapy for Maintaining Remission (Part 2)
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Association between Patient-reported Outcomes and Endoscopic Healing in Ulcerative Colitis: A meta-analysis

Narrative Summary:
When treating patients with ulcerative colitis (UC), patient-reported symptoms of rectal bleeding and increased stool frequency are accompanied by endoscopic changes. The goal of treatment is to normalize symptoms and improve quality of life for patients. Many opinion leaders are now proposing targeting mucosal healing as a goal of treatment in UC. However, repeated endoscopic assessments are expensive so surrogates of mucosal healing are important to identify and use. The purpose of this study is to conduct a meta-analysis of data from biologic studies in UC correlating patient-reported outcomes (stool frequency, rectal bleeding) with endoscopic healing.

Scientific Abstract:
Background: When treating patients with ulcerative colitis (UC), patient-reported symptoms of rectal bleeding and increased stool frequency are accompanied by endoscopic changes. The goal of treatment is to normalize symptoms and improve quality of life for patients. Many opinion leaders are now proposing targeting mucosal healing as a goal of treatment in UC. However, repeated endoscopic assessments are expensive so surrogates of mucosal healing are important to identify and use.
Objective: The purpose of this study is to conduct a meta-analysis of data from biologic studies in UC correlating patient-reported outcome scores (stool frequency, rectal bleeding) with endoscopic healing.
Study Design: Meta-analysis of clinical trial data for all approved biologics in UC (infliximab, adalimumab, golimumab, vedolizumab)
Participants: Moderate-Severe UC patients from clinical trial programs who were treated with biologic therapies
Main Outcome Measure: Pooled sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of rectal bleeding score =0, stool frequency score=0, and combined rectal bleeding + stool frequency score = 0 to predict endoscopic healing.
Statistical analysis: Comprehensive meta-analysis software will be used. Individual study level data will be combined to determined pooled sensitivity, specificity, PPV, and NPV of all the independent variables of interest. Receiver operating characteristic curves will be drawn for each of the variables of interest to compare relative performance.

Brief Project Background and Statement of Project Significance:
When treating patients with ulcerative colitis (UC), patient-reported symptoms of rectal bleeding and increased stool frequency are accompanied by endoscopic changes. The goal of treatment is to normalize symptoms, heal the mucosa, and improve quality of life for patients. In clinical trials involving patients with UC, clinical remission or response is commonly defined using the Mayo score which is a composite of patient reported outcomes (i.e. stool frequency and rectal bleeding subscores) and physician reported outcomes (ie, endoscopy subscore and physician's global assessment [PGA]).
Recently, the STRIDE initiative proposed a composite remission target based on clinical and patient-reported outcomes (including resolution of rectal bleeding and diarrhea/altered bowel habits)and the absence of ulceration on endoscopy (either flexible sigmoidoscopy or colonoscopy). However, repeated endoscopic assessment for mucosal healing is expensive and may not be feasible at some centres or in certain countries. Biomarkers or

surrogates of mucosal healing are important to identify in this case.
Studies of biologic therapies which have been approved for UC, including infliximab, golimumab, adalimumab, and vedolizumab, all include endoscopic assessments and Mayo scores including the patient-reported outcomes. A publication looking at the association of patient-reported outcomes with mucosal healing in adalimumab-treated patients reported that the positive predictive value of combined patient-reported outcomes of stool frequency and rectal bleeding scores equal to zero was reasonably high (90%) for complete mucosal healing (1). They also reported that the sensitivity of stool frequency alone is only 29% in patients with complete mucosal healing, so this symptom alone cannot predict mucosal healing (1).
The objective of this meta-analysis is to explore the association of patient-reported outcomes of stool frequency or rectal bleeding with endoscopic healing in patients treated with biologic therapies. This will help determine whether patient symptoms are useful enough to predict mucosal healing, or whether endoscopy or other biomarker tests need to be conducted to be reasonably confident this outcome has been achieved.

Specific Aims of the Project:
Study hypothesis:
Can patient-reported outcomes be used as a surrogate to monitor patients who achieved mucosal healing on biologic therapies?
Study objectives:
1. Evaluate the association of rectal bleeding score = 0 to predict mucosal healing (endoscopic subscore = 0 or 1).
2. Evaluate the association of stool frequency score = 0 to predict mucosal healing (endoscopic subscore = 0 or 1).
3. Evaluate the association of combined rectal bleeding and stool frequency score = 0 to predict mucosal healing (endoscopic subscore = 0 or 1)

What is the purpose of the analysis being proposed? Please select all that apply. Summary-level data meta-analysis
Summary-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Data sources:
Post-hoc analyses of adalimumab, vedolizumab, and golimumab studies examining association of patient-reported outcomes and endoscopic healing have been published or presented in abstract form and have already been attained. We are seeking this same data from the infliximab in ulcerative colitis study (ACT2) in order to conduct this meta-analysis.
Inclusion:
All studies including UC patients treated with biologic therapies at which there is data available which correlate patient-reported outcomes with mucosal healing at a short-time interval from initiating of therapy (<= 12 weeks) and/or a long-time interval (> 12 weeks)
Exclusion:
Studies of patients with Crohn's disease
Studies of non-biologic therapies
Studies without endoscopic healing assessments

Main Outcome Measure and how it will be categorized/defined for your study:
From each biologic study for UC, we will create a 2X2 table looking at the sensitivity, specificity, positive predictive value, and negative predictive value of the following:
1. rectal bleeding score = 0 vs rectal bleeding score >=1 compared to mucosal healing score = 0 vs. mucosal healing score >=1
2. rectal bleeding score = 0 vs rectal bleeding score >=1 compared to mucosal healing score = 0 or 1 vs. mucosal healing score >=2
3. stool frequency score = 0 vs stool frequency score >=1 compared to mucosal healing score = 0 vs. mucosal healing score >=1
4. stool frequency score = 0 vs stool frequency score >=1 compared to mucosal healing score = 0 or 1 vs. mucosal healing score >=2
5. rectal bleeding score = 0 and stool frequency score = 0 vs all other values for rectal bleeding/stool frequency compared to mucosal healing score = 0 vs. mucosal healing score >=1

6. rectal bleeding score = 0 and stool frequency score = 0 vs all other values for rectal bleeding/stool frequency compared to mucosal healing score = 0 or 1 vs. mucosal healing score >=2
We will use meta-analysis software to pool these numbers together and create receiver operating characteristic curves.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Predictor variables are the patient-reported outcomes, and they will be categorized as above.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
For the purpose of this meta-analysis, we are only seeking data of patient-reported outcomes and their association with Mayo endoscopic subscore.

Statistical Analysis Plan:
Meta-analysis software (Comprehensive meta-analysis) will be used to conduct this meta-analysis. Individual study level data will be combined to determined pooled sensitivity, specificity, positive predictive value, and negative predictive values of all the independent variables of interest. Receiver operating characteristic curves will be drawn for each of the variables of interest to compare their relative performance.

Project Timeline:
Anticipated project start date: January 1, 2018
Anticipated analysis completion date: January 31, 2018
Date manuscript drafted and first submitted for publication: February 28, 2018
Date results reported back to the YODA project: May 31, 2018

Dissemination Plan:
We plan to disseminate the results with a manuscript publication. We anticipate publication in a mid-tier gastroenterology journal such as Alimentary Pharmacology & Therapeutics or Journal of Crohn's and Colitis.

Bibliography:
(1) Jharap et al. Randomised clinical study: discrepencies between patient-reported outcomes and endoscopic appearance in moderate to severe ulcerative colitis. Aliment Pharmacol Ther 2015; 42(9): 1082-92.