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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?: Scientific Publication

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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
NCT00207675 - A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF a Chimeric Monoclonal Antibody (Infliximab, REMICADE) in Pediatric Subjects With Moderate to Severe CROHN'S Disease
NCT00094458 - 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
NCT00336492 - A Phase 3, Randomized, Open-label, Parallel-group, Multicenter Trial to Evaluate the Safety and

Efficacy of Infliximab (REMICADE) in Pediatric Subjects With Moderately to Severely Active Ulcerative Colitis
NCT00487539 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis
NCT00207662 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease
NCT00207766 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease
NCT00004941 - A Placebo-controlled, Repeated-dose Study of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Enterocutaneous Fistulae as a Complication of Crohn’s Disease
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)
NCT01551290 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis
NCT00771667 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With T
NCT01369329 - 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
NCT01369342 - 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)
NCT00488631 - A Phase 3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects With Moderately to Severely Active Ulcerative Colitis
NCT01369355 - 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 Obesity on Disease Course and Response to Biologic Therapy in Inflammatory Bowel Disease: A Post-Hoc Analysis of RCTs

Narrative Summary:
Over 1/3rd of adults in the United States are obese. Fat releases toxins that can cause several diseases like diabetes and heart disease. Inflammatory bowel diseases are autoimmune diseases, affecting over 1.6 million Americans. The bowels are richly surrounded by fat, which plays a part in causing disease. We will evaluate the impact of obesity on IBD disease outcomes and response to therapy, through analyses of late stage (Phase III), placebo-controlled trials of infliximab and golimumab in IBD. This will advance understanding of factors that influence disease course of IBD, and results will be directly applicable to patient care, offering potential for personalized therapy.

Scientific Abstract:
Background: Over 1/3rd of adults in the US are obese, and its prevalence is high in patients with inflammatory bowel diseases (IBD). It is unclear how obesity may modify IBD outcomes and response to therapy
Objective: To evaluate the effect of obesity, measured using body mass index (BMI), on IBD outcomes and response to anti-tumor necrosis factor (TNF)-? therapy.
Study Design: Individual participant level pooled analysis of RCTs of infliximab (IFX) and golimumab (GLM) in patients with UC and CD

Participants: Patients enrolled in phase III RCTs of IFX or GLM in moderate-severe UC and CD, receiving either placebo (impact of obesity on disease outcomes, in absence of intervention) or active agent (impact of obesity on response to biologic therapy)
Main Outcome Measures: Clinical remission/response and biochemical remission (mucosal healing for UC)
Statistical Analysis: We will pool data of patients in placebo arms (impact of obesity on IBD outcomes) and of patients in active agent arms (IFX/GLM separately, impact of obesity on response to biologic therapy), to analyze outcomes, stratified by BMI at time of enrollment (low <18.5kg/m2, normal 18.5-25.0kg/m2, overweight, 25.1-29.9kg/m2, class I obesity, 30.0-34.9kg/m2 and class II/III obesity, ?35.0kg/m2), using logistic regression analysis. Patients with UC/CD, adults/ children, will be analyzed separately, and all analysis will be adjusted for factors that modify pharmacokinetics of anti-TNF agents (sex, concomitant immunomodulator therapy, baseline C-reactive protein, albumin) and serum drug level

Brief Project Background and Statement of Project Significance:
Obesity is a growing epidemic; currently, over 34% adults and 16% adolescents in the United States are obese.1 Obesity denotes a state of chronic inflammation and insulin resistance, and contributes to diabetes, cardiovascular diseases and cancers including gastrointestinal cancers.2 Inflammatory bowel diseases, a group of autoimmune diseases of unclear etiology, affect over 1.6 million Americans , with a rising incidence.3,4 About 18-30% of IBD patients are obese,5,6 and there is increasing evidence that mesenteric fat contributes to IBD pathogenesis by inducing a chronic, low-grade systemic inflammation.7 Though obesity might increase the risk of developing IBD,8 it is unclear how obesity may modify the course of IBD, with retrospective observational studies having conflicting results.6,9 Pro-inflammatory cytokines are known to impact response to biologic therapy through alterations in pharmacokinetics, a key treatment strategy for patients suffering from severe IBD, and hence, concerns arise that obesity among IBD patients may represent a blunt response to emerging biologics.10
The overall objective of this proposal is to understand how obesity modifies the clinical course and treatment response in patients with moderate-severe IBD. Our central hypothesis is that obesity portends a worse prognosis in adults with IBD, as compared to normal BMI individuals, with complicated disease course and poor treatment response to biologic agents. The long-term goal of our program is to identify modifiable predictors of disease course and response to therapy, to improve long-term prognosis in patients with IBD. The significance of this work lies in comprehensively assessing how obesity may modify clinical course and treatment response to anti-TNF therapy in IBD, using a novel, innovative approach through post-hoc analyses of robust, late-stage clinical trials in IBD. The information generated through this study would be invaluable to inform both science and patient care. From a scientific perspective, it will advance understanding of IBD pathophysiology, offering potential clues into role of mesenteric fat, adipocytokines and gastrointestinal hormones in IBD pathogenesis as well as pharmacokinetics of biologic therapy. From a clinical perspective, information generated from this study on treatment response to biologic therapy, will be generalizable and directly applicable to patient care offering potential for personalized therapy based on body habitus, while simultaneously enhancing design of future clinical trials. It may enable an innovative therapeutic approach to IBD management by targeting obesity through lifestyle modification, pharmacological and/or endoscopic weight loss procedures, to modify IBD outcomes.

Specific Aims of the Project:
Specific aim #1: To compare IBD outcomes across strata of BMI (class II/III obesity, class I obesity, overweight vs. normal BMI; low vs. normal BMI), in post-hoc analysis of phase III RCTs of IFX and GLM in IBD.
Hypothesis: Obese patients will have worse disease outcomes (lower rates of clinical and biochemical remission) as compared to normal BMI individuals with similar baseline disease activity, after adjusting for variations in baseline inflammatory markers (C-reactive protein, fecal calprotectin in GLM trials), interventions (immunomodulator and/or steroid use) and known clinical prognostic factors.

Specific aim #2: To compare treatment response to fixed dose (GLM) and weight-based (IFX) biologic therapy across strata of BMI (class II/III obesity, class I obesity, overweight vs. normal BMI, low vs. normal BMI) in patients with IBD, in post-hoc analysis of phase III RCTs of IFX and GLM in IBD.
Hypothesis: Obese patients will have inferior response (lower rates of clinical and biochemical remission), as compared to normal BMI individuals, to GLM and IFX, after adjusting for variations in baseline disease activity (CRP, FC), co-interventions (concomitant immunomodulators), factors known to influence pharmacokinetics (sex, albumin) and serum drug level.

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 Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Data sources:
• Trials of golimumab in ulcerative colitis (NCT00487539)
• Trial of infliximab in ulcerative colitis (NCT00036439, NCT00096655, NCT00336492, NCT00537316)
• Trials of infliximab in Crohn's disease (NCT00207662, NCT00207675, NCT00207766, NCT00004941, NCT00094458)
Inclusion criteria:
• Patients (adults or pediatric) with moderate-severe ulcerative colitis (defined as Mayo Clinic score [MCS] of 6 to 12 points, with an endoscopic sub-score of 2 or 3) or Crohn's disease (defined as Crohn's Disease Activity Index [CDAI] score >200 but less then 450, for adults; defined as pediatric CDAI (PCDAI) >30, for children)
• Treated with infliximab or golimumab or placebo for induction and/or maintenance
• Recorded body weight at time of enrollment (if height is available, then BMI can be estimated; however, if height is not recorded, then data would be analyzed based on body weight divided into quartiles)
Exclusion criteria
• Lack of information on body weight at time of enrollment
• Patients lost to follow-up or did not participate in trial after randomization (without receiving any dose of the medication)

Main Outcome Measure and how it will be categorized/defined for your study:
For ulcerative colitis trials
o Primary outcome – clinical remission (MCS?2, with no individual sub-score exceeding 1) after induction therapy (4-12 weeks) or after maintenance therapy (week 24-60)
o Secondary outcomes – clinical response (decrease in MCS by ?3 points and 30%, with decrease in the rectal bleeding sub-score by ?1 point, or an absolute sub-score of 0 or 1); mucosal healing (absolute endoscopy sub-score on MCS of 0 or 1); biochemical remission (CRP<0.5mg/dl; fecal calprotectin<150mcg/g), to be assessed only in patients with elevated values at baseline

For Crohn's disease trials
o Primary outcome – clinical remission (CDAI<150 for adults; PCDAI<10 for children; complete fistula closure at 2 consecutive visits, for fistulizing CD) after induction (4-12 weeks) or after maintenance therapy (week 24-60)
o Secondary outcome – clinical response (decrease in CDAI by 100 [CR100] or 70 points [CR70] from baseline for adults; decrease in PCDAI to 11-30, for children; reduction in number of draining fistulae by 50% from baseline, for fistulizing CD); biochemical remission (CRP <0.5mg/dl), to be assessed only in patients with elevated CRP at baseline

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Main predictor/independent variable will be body mass index (BMI) at baseline (to be estimated from weight and height at study enrollment), and this would be categorized into WHO-defined obesity categories – low BMI (BMI<18.5kg/m2), normal BMI (BMI between 18.5-25.0kg/m2), overweight (BMI between 25.1-29.9 kg/m2), class I obesity (BMI between 30.0-34.9kg/m2), class II/III obesity (BMI?35.0kg/m2). If data on BMI is not available/not calculable in candidate trials, then patients will be stratified into quartiles by weight (in kg) at time of enrollment.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Key confounding variables of interest in our study are:
o Biochemical measures of disease severity – baseline C-reactive protein as a categorical variable (<0.5mg/dl or ?0.5mg/dl), fecal calprotectin (where available, <150mcg/g vs. ?150mcg/g)
o Co-interventions – concomitant use of immunomodulators like azathioprine, 6-mercaptopurine or methotrexate (yes vs. no), concomitant use of steroids (yes vs. no)
o Factors known to modify pharmacokinetics of anti-TNF therapy – baseline albumin as a categorical variable (<3.5g/dl vs. ?3.5g/dl), sex (males vs. females)
o Serum drug level, categorized into quartiles (to assess whether obesity modifies treatment response, independent of drug exposure)

All analysis will be stratified by age group of participants (adults vs. children), IBD phenotypes (UC vs. CD, and within CD, luminal CD vs. fistulizing CD); trials of induction and maintenance therapy will be analyzed separately

Statistical Analysis Plan:
Descriptive analysis: We will report proportions to present distribution of demographic, clinical and biochemical characteristics of participants stratified by baseline BMI, in both active agent and placebo arm of RCTs, and calculate differences between groups using chi-square tests.
Univariate analysis: To assess how obesity may modify IBD disease activity/outcome, we will pool data from placebo-arms of all included trials. We will estimate whether baseline BMI influences IBD disease course by comparing proportion of patients achieving primary outcome (clinical remission) and secondary outcomes (clinical response, biochemical remission and mucosal healing) to induction and maintenance therapy in each strata of BMI using chi-square test. Similarly, to analyze impact of obesity on response to anti-TNF therapy, we will pool data from active agent arms of all included trials. In this, we will estimate whether BMI influences response to therapy by comparing proportion of patients achieving primary and secondary outcomes by baseline BMI category; IFX and GLM trials will be analyzed separately.
Multivariable analysis: To evaluate the impact of obesity independently on outcomes and response to therapy in IBD, we will perform logistic regression analysis after adjusting for key a priori identified confounders including baseline disease activity (CRP, fecal calprotectin), co-interventions (concomitant immunomodulators), factors known to influence pharmacokinetics (sex, albumin) and serum drug level.

ADDENDUM: Feb 16, 2017
We will also be performing a similar analysis, evaluating the impact of obesity on response to vedolizumab and certolizumab pegol with individual participant level data for trials in IBD (available from https://clinicalstudydatarequest.com). We propose to download summary level data from both YODA and CSDR. Given similar study design, all of these summary data will be analyzed together (clustered by trial, and stratified by drug and disease type). This is not a comparative analysis. This will help us comprehensively understand impact of obesity on natural history and response to biologic therapy.

Project Timeline:
Once study is approved and data access provided (assuming by December 2015), our key milestones dates are:
o Project start date: January 1, 2015
o Analysis completion date: March 31, 2016
o Manuscript drafted: May 31, 2016
o Manuscript submitted for publication: July 1, 2016
o Date results reported back to YODA: July 1, 2016

Dissemination Plan:
We anticipate generation of at least 2 manuscripts from this project – one related to impact of obesity on IBD disease course (using placebo arms of included trials), and other related to impact of obesity on treatment outcome (using active arms of included trials). The target audience would be clinical gastroenterologists as well as physician-scientists with interest in IBD and/or obesity. Potentially suitable journals for these manuscripts would be: Gastroenterology, Gut, American Journal of Gastroenterology, Inflammatory Bowel Diseases.

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Supplementary Material: supplementary_material.docx