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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

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2020/02/signed_yoda_fcoi.pdf
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content/uploads/2014/10/yoda_project_coi_form_for_data_requestors_2019_fp.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. NCT00036439 - C0168T37 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
2. NCT00096655 - C0168T46 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
3. NCT00207675 - C0168T47 - 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
4. NCT00336492 - C0168T72 - 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
5. NCT00487539 - C0524T17 - 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
6. NCT00207662 - C0168T21 - 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
7. NCT00207766 - C0168T26 - 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
8. NCT01551290 - CR018769; REMICADEUCO3001 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis
9. NCT00269854 - C0168T16 - A Placebo-Controlled, Dose-Ranging Study Followed by a Placebo-Controlled, Repeated-Dose Extension of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients With Active Crohn's Disease
10. - C0168T16 - Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease.
11. NCT00771667 - C0743T26 - 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 TNF Antagonist Therapy
12. 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)
13. 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)
14. NCT00488631 - C0524T18 - 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
15. 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
16. NCT00488774 - C0524T16 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Intravenously, in Subjects With Moderately to Severely Active Ulcerative Colitis
17. NCT00265122 - C0379T07 - A Multicenter, Randomized, Phase 2a Study of Human Monoclonal Antibody to IL-12p40 (CNTO 1275) in Subjects With Moderately to Severely Active Crohn's Disease
18. NCT01863771 - CNTO148UCO3001 - A Safety and Effectiveness Study of Golimumab in Japanese Patients With Moderately to Severely Active Ulcerative Colitis
19. NCT01988961 - CNTO148UCO2001 - A Study to Evaluate the Accuracy of a Subset of the Length-109 Probe Set Panel (a Genetic Test) in Predicting Response to Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis
20. NCT02407236 - CNTO1275UCO3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis

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

Research Proposal

Project Title

Influence of Race and Ethnicity on the Efficacy of Biologic Drugs for Inflammatory Bowel Disease

Narrative Summary:

There is growing recognition of differences in inflammatory bowel disease (IBD) between racial and ethnic groups, such as in distribution of intestinal activity and rates of medication use or surgery. Clinical trials of IBD biologics have not specifically evaluated response by race/ethnicity, and most studies predominately include persons of European ancestry. Research in IBD genetics demonstrates that genetic risk loci differ based on race/ethnicity and may result in different underlying pathogenesis and clinical phenotypes. The purpose of this study is to evaluate the efficacy of biologic therapies among non-white/European (NW) IBD patients compared to white/European ancestry patients.

Scientific Abstract:

Background
Inflammatory bowel disease (IBD) is a condition of chronic intestinal inflammation that contributes to significant morbidity and affects up to 3 million adults in the United States, with a growing global disease burden.1,2 However, to our knowledge, no studies to date have specifically evaluated treatment response in clinical trials based on race/ethnicity.
Objective
The purpose of this study is to determine if there is evidence of a differential response to biologic treatment in IBD based on race/ethnicity.
Study Design
We will conduct a pooled analysis of individual participant data from randomized controlled clinical trials of infliximab, golilumab and ustekinumab in IBD. We will compare outcomes between white patients and non-white IBD patients enrolled in these trials.
Participants
Biologic-treated IBD patients

Main Outcome Measure(s)
Primary outcome is clinical remission (defined by CDAI < 150 for Crohns disease or Mayo Clinical Score < 3 for UC).
Secondary outcomes are clinical response (CDAI decrease of 70 or 100 points for Crohns and decrease from baseline in the Mayo score by ? 30% and ? 3 points for UC) and mucosal healing (absence of ulcerations in Crohn?s and Mayo endoscopic sub-score of 0 or 1).
Statistical Analysis
Baseline characteristics will be summarized by frequency and mean/median. Statistical significance of baseline variables will be assessed using chi-square tests for categorical variables and ANOVA, t-tests for continuous variables. Outcome measures by ethnicity will be analyzed by multivariable logistic regression.

Brief Project Background and Statement of Project Significance:

The inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohns disease (CD), are conditions of chronic intestinal inflammation with increasing global incidence.1,2 Although the exact trigger of disease onset is yet unclear, the pathogenesis of IBD is thought to occur as a result of both environmental and genetic influences. For instance, factors such as breastfeeding, antibiotic use, and food additives have been implicated in exerting influence on the intestinal microbiome in a genetically predisposed individual thus triggering manifestations of IBD.2,3
Previous studies have described distinct IBD genotypic and phenotypic characteristics among different ethnic groups.4-6 For example, among individuals of European ancestry, NOD2 and IL23R are some of the more than 200 established loci of single nucleotide polymorphisms (SNPs) for Crohn?s disease. SNPs at ZNF649 and LSAMP have more recently been described to associate with UC among those of African ancestry, and other variant genetic mutations and susceptibility genes have been identified in Asian subpopulations.5,6 There is evidence of IBD phenotypic variation by ethnicity, for instance, with evidence of increased peri-anal involvement among individuals of African and Asian ancestry.7 There have also been disparities in clinical outcomes noted in IBD, with for example, higher rates of hospitalizations and complications among African American patients, although it is unclear if this difference is due to care patterns or underlying disease phenotype.8-11
Whether or not genotypic and phenotypic variations in IBD among different ethnic groups contribute to a differential response to IBD therapies is also unclear. Most studies of anti TNF biologics, for example, have included relatively few individuals of non-white/European ancestry and those studies that do look at ethnic differences tend to focus on the comparative use of various IBD medications or use of surgery. Whether or not differences in outcome pertain to different underlying disease processes rather than to external system or practice-based factors is an area of uncertainty. No study to our knowledge has specifically evaluated the efficacy of IBD therapies by ethnicity.
Knowledge of differential response to IBD medications based on racial/ethnic background may serve as an important component of personalizing the approach to treatment in an increasingly diverse population of IBD patients. In the absence of significant differences in response/remission rates in the controlled research setting of randomized control trials, differences in patient outcomes by ethnicity may point to other processes, such as health care systems, as opposed intrinsic differences in disease and drug response biology related to genetic background.

Specific Aims of the Project:

Aim 1: Compare rates of induction and maintenance of clinical response and remission in CD/UC/IBD patients treated with biologic drugs (anti-TNF, infliximab, golimumab; anti-IL 12/23, ustekinumab) stratified by race/ethnicity.
Aim 2: Compare rates of induction and maintenance of endoscopic remission in patients CD/UC/IBD patients treated with biologic drugs (anti-TNF, infliximab, golimumab; anti-IL 12/23, ustekinumab) stratified by race/ethnicity.

Research Methods

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

Inclusion: CD and UC patients in induction and maintenance RCTs for biologic therapy. Adults (age 18 or older)
Exclusion: Insufficient data available to determine outcomes and/or primary variable of interest (race/ethnicity). Age < 18 years.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary outcome will be clinical remission defined as Crohn?s disease activity index (CDAI) < 150 for CD or Mayo Clinical Score (MCS) < 3 for UC at end of induction and end of maintenance. This will be a dichotomous outcome.
Secondary outcomes will include:
Clinical response (CDAI decrease of 70 or 100 points for CD or decrease from baseline in the MCS by ? 3 points and at least 30% from baseline for UC).
Endoscopic healing (absence of ulcerations in CD and Mayo endoscopic sub-score of 0 or 1 in UC).

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

Our primary predictor/independent variable will be race/ethnicity categorized as white versus non-white. Non-white patients will be defined as African, African-American, Black, Asian/Pacific Islander/SE Asian, Hispanic/Latino, or other non-white race. If sample size allows, we will look at specific non-white race/ethnicity groups including African/African American/Black, Asian, and Hispanic/Latino individually.

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

Other baseline variables of interest that will be included in our analysis include IBD type (UC or CD; categorical), peri-anal disease (categorical); disease duration (continuous), age (continuous), gender (categorical), disease location for CD and UC (categorical by Montreal classification), disease behavior for CD (categorical by Montreal classification), prior biologic use (categorical), smoking history (current versus former/never), baseline disease activity (continuous based on disease activity index, alternatively can categorize by pre-defined ranges for mild/moderate/severe disease), baseline albumin (continuous), baseline CRP (continuous), concomitant steroids at start of trial (categorical), concomitant immunomodulators at start of trial (categorical), extra-intestinal manifestations (categorical), dose of biologic (categorical), and trial design (induction vs. maintenance trial; categorical). We will also include individual study (categorical) as a variable to account for any differences between studies. Specific biologic studied will also be assessed (infliximab, golimumab, or ustekinumab as a categorical variable).

Statistical Analysis Plan:

Descriptive statistics will be performed using medians (interquartile range) and means (standard deviation) for continuous variables and proportions for categorical variables. Data distribution will be analyzed using Q-Q plots and the Shapiro-Wilk test. Continuous data between two groups will be analyzed using two-sample, non-paired t-tests for parametric data and the Wilcoxon rank-sum test for non-parametric data. To compare continuous data across more than two groups (for example, age across different non-white race/ethnicity subgroups), we will use ANOVA for parametric data and the Kruskal-Wallis test for non-parametric data. Categorical variables will be compared using chi-square or Fisher exact test where appropriate.
We will first perform univariable analyses using logistic regression assessing the relationship between our covariables and the primary and secondary outcomes for all IBD patients. These outcomes will be stratified by induction versus maintenance studies (different regression models). We will also perform subgroup analyses based on disease type. We will first evaluate response to all biologics together and then by class (anti-TNF and anti-IL12/23). We will then construct multivariable models including those baseline characteristics with a p-value ?i 0.10 in the univariable analysis for

the primary and secondary outcomes. We will a priori include baseline disease activity score, prior biologic exposure, and concomitant immunomodulator use in all multivariable models. All statistical tests will be two-sided with a p value < 0.05 considered statistically significant.

Software Used:

Open Office

Project Timeline:

Project Start Date: October 2018
Analysis Completion Date: April 2019
Manuscript Submission: May 2019
Publication Submission Date: May 2019
Results Report to YODA: June 2019

Dissemination Plan:

We will disseminate results first in abstract form at national gastroenterology conferences, with target conference being Digestive Disease Week or Annual American College of Gastroenterology Meeting. We will then plan to submit a manuscript of the results to a peer-reviewed gastroenterology journal such as Gastroenterology, American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, or Inflammatory Bowel Disease Journal.

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