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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_project_coi_form_for_data_requestors_2018_0.docx
https://yoda.yale.edu/system/files/shah_yoda_coi.pdf
https://yoda.yale.edu/system/files/yoda_coi_ma.pdf
https://yoda.yale.edu/system/files/jfc_yoda_coi_final.pdf
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https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2018_francesca_petralia_signed.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. 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)
5. 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
6. 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
7. 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
8. 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
9. NCT00004941 - C0168T20 - 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
10. NCT00537316 - P04807 - 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)
11. NCT01551290 - CR018769 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis
12. NCT01190839 - REMICADECRD3001 - Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE (Infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at Increased Risk of Recurrence
13. 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
14. C0168T16 - Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease.

15. 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
16. 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)
17. 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)
18. 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
19. 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
20. 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
21. 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
22. NCT01863771 - CNTO148UCO3001 - A Safety and Effectiveness Study of Golimumab in Japanese Patients With Moderately to Severely Active Ulcerative Colitis
23. 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

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

Research Proposal

Project Title

Gender-based Differences in Response to Therapy in Inflammatory Bowel Disease

Narrative Summary:

Inflammatory bowel diseases (IBD), i.e., Crohn’s disease (CD) and ulcerative colitis (UC) are immunologically-mediated diseases with progressive intestinal injury if untreated (1,2). Identifying predictors of response is critical to improve outcomes (1,2).
A pooled analysis of 17 population-based studies found higher CD risk in females 25-29 and >35 years old (4). Hormonal therapy and pregnancy are associated with severe IBD (5). Experimental data is supportive (6,7). Sparse data suggest lower response to anti-TNF(8) and higher risk of anti-drug antibodies (9) in women.
We will conduct a pooled analysis of available data to delineate the impact of gender on response to therapy in IBD.

Scientific Abstract:

Background
IBD often necessitates systemic biologic therapy to achieve disease remission and avoid adverse outcomes. Risk stratification is key to precise and personalized therapy, and ensuring optimal patient outcomes. While gender-based differences in IBD are increasingly recognized, the effect of gender on therapeutic response is not known.

Objective
To define gender-based differences in response to biologic therapy in IBD

Study Design
We will conduct a pooled analysis of data from randomized clinical trials in IBD where the primary outcome was response to biologic therapy.

Participants
Patients in phases 2-4 randomized clinical trials on the efficacy of infliximab, golimumab and ustekinumab will be included when data on response to therapy, stratified by sex, is available

Main Outcome Measure(s)
Primary outcome (Aim 1): Endoscopic remission, defined as CD endoscopic index of severity (CDEIS) <3 (CD) or modified Mayo endoscopic sub-score (MMES) <=1 (UC)

Secondary outcome (Aim 1): Biochemical remission defined as normalization of C-reactive protein (CRP) or fecal calprotectin

Primary outcome (Aim 2): Clinical remission, defined as Harvey-Bradshaw Index (HBI) of <5 in CD or partial Mayo score of <=1 in UC

Statistical Analysis
We will pool comparable data and determine the summary study estimate with gender as a variable using descriptive and multivariable techniques. We will pool survival data by using logistic regression and perform stratified and sensitivity analyses to determine the impact of other variables on outcomes.

Brief Project Background and Statement of Project Significance:

Background and Statement of Project Significance

Inflammatory bowel diseases (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), are chronic, progressive, and disabling inflammatory disorders of the gastrointestinal tract. Their pathogenesis is incompletely understood, but involves the complex interaction between environmental determinants, immune dysregulation, and gut dysbiosis in a genetically susceptible host (1, 2) IBD can present at any age, but tends to affect adolescents and young adults most frequently. Mucosal healing with early aggressive biologic therapy, e.g. tumor necrosis factor alpha (TNF-alpha) inhibitors, improves long-term outcomes and prevents complications (3). Conversely, lack of adequate therapy and resultant high inflammatory burden carries the risk of progressive intestinal injury and complications including colorectal neoplasia. However, not all patients benefit from biologic agents and remain at risk of disease complications. Therefore, defining predictors of response to biologics is critical to the development of precise, personalized treatment strategies to improve patient important outcomes. (1, 2)

We hypothesize that gender is one clinical factor that might affect response to biologic therapy in IBD. There are emerging epidemiological data implicating sex in IBD pathogenesis, although the exact mechanisms are yet to be defined. A recent pooled analysis of 17 population-based studies from Western industrialized countries found that males were at higher risk for CD until age 10-14 years, with a higher risk in females at ages 25-29 and >35 years (4). Hormonal contraceptives and pregnancy have also been associated with worsening of IBD, lending weight to the role of sex hormones in gender-specific IBD phenotype (5). Experimental evidence is also supportive (6, 7). While sparse data suggest lower response to TNF-alpha inhibitors in women (8) and higher likelihood of drug neutralizing anti-TNF alpha antibodies (9), no single study has adequately investigated gender-specific differences in therapeutic responses in IBD. The primary aim of the present proposal is to systematically and comprehensively define gender-based differences in response to IBD biologic therapy.

The Yale University Open Data Access Project (YODA) is a powerful resource as it provides open access to primary trial data for clinical research. Using such data, we will conduct a pooled analysis to delineate whether gender predicts or modifies response to therapy as pre-defined by standardized, objective measures. We will conduct several sensitivity and stratified analyses as detailed below.

This would be the first comprehensive study to determine the impact of gender on therapeutic response to biologic therapy in patients with IBD. Our findings have immediate clinical implications and are an important step forward towards targeted treatment algorithms based in evidence that are expected to result in improved patient outcomes. Furthermore, our findings will contribute to better patient education and ability to better manage patient

expectations with therapy.

Specific Aims of the Project:

Aim 1. To define gender-based differences in endoscopic response to biological therapy among patients with active CD or UC, in a pooled analysis of randomized clinical trials (RCTs)
Hypothesis 1. Female patients with CD or UC are less likely to achieve endoscopic remission than male patients around biological milestones such as menarche, child-bearing years and menopause.

Sub aim 1. To define gender-based differences in biochemical response to biological therapy among patients with active CD or UC

Sub aim 2. To determine if the age at initial diagnosis of CD or UC impacts the effect of gender on endoscopic remission

Aim 2. To define gender-based differences in clinical response to biological therapy among patients with active CD or UC, in a pooled analysis of RCTs
Hypothesis 2. Female patients with CD or UC are less likely to achieve clinical remission compared with male patients around biological milestones such as menarche, child-bearing years and menopause.

Sub aim 2. To determine if gender impacts clinical improvement with TNFalpha inhibitors, defined as decrease in HBI by >=3 points or partial Mayo by >=2 points, but not meeting criteria for remission

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis
Summary-level data meta-analysis using only data from YODA Project
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project

Research Methods

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

This will be a pooled analysis of primary trial data included in YODA on the efficacy of biologics for CD and UC to determine if gender impacts response to therapy.

Inclusion: All phases 2-4 RCTs on the efficacy of infliximab and golimumab (TNF-alpha), and ustekinumab (interleukin-12/23 inhibitor); drugs for which sub-trial data is available through YODA and for which the results are stratified by sex.

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

Primary outcome (Aim 1): Endoscopic remission (CDEIS <3 (CD) or MMES <=1 (UC)
Secondary outcome (Aim 1): Biochemical remission (normalization of CRP or fecal calprotectin)

Primary outcome (Aim 2): HBI <5 (CD) or partial Mayo score <=1 (UC)

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

The main predictor variable will be gender (male, female), which is a categorical variable.

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

Covariates (adjustment variables), to be defined at time of initiation of biologic (T0) unless otherwise specified: drug class, age at initial diagnosis, age at initiation of biologic, BMI, race/ethnicity, smoking history (duration and amount), disease duration, Montreal classification (behavior, location), presence of peri-anal disease (CD), severity at diagnosis, severity at initiation of biologic, prior IBD-related surgery (binary yes/no, and type of surgery), history

of colorectal neoplasia, history of any cancer (other than non-melanomatous skin), prior IBD therapy exposure such as corticosteroids and immunomodulators (type, dose, duration). Medication exposure is defined as at least 30 days of use. These variables were selected as they are known to impact disease severity and response to treatment.

Statistical Analysis Plan:

We will compile summary statistics for the pooled data as well as each study individually, and present both the grouped summary data and stratified by sex. Chi square and Student's t-test will be used to determine significance for categorical and continuous variables, respectively. We will pool the raw primary data of studies meeting inclusion criteria (defined above) and determine study estimates for the total pooled group and stratified by gender. We will perform multivariable analyses and adjust for co-variates that are associated with the outcome of interest with $p < 0.10$. We will pool survival data by using logistic regression. We will test for interactions and effect modifiers such as age, disease severity, prior medications, surgery etc. Lastly, we will perform sensitivity analyses and meta-regression to determine sources of heterogeneity.

There are no prior data on expected magnitude of differences in therapeutic response based on gender. However, we expect that an at least 15% difference in response between genders is would be clinically relevant. Assuming a conservative response rate to biologics of 60%, a sample of 350 patients would be required to detect a clinically meaningful difference.

Project Timeline:

- Submission of proposal to YODA, approval and access: 4-6 weeks
- Data extraction: 8 weeks
- Analysis: 8 weeks
- Manuscript writing: 12 weeks

Dissemination Plan:

We intend to submit our final results and their interpretation as a manuscript to a high-impact journal in IBD and/or Gastroenterology.

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