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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_0.pdf
https://yoda.yale.edu/system/files/yoda_coi_-_wong_0.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

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

Research Proposal

Project Title

Comparative Effectiveness of Vedolizumab vs. Infliximab in Ulcerative Colitis

Narrative Summary:

Vedolizumab and infliximab are two biologic therapies that have demonstrated efficacy in achieving and maintaining remission through several pivotal placebo-controlled trials, including ACT 1, ACT 2, and GEMINI 1. Recently, the VARSITY trial used an active-comparator approach to demonstrate the superiority of vedolizumab to adalimumab among patients with moderate to severe ulcerative colitis. No head-to-head studies have compared vedolziumab and infliximab; thus, further reseach is neededto understand the positioning of vedolizumab as a treatment. This study aims to compare the efficacy of vedolizumab and inflixiximab in biologic-naïve patients with ulcerative colitis.

Scientific Abstract:

Background:
Head-to-head comparisons of vedolizumab and infliximab are needed to better understand the positioning of vedolizumab as a treatment for ulcerative colitis.

Objective:
The primary objective of this study is to compare the efficacy of vedolizumab and infliximab to achieve post-induction (week 6) clinical remission and one year mucosal healing . The secondary objectives of this study include post-induction and/or one year clinical remission, mucosal healing, clinical response, reduction in fecal calprotectin, C-reactive protein, and histologic measures of disease activity.

Study Design:
Data from GEMINI 1 and VARSITY, which is being requested from Vivli, will be pooled to obtain a cohort of biologic-naïve UC patients treated with vedolizumab. Biologic-naïve patients treated with infliximab in ACT 1 and ACT 2 which is being requested from the YODA Project, will be pooled to comprise the infliximab cohort.

Participants:
Biologic-naïve patients from ACT1, ACT 2, GEMINI, and VARSITY with baseline partial and/or total Mayo Scores will be included. Those with missing outcome data will be excluded and a separate intention-to-treat analysis will be conducted.

Main Outcome Measure(s):
Clinical remission at week 6 (partial Mayo Score<2 and rectal bleeding subscore=0), and one year mucosal healing (Mayo endoscopic subscore ?1).

Statistical Analysis:
Logistic regression and propsensity score matching (1:1 basis) will be conducted. Variables with p<0.10 on univariate analyses will be included in multivariate model.

Brief Project Background and Statement of Project Significance:

Ulcerative colitis is an inflammatory bowel disease that affects the large intestine and is characterized by diarrhea, rectal bleeding, abdominal pain, urgency, and tenesmus. (1,2) Patients with severe ulcerative colitis and/or corticosteroid-refractory disease are candidates for biologic monoclonal antibody treatments.

Vedolizumab and infliximab are two biologic therapies that have demonstrated efficacy in achieving and

maintaining remission through several pivotal placebo-controlled trials, including ACT 1 (NCT00036439), ACT 2 (NCT00096655), and GEMINI 1 (NCT00783718).(3,4) Recently, the VARSITY trial used an active-comparator approach to demonstrate the superiority of vedolizumab to adalimumab among patients with moderate to severe ulcerative colitis.(5) However, network meta-analyses have suggested superiority of infliximab over adalimumab as a first-line biologic treatment in UC patients.(6) There are no head-to-head trials comparing vedolizumab and infliximab.

Given the routine use of vedolizumab and infliximab as a treatment for ulcerative colitis, head-to-head comparisons are needed to better understand the positioning of vedolizumab as a treatment for biologic-naïve ulcerative colitis patients.

Specific Aims of the Project:

The proposed study aims to compare the efficacy of vedolizumab and infliximab to achieve post-induction (week 6) clinical remission and one year mucosal healing as determined by the Mayo Score. Other outcomes such as clinical, endoscopic, and histologic improvement in disease activity will be evaluated in planned secondary analyses. We hypothesize that biologic-naïve UC patients treated with vedolizumab have a similar likelihood of achieving clinical remission at post-induction (week 6) and mucosal healing at one year compared to biologic-naïve UC patients treated with infliximab.

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 comparison group

Research Methods

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

Participants must be biologic-naïve and have complete baseline partial and/or total Mayo Scores and complete outcome data available (e.g. in the case of one year mucosal healing, participants must have one year endoscopy data available through the total Mayo Score). A separate intention-to-treat analysis will include those with missing outcome data as non-responders and they will be assumed to not have achieved the outcome of interest.

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

The Mayo Score is a tool that is used to determine ulcerative colitis disease activity and is comprised of four patient-reported and endoscopic parameters: stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment. Each parameter is scored from 0 to 3, with higher scores indicating greater disease severity. The total Mayo Score ranges from 0 to 12, while the partial Mayo Score excludes the endoscopic subscore and thus ranges from 0 to 9. (6) While Mayo Scores have been widely used in clinical trials for ulcerative colitis as primary endpoints, mucosal healing (determined by endoscopy) remains an important target of treatment as well.

The primary outcome of interest is clinical remission at post-induction (week 6), defined as partial Mayo Score < 2 and rectal bleeding subscore of 0, and mucosal healing at one year, defined as endoscopic subscore ? 1 on the Mayo Score.

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

The independent variable is the type of treatment, vedolizumab or infliximab, which will be determined based on the randomization arm assigned to the participant.

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

Univariate analyses will also be conducted to evaluate associations that may exist between covariates (e.g. disease duration, sex, age, disease location) and the outcome of interest. Variables found to have an association ($p<0.10$) will be included in the multivariate model.

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Statistical Analysis Plan:

In GEMINI 1, 746 patients were randomized to vedolizumab, of which 388 were biologic-naïve. In VARSITY, 385 patients were randomized to vedolizumab, of which 305 were biologic-naïve. All patients who received infliximab in ACT 1 (n=243, 121 received 5mg/kg infliximab and 122 received 10mg/kg infliximab) and ACT 2 (n=241, 121 received 5mg/kg infliximab and 120 received 10mg/kg infliximab) were biologic-naïve. Therefore, the eligible study population includes 484 (243 from ACT 1 and 241 from ACT 2) in the infliximab cohort and 693 (388 from GEMINI 1 and 305 from VARSITY) in the vedolizumab cohort. Data from these trials are being requested as common time points were used. Mayo Scores were captured at two common time points of interest (week 6 and one year) in GEMINI 1, VARSITY, ACT 1 and ACT 2.

Patients with missing outcome data (e.g. one year Mayo Score) will be excluded from the primary analysis. A separate intention-to-treat analysis will be conducted where patients with missing data will be assumed to not have achieved the outcomes of interest.

Logistic regression will used to assess the treatment effect on the outcome of interest. Univariate analyses will be conducted to identify associations between covariates and the outcome of interest, and any variables with a p-value < 0.10 will be included in the multivariate model.

In addition, propensity score matching on a one-to-one basis using k-nearest neighbour without replacement will be performed. The propensity score represents the conditional probability of receiving vedolizumab or infliximab, given the observed co-variates.8 The propensity scores will be estimated using a nonparsimonious logistic regression model that will consider baseline covariates. The treatment group will be regressed on these baseline covariates. Subsequently, graphs of the propensity scores for participants treated in both studies will be compared to assess the region of common support. This assesses the propensity score distributions between both groups and identifies the region of common support (overlap).

Continuous variables will be presented as means (and standard deviations [SD] or as medians and interquartile ranges [IQR]), if the data is skewed. Binary variables will be presented as proportions or percentages. Descriptive statistics will be used to summarize baseline demographics, disease characteristics and outcome parameters of included patients. Differences between groups will be compared using the Mann-Whitney U test or chi-squared test. Data will be analyzed using Stata, which is available on the Vivli and YODA Project secure platform.
Software Used:
STATA

Project Timeline:

Date to Start Project: November – December 2020.
Date to Complete Analysis: December 2020– January 2021.
Date to Draft Manuscript: January – February 2021.
Date to Submit Manuscript: February – March 2021.

Dissemination Plan:

Anticipated products include abstracts and posters, which may be presented at scientific meetings such as Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn’s and Colitis Organization. A manuscript is expected to result from this study and will be submitted to peer-reviewed journals such as Gastroenterology, American Journal of Gastroenterology, and Clinical Gastroenterology and Hepatology. All products resulting from this research project, which may include abstracts, manuscripts, posters, and slide decks will be shared with Vivli and the YODA Project at least 30 days prior to the time of submission or public disclosure. Target audiences include clinicians and researchers with an interest in inflammatory bowel disease.

Bibliography:

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Danese S, Fox I. Vedolizumab as induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine. 2013 Aug 22;369(8):699-710.
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6. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta?analysis: first?and second?line pharmacotherapy for moderate?severe ulcerative colitis. Alimentary pharmacology & therapeutics. 2018 Jan;47(2):162-75.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/supplemental_text_for_2020-4457.pdf