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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_2022-4882_-_wong.pdf
https://yoda.yale.edu/system/files/yoda_coi_2022-4882_-_narula.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. 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

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 Steroid Weaning Regimens on Outcomes in Clinical Trials of Ulcerative Colitis

Narrative Summary:

Ulcerative colitis (UC) is a type of inflammatory bowel disease that affects the large intestine. Patients with UC experience symptoms such as diarrhea, rectal bleeding, abdominal pain, and urgency [1, 2]. Patients with severe disease or those who lack response to corticosteroids are candidates for biologic and small molecule treatments. Patients enrolled in trials often require corticosteroids at the time of entry to manage their symptoms. Corticosteroid use can reduce symptoms that indicate active disease and therefore its use can impact outcomes in clinical trials. It remains unclear what impact steroid tapering protocols have on trial outcomes.

Scientific Abstract:

Background
Ulcerative colitis (UC) is a type of inflammatory bowel disease that affects the large intestine. Patients with UC experience symptoms such as diarrhea, rectal bleeding, abdominal pain, and urgency [1, 2]. Patients with severe disease or those who lack response to corticosteroids are candidates for biologic and small molecule treatments. Patients enrolled in trials often require corticosteroids at the time of entry to manage their symptoms. Corticosteroid use can reduce symptoms that indicate active disease and therefore its use can impact outcomes in clinical trials. However, protocols for managing steroids during trials vary. In the VARSITY trial, steroid tapering was adaptive and up to the physician’s discretion. Other trials implement a fixed steroid tapering protocol that must be strictly adhered to. Although trials must transparently document steroid tapering protocols, there remains a lack of consistent or standardized tapering definitions across trials. Therefore, it remains unclear what impact steroid tapering protocols have on trial outcomes.

Objective
The primary objective of this study is to evaluate whether differences in steroid tapering regimen between clinical trials influenced one-year corticosteroid-free CR among patients with steroid use at baseline.

Study Design
Patient-level data from several clinical trials of UC will be aggregated to evaluate the impact of steroid tapering regimens on the outcome of one-year corticosteroid-free CR. Patients will be grouped based on treatment exposure.

Participants
Patients who were treated throughout the trial with active therapy (VARSITY, ACT 1, ACT 2, and ULTRA 2) will be included in analyses evaluating steroid tapering regimen influenced corticosteroid-free CR at one-year. Patients who responded to induction therapy and were re-randomized (PURSUIT, GEMINI 1, and OCTAVE) during maintenance will be further stratified based on treatment (active therapy or placebo).

Main Outcome
The primary outcome of interest is one-year corticosteroid-free CR, defined as absence of corticosteroid use at the time of assessment with a total Mayo Score ≤2, with no subscore >1.

Statistical Analysis
Univariate analyses will be conducted to identify covariates with an association with the outcome of interest, and

any covariate with a p-value < 0.10 will be included in the multivariate model. Logistic regression and will be used to assess the treatment effect on the outcome of interest.

Brief Project Background and Statement of Project Significance:

Ulcerative colitis (UC) is a type of inflammatory bowel disease that affects the large intestine. Patients with UC experience symptoms such as diarrhea, rectal bleeding, abdominal pain, and urgency [1, 2]. Patients with severe disease or those who lack response to corticosteroids are candidates for biologic and small molecule treatments. Vedolizumab and adalimumab are two biologic therapies that have been approved for the treatment of moderate-to-severe UC on the strength of several placebo-controlled trials demonstrating efficacy and ability to maintain response, including ACT 1 (NCT00036439) and ACT 2 (NCT00096655), ULTRA 2 (NCT00408629), and GEMINI 1 (NCT00783718) [3-6]. Recently, the VARSITY trial (NCT02497469) was a head-to-head trial that demonstrated the superiority of vedolizumab to adalimumab in moderate-to-severe UC [7]. Golimumab is another biologic therapy that demonstrated efficacy in PURSUIT (NCT00488631), which was a placebo-controlled trial [8]. In addition to biologic therapies, small molecule therapies are a treatment option that has recently emerged. Tofacitinib was recently approved on the strength of the placebo-controlled OCTAVE trials (NCT01465763, NCT01458951, and NCT01458574)[9].
The Mayo Score is a tool that is used in clinical practice and trials to determine the severity of UC and is comprised of several patient-reported and endoscopic sub-scores, including stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment. Each subscore 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. The Mayo Score is widely used in clinical trials for UC to evaluate primary endpoints, such as clinical remission (CR). Corticosteroid-free CR is also an important endpoint and is often included as part of co-primary or secondary endpoints. Patients enrolled in trials often require corticosteroids at the time of entry to manage their symptoms. Corticosteroid use can reduce symptoms that indicate active disease and therefore its use can impact outcomes in clinical trials. However, protocols for managing steroids during trials vary. In the VARSITY trial, steroid tapering was adaptive and up to the physician's discretion. Other trials implement a fixed steroid tapering protocol that must be strictly adhered to. Although trials must transparently document steroid tapering protocols, there remains a lack of consistent or standardized tapering definitions across trials. Therefore, it remains unclear what impact steroid tapering protocols have on trial outcomes.
The primary objective of this study is to evaluate whether differences in steroid tapering regimen between clinical trials influenced one-year corticosteroid-free CR among patients with steroid use at baseline. The secondary objectives of this study include CR at one-year and corticosteroid-free CR among all patients, regardless of baseline steroid use.

Specific Aims of the Project:

The proposed study aims to evaluate whether differences in steroid tapering regimen between clinical trials influenced one-year corticosteroid-free CR. We hypothesize among UC patients with baseline steroid use, adaptive steroid tapering regimens influences the rate of corticosteroid-free CR.

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:

Patient-level data from ULTRA 2, GEMINI 1, VARSITY, and OCTAVE is being requested from Vivli. Patient-level data from ACT 1, ACT 2, and PURSUIT is being requested from the YODA Project. Patients will be grouped based on treatment exposure. Patients who were treated throughout the trial with active therapy (VARSITY, ACT 1, ACT 2, and ULTRA 2) will be included in analyses evaluating steroid tapering regimen influenced corticosteroid-free CR at one-year. Patients who responded to induction therapy and were re-randomized (PURSUIT, GEMINI 1, and OCTAVE) during maintenance will be further stratified based on treatment (active therapy or placebo).

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

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The primary outcome of interest is one-year corticosteroid-free CR, defined as absence of corticosteroid use at the time of assessment with a total Mayo Score ≤2, with no subscore >1. This is the standard outcome definition of corticosteroid-free remission that is used by clinical trials of ulcerative colitis. This time point was chosen as it was a common timepoint between all trials. Secondary outcomes of interest include corticosteroid-free CR, defined more stringently as absence of corticosteroid use at least 4 weeks prior to the time of assessment, one-year CR, and clinical response (defined as partial Mayo Score reduction (i.e. stool frequency, rectal bleeding, and physician's global assessment) of ≥2 and ≥25% from baseline, with a decrease in rectal bleeding subscore of ≥1). Sensitivity analyses are planned to evaluate outcomes stratified by treatment and/or other covariates, if differences between treatments and/or other covariates are observed in the primary analysis.

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

The independent variable is the type of steroid tapering regimen (fixed vs. adaptive) that a participant adhered to. Participants in the VARSITY trial were subjected to an adaptive regimen while all other trials in this analysis used a fixed regimen.

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

Three other variables of interest will be evaluated in this analysis, including baseline steroid dose, time point of steroid taper starting (week 8 or week 5-6), and steroid dose at which the switched to 2.5mg occurred (at 10mg or 20mg). Univariate analyses will also be conducted to evaluate associations that may exist between covariates (e.g. sex, age, disease duration, disease location, treatment) and the outcome of interest. Variables found to have an association ($p<0.10$) will be included in the multivariate model.

Statistical Analysis Plan:

In GEMINI 1, OCTAVE, and PURSUIT, patients who received active therapy during the induction phase were re-randomized to receive placebo or continue active therapy during maintenance based on clinical response. Data from these trials will be aggregated to form two cohorts: 1) re-randomized to active therapy and 2) re-randomized to placebo. In ACT 1, ACT 2, ULTRA 2 and VARSITY, patients were randomized to active therapy or placebo for the entire duration of the trial. Data from these trials will be aggregated to form a cohort of participants who were treated-straight-through with active therapy. One-year was a common timepoint across all trials. An indicator variable will be used to distinguish between trials.

GEMINI 1 and ULTRA 2 had similar steroid weaning protocols, with an incremental decrease by 5mg every week starting at week 6 until 10mg, with subsequent decreases of 2.5mg per week. Similarly, ACT 1, ACT 2, and OCTAVE had similar tapering regimens (decrease by 5mg every week starting at week 8 (week 5 for OCTAVE) followed by a decrease of 2.5mg per week by 20mg). The maximum steroid doses allowed varied between trials but ranged from 20-40mg. In VARSITY, steroid tapering began at week 6 but was adaptive at the discretion of the physician, with the ability to increase steroid dose if the first attempt at weaning was unsuccessful.

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

Descriptive statistics will be calculated to compare the rate of achievement of outcomes between groups. 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.

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 secure platform.
Software Used:
STATA

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Project Timeline:

Start date - May 1, 2022
Analysis completion date - September 1, 2022
Date manuscript draft - October 1, 2022
Date results reported back to the YODA Project - March 1, 2023

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 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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7. Sands, B.E., et al., Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med, 2019. 381(13): p. 1215-1226.
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9. Sandborn, W.J., et al., Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med, 2017. 376(18): p. 1723-1736.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/extended_research_protocol_for_yoda_0.docx