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Requires Data Access? Yes

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Requires Data Access? Yes

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/wp-content/uploads/2024/08/Neeraj-Narula-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2024/08/Hasan-Hamam-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2024/08/Emily-Wong-COI.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
4. 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

Impact of Concomitant Steroid Use on Adverse Events in Ulcerative Colitis Clinical Trials

Narrative Summary:

Ulcerative colitis (UC) is a chronic condition causing inflammation in the colon, leading to symptoms like diarrhea, bleeding, and pain. Treatment often involves biologics (e.g., infliximab, vedolizumab) and small molecules (e.g., tofacitinib), especially when corticosteroids alone aren't effective. Corticosteroids help with short-term symptoms but can cause serious long-term side effects like infections and cancer. This study will analyze data from several clinical trials to see if continuing steroid use alongside biologics increases these risks. Adverse event rates will be compared between patients who used steroids and those who stopped or never used them during the trials.

Scientific Abstract:

Background:
Ulcerative colitis (UC) is a chronic inflammatory bowel disease causing symptoms like diarrhea, rectal bleeding, and abdominal pain. While biologics and small molecules are advanced treatments, corticosteroids are still used for acute relief. However, long-term steroid use is linked to serious adverse events (AEs).

Objective:
To determine if ongoing corticosteroid use during maintenance therapy in UC patients increases the rate of adverse events compared to those who stop or never use corticosteroids.

Study Design:
Post-hoc analysis of participant-level data from multiple placebo-controlled clinical trials (GEMINI 1, ULTRA 2, OCTAVE-1, VARSITY, ACT 1, and PURSUIT).

Participants:
Patients categorized by corticosteroid use at baseline and during maintenance therapy, including those who continued, stopped, or never used corticosteroids.

Primary and Secondary Outcome Measure(s):
Primary Outcome: Incidence of adverse events in baseline corticosteroid users vs. non-users.
Secondary Outcome: Incidence of adverse events among baseline corticosteroid users who achieved steroid-free remission at one year vs. those who did not.

Statistical Analysis:
Univariate analyses will identify covariates for adverse events, with significant variables (p < 0.05) included in a multivariate model. Logistic regression will evaluate corticosteroid impact on AEs.

Continuous variables will be reported as means/medians, and dichotomous variables as proportions/percentages. Statistical significance is set at p < 0.05. Data analysis will use Stata IC 15.0 on the Vivli secure platform.

Brief Project Background and Statement of Project Significance:

Ulcerative colitis (UC) is a chronic, bowel disease that causes inflammation in the colon, the part of the digestive system that stores and processes waste. Symptoms of UC involve diarrhea, bleeding from the rectum, and stomach pain. For some people, these symptoms are so severe that they need stronger treatments. These treatments include biologic drugs and small molecule therapies.

Biologics are a type of drug made from living cells and can help reduce inflammation. Examples are infliximab, vedolizumab, and adalimumab, and clinical trials have shown they can be very effective. Small molecules such as tofacitinib are another option. Both biologics and small molecules have changed the way doctors treat UC.

Another common treatment is corticosteroids, which can help manage UC flare-ups, but they have side effects if used for a long time. These side effects can include infections, cancer, and other serious problems. Researchers are concerned about what happens when corticosteroids are used along with biologics or other immune-suppressing drugs. Current literature lacks direct comparisons on whether people with UC who use corticosteroids along with biologic treatments have more side effects compared to those who don't use corticosteroids. This study aims to fill this gap by evaluating whether ongoing corticosteroid use during maintenance therapy correlates with higher Adverse Event (AE) rates compared to patients who cease corticosteroids or never used them.

The primary objective of this study is to evaluate whether patients who continue to use corticosteroids during maintenance within clinical trials have a higher rate of AEs compared to those who stopped corticosteroids and those not using steroids.
To do this, we are requesting detailed patient information from several clinical trials: ULTRA 2, GEMINI 1, VARSITY, and OCTAVE-1 from Vivli, and ACT 1 and PURSUIT from the YODA Project.

Specific Aims of the Project:

This study aims to assess the impact of corticosteroid use on AE rates in UC patients receiving biologic therapy. We hypothesize that UC patients continuing corticosteroids during maintenance therapy experience higher AE rates compared to those who were not using steroids at study entry, or those who discontinue corticosteroids successfully during the trial.

Study Design:

Meta-analysis (analysis of multiple trials together)

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 Source:
The following studies will be used for data analysis: GEMINI 1 (NCT00783718), ULTRA 2 (NCT00408629), OCTAVE-1 (NCT01465763), VARSITY (NCT02497469), ACT 1 (NCT00036439), and PURSUIT (NCT00488631). The studies will be obtained from the YODA and VIVLI platforms. Data analysis will be conducted using STATA on the VIVLI secure platform.

Inclusion Criteria:
- Patients diagnosed with ulcerative colitis.
- Availability of complete data on corticosteroid use and adverse events.

Exclusion Criteria:
- Patients with incomplete data on corticosteroid use or adverse events.

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

The primary outcome of interest is comparing the incidence of AE between patients using corticosteroids at baseline vs non-steroid users. Then, among baseline corticosteroid users, incidence of AE will be compared between those who achieved steroid-free clinical remission at one-year vs those who were not able to either wean off corticosteroids or achieve clinical remission at one-year assessment. Steroid-free clinical remission is defined as the absence of corticosteroid use at the one-year assessment with a total Mayo Score of <=2 with no subscore > 1.

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

The independent variable is the corticosteroid use at baseline.

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

Demographics (age, sex, race, weight, etc.), disease characteristics (total Mayo score and endoscopic Mayo score), previous therapies (immunomodulators and TNF inhibitors), AE severity (mild, moderate, and severe), and types of AEs (infection, colitis exacerbation, headache, upper respiratory tract infection, nasopharyngitis, anemia, and arthralgia). Univariate analyses will also be conducted to evaluate associations that may exist between covariates (e.g. sex, age, disease duration, etc.) and the outcome of interest. Variables found to have an association (p<0.05) will be included in the multivariate model.

Statistical Analysis Plan:

This is a post-hoc analysis of data from five clinical trial programs. Descriptive statistics will be provided for each comparison. Logistic regression will be used to assess the corticosteroids' 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 < 0.05 will be included in the multivariate model.

Continuous variables will be presented as means [and standard deviations (SD)] or medians [and interquartile ranges (IQR)]. Dichotomous variables will be summarized as proportions or percentages. The patient pool will be grouped into those who used corticosteroids at baseline and those who did not. Then, among those who used corticosteroids at baseline, these participants will be further categorized into those who achieved steroid-free clinical remission at one year and those who were not able to wean off steroids or achieve steroid-free clinical remission at one year. The AEs will be grouped based on severity as determined by local investigators and reported within the clinical trial: mild, moderate, and severe. The most frequent AEs from each group will also be noted. Statistical significance is chosen to be at p < 0.05. Data will be analyzed using Stata IC 15.0, which is available on the Vivli secure platform.

In this analysis, any missing data will be excluded. This decision is based on the aim to ensure the integrity and accuracy of the findings. By excluding missing data, we acknowledge the potential limitation that the sample size may be reduced, but this approach prevents the introduction of bias that could occur through imputation methods.

Software Used:

STATA

Project Timeline:

Target Analysis Start Date: 9/1/24
Estimated Analysis Completion Date: 9/1/25

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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