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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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2016/01/yoda_coi_cma.pdf
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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. [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](link)
2. [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](link)
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](link)
4. [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](link)
5. [NCT01863771 - CNTO148UCO3001 - A Safety and Effectiveness Study of Golimumab in Japanese Patients With Moderately to Severely Active Ulcerative Colitis](link)

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

Research Proposal

Project Title

Responsiveness of the UC-100 Score in Patients with Moderately to Severely Active Ulcerative Colitis

Narrative Summary:

Ulcerative colitis (UC) is a disease that causes swelling and pain, most commonly in the large bowel and rectum. While there is no cure for UC, there are several approved drugs to help control the symptoms and there is a need for other effective and safe drugs. In studies for UC, disease activity is often measured using the Mayo Clinic Score (MCS) (1), but other measures, including the partial MCS, and Robarts Histopathology Index (RHI) also exist. Early research results suggest that a measure of UC disease activity called the UC-100 (2) is more sensitive than the MCS or other existing measures. The aim of the study is to confirm whether this is true.

Scientific Abstract:

Background: Ulcerative colitis (UC) is a chronic,debilitating disease resulting from inflammation in the digestive tract, most notably the large bowel and rectum. Several drugs are currently approved for the treatment of UC but safe and effective alternatives are needed. The effectiveness of a drug is evaluated in controlled clinical trials. In clinical trials for UC, disease activity is primarily measured using the Mayo Clinic Score (MCS).(1) We previously developed a more sensitive measure of disease activity in UC, called the UC-100 score.(2) Although preliminary results suggest that the UC-100 is a more sensitive measure of UC disease activity than the MCS, these results need to be verified in

other UC trial datasets.

Objective: The primary objective of this study is to compare the responsiveness of the UC-100 to the MCS, adapted 9-point MCS, pMCS, and RHI.

Study Design: This study will use available clinical, endoscopic, and histologic data from completed phase 2 and phase 3 induction trials. Responsiveness of the UC-100 will be compared to the MCS, adapted 9-point MCS, partial MCS (pMCS), and Robarts Histopathology Index (RHI).

Participants: Data will only be used from subjects with available MCS subscores (and individual subscores), RHI scores (or Geboes score with individual subcomponent scores), and fecal calprotectin (FCP) concentration at both baseline and end of induction.

Main Outcome Measure(s): The following variables will be collected at both baseline visit and end of induction visit: change of FCP concentration, change of C-reactive protein, change in MCS and individual subscores (PGA, MES, RB and SF subscores), change in RHI score or individual Geboes subcomponent scores. For trials that used the Geboes score, the RHI score will be calculated from the Geboes subcomponent scores.

Statistical Analysis: Statistical analyses will only be performed on the data received, using a complete-case analysis basis. No methods for imputation of missing data will be used. We will evaluate the responsiveness of the UC-100, the MCS, adapted 9-point MCS, pMCS, and RHI, to determine which index is most responsive. Responsiveness will be evaluated in two ways: longitudinal validity and treatment effect size.

Brief Project Background and Statement of Project Significance:

UC is a chronic, debilitating disease resulting from inflammation in the digestive tract, most notably the large bowel and rectum. Characterized by diarrhea and bloody stools, several drugs are currently approved for the treatment of UC. Unfortunately, any one drug is not effective in every patient and some drugs lose their effectiveness over time. Therefore, safe and effective alternatives are needed. The effectiveness of a drug is evaluated in controlled clinical trials, where some patients receive the drug while other patients receive an inactive placebo. In clinical trials for UC, disease activity is primarily measured using the MCS, which adds up scores for the stool frequency, rectal bleeding, visible signs of disease activity at endoscopy, and a general rating of disease severity provided by a physician.[1] In a clinical trial, if the number of trial participants below a predefined MCS threshold representing disease remission is statistically greater in the drug treatment group than the placebo group then the drug is considered effective. This approach has led to the approval of several drugs for the treatment of UC over the years; however, this approach requires a large number of trial participants to determine whether a drug is effective and is relatively expensive, making this approach neither efficient nor cost-effective.

We previously developed a more sensitive measure of disease activity in UC, called the UC-100 score.[2] The UC-100 is calculated from the rectal bleeding, stool frequency, and endoscopic subscores of the MCS, and a measure of microscopic disease activity, the RHI score. During development of the UC-100, it was found to be more sensitive for detecting changes in UC disease activity than the MCS. This is important because the greater sensitivity could increase the likelihood of detecting a drug effect in clinical trials, decrease the number of clinical trial participants needed to detect an effect, and decrease drug development costs. Although preliminary results suggest that the UC-100 is a more sensitive measure of UC disease activity than the MCS, these results need to be verified in other UC trial datasets. The aim of this study is to compare the UC-100 to other measures (MCS, partial MCS, adapted 9-point MCS, and RHI) in terms of its ability to detect changes in UC disease activity. Using data from previously completed clinical trials that evaluated the efficacy of biologic or small molecule drugs in moderate to severe UC with the MCS and RHI (or Geboes Score), we will compare the ability of disease activity measures to detect changes in disease activity. If this study finds that the UC-100 is a more sensitive measure of UC disease activity than other measures across several clinical trial datasets, this could significantly impact the design of future clinical trials. By enabling the detection of effects that could otherwise be missed with less sensitive measures, the UC-100 could decrease the likelihood of mislabeling a potentially effective drug as ineffective during the early drug development process. This could lead to the approval of more safe and effective drugs for UC.

Specific Aims of the Project:

This study's primary objective is to evaluate the responsiveness of the UC-100 to the MCS, adapted 9-point MCS, pMCS, and RHI. This primary objective will be achieved by:
1. Comparing the Spearman?s correlation coefficients between the change of UC-100 score, the MCS, adapted 9-point MCS, pMCS, and RHI, with the change of FC and CRP from baseline to the end of induction.
2. Comparing the treatment effect sizes for the UC-100 score, the MCS, adapted 9-point MCS, pMCS, and RHI.

Research Methods

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

Eligible trials include completed phase 2 and 3 induction trials that investigated the efficacy of either a biologic or small molecule drug in subjects with moderately to severely UC. In addition, selected RCTs will need to fulfill the following eligibility criteria:
1. The investigational therapeutic was shown to be significantly more effective than placebo in achieving the primary endpoint.
2. Assessed clinical disease activity with the MCS (with individual MCS subscores available), using the modified definition of ?no friability? for an MES = 1 as recommended by USFDA Guidance.(3)
3. Assessed histologic disease activity with either the RHI and/or the Geboes score. If the Geboes score was used, individual subcomponent scores will need to be available for calculating the RHI score.
4. FCP concentration was measured at baseline and end of induction.
Data will only be used from subjects with available MCS subscores, RHI scores and FCP concentration at both baseline and end of induction. Other studies will be from Vivli and analysis will be conducting in Vivli. Rest of the studies are; NCT00385736, NCT00408629, NCT00853099, NCT00783718 and NCT02039505.

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

The following variables will be collected at both baseline visit and end of induction visit:
1. Change of fecal calprotectin (FC) concentration (mean, standard deviation (SD), median, interquartile range (IQR))
2. Change of C-reactive protein (mean, standard deviation (SD), median, interquartile range (IQR))
3. Change in Mayo Clinic Score (MCS) and individual subscores (PGA, MES, RB and SF subscores) (median, IQR)
4. Change in RHI score (mean, median, IQR) or individual Geboes subcomponent scores (median, IQR). For trials that used the Geboes score, the RHI score will be calculated from the Geboes subcomponent scores.

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

The followings will be included as independent variables:
1. Change of FC concentration
2. Change of C-reactive protein
3. Change of Mayo Clinic Score (MCS)
4. Change of adapted 9-point MCS, which include stool frequency, rectal bleeding, and endoscopic appearance three subscores of MCS.
5. Change of partial Mayo Clinic Score (pMCS), which include stool frequency, rectal bleeding and physician assessment three subscores of MCS.
6. Change of RHI. If only Geboes Score available, RHI score will be calculated from subcomponent score of Geboes score, including chronic inflammatory, lamina propria neutrophils, neutrophils in epithelium, and erosion or ulceration. The erosion or ulceration will be re-defined as 0=No erosion, ulceration, or granulation tissue; 1=Recovering epithelium + adjacent inflammation;1=Probable

erosion-focally stripped; 2=Unequivocal erosion; 3=Ulcer or granulation tissue. RHI =1*chronic inflammatory+2* lamina propria neutrophils +3* neutrophils in epithelium + 5* erosion or ulceration.
7. Change of UC-100 score, which is calculated as (1 + 16 Mayo Clinic stool frequency subscore [0 to 3] + 6 Mayo Clinic endoscopic subscore [0 to 3] + 1 RHI [0 to 33])

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

The following data will be collected at the Baseline visit:
1. Age at enrollment (months)
2. Sex
3. Disease duration at baseline (months)
4. Previous exposure to a biologic (yes; no). If yes, number of biologics exposed to (if available).
5. Previous failure or intolerance to a biologic (yes; no). If yes, number of biologics failed or intolerant to (if available).
The following data will be collected, if available:
1. Previous exposure to conventional UC therapies (i.e., 5-aminosalicylic acid (5-ASA) drugs, immunomodulators [azathioprine (AZA), methotrexate (MTX), 6-mercaptopurine (6-MP)], oral corticosteroids, calcineurin inhibitors [cyclosporine, tacrolimus]) (yes; no).
2. Previous failure or intolerance to conventional UC therapies (i.e., 5-ASA drugs, immunomodulators [AZA, MTX, 6-MP], oral corticosteroids, calcineurin inhibitors [cyclosporine, tacrolimus]) (yes; no).
3. CRP concentration

Statistical Analysis Plan:

This study is a retrospective analysis of existing clinical, endoscopic, and histologic data from completed phase 2 and phase 3 induction trials where an investigational biologic or small molecule drug was shown to be more effective than placebo for the treatment of moderately to severely active UC. Subject-level demographics, disease characteristics, and clinical data at baseline and inflammatory biomarker concentrations, MCS, MCS subscores, and Geboes and/or RHI scores at baseline and end of induction will be collected from trial databases.
Statistical analyses will only be performed on the data received, using a complete-case analysis basis. No methods for imputation of missing data will be used.
We will evaluate the responsiveness of the UC-100, the MCS, adapted 9-point MCS, partial MCS (pMCS), and RHI, to determine which index is most responsive. Responsiveness will be evaluated in two ways: longitudinal validity and treatment effect size.
Summary statistics for demographic and baseline characteristics will be calculated and presented. These will include age, disease duration, and sex, depending on availability.
The longitudinal validity will be assessed by determining the correlation between changes in the UC-100 score, MCS, adapted 9-point MCS, pMCS, and RHI and changes in fecal calprotectin (FC) and C-reactive protein (CRP) from baseline to the end of induction. The correlations will be measured using Spearman?s correlation (depending on the distribution of the data), with the associated 95% confidence intervals (CI) calculated using Fisher?s z-transformation. The Cohen benchmarks, where the small, medium, and large effects correspond to the correlations of 0.1, 0.3, and 0.5, will be applied to interpret the strength of correlation. Parallel line plots will be used to depict baseline, follow-up, and changes in scores.
For assessing the treatment effect size of the UC-100 score, MCS, adapted 9-point MCS, pMCS, and RHI, the criteria for meaningful change will be determined by the treatment assignment, with the active drug group in each trial considered ?changed? and the placebo group considered ?unchanged?. Treatment effect sizes will be assessed by two approaches. First, assuming that the indices at the end of induction are all normally distributed, the extent of responsiveness will be qualified using the standardized mean difference between the changed and the unchanged groups. The standardized mean difference is defined as the mean changes in the induction phase divided by the pooled estimate of standard deviation for the induction phase changes. Associated 95% CI will be calculated using the exact method.5 Interpretation of standardized mean difference will be based on Cohen?s benchmarks of .2, .5, and .8 suggesting ?small?, ?moderate?, and ?large? effect sizes respectively.
The second approach uses the non-parametric estimate of the probability to assess the treatment

effect size, equal to the area under the receiver operating characteristic (ROC) curve. This approach could help to qualify the ability of the indices to discriminate subjects with and without meaningful changes and doesn?t need any assumption about the indices. Associated 95% CI for the area under the ROC curve will be obtained based on the log-odds transformation. These estimates will be interpreted according to the benchmark of 0.56, 0.64, and 0.71 correspond to ?small?, ?medium?, and ?large? respectively. The difference of the estimate of the area under the ROC curve between the UC-100 score and the other 4 indices and the associated 95% CI will be presented. The test of whether the difference is equal to zero will be performed using Fisher?s z-transformation with a simple variance estimator.

To combine the results from different platforms the estimates from all studies will be pooled as conventional meta-analysis using Two-stage meta-analyses for both the treatment effect sizes and the correlation.

Project Timeline:

31 Jan 2022 ? 31 Dec 2024
- Project start date: 31 Jan 2022
- Analysis completion date: 1 Jul 2023
- Abstract & Manuscript drafted: 1 Nov 2023
- Abstract submitted to congress: 31 Dec 2023
- Manuscript submitted for publication: 1 Apr 2024
- Results reported back to the YODA project: 1 Oct 2024
- Project completion date: 31 Dec 2024

Dissemination Plan:

We anticipate that the analysis will result in a manuscript in a clinical gastroenterology journal, we also anticipate the sharing of the resulting information through presentation at relevant international conferences (e.g., Digestive Disease Week, and the European Crohn?s and Colitis Organization Congress). The results from this study will have several stakeholders. The immediate target audience are those involved in designing clinical trials (primarily researchers, investigators, and industry).

Bibliography:

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2. JAIRATH, V., JEYARAJAH, J., ZOU, G., PARKER, C. E., OLSON, A., KHANNA, R., D'HAENS, G. R., SANDBORN, W. J. & FEAGAN, B. G. 2019. A composite disease activity index for early drug development in ulcerative colitis: development and validation of the UC-100 score. Lancet Gastroenterol Hepatol, 4, 63-70.
3. US Food and Drug Administration. Ulcerative colitis: clinical trial endpoints. Guidance for industry (draft guidance)2016 March 15, 2017. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformat....