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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/2023/11/YODA_VOI_VJairath.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. 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. 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
4. 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
5. 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)
6. 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)
7. 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

8. 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
9. 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
10. NCT01863771 - CNTO148UCO3001 - A Safety and Effectiveness Study of Golimumab in Japanese Patients With Moderately to Severely Active Ulcerative Colitis
11. 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

Determining Endoscopic Treatment Response in Ulcerative Colitis and Crohn's Disease using the Win Probability Approach

Narrative Summary:

The MES and SES-CD are ordinal scores (meaning that it consists of different levels, but that the difference between levels is not the same, i.e., the difference between MES=0 and MES=1 is not necessarily the same as between MES=1 and MES=2). Therefore, analyzing this data by dichotomizing it into yes/no outcomes, or treating this data as a continuous scale (meaning the differences between each level are the same), is not true to the nature of the information that is being analyzed.
Appropriate statistical methods to managing ordinal data have been recently developed by our group (1). We propose using the win probability (WinP), which is defined as the probability that a treated participant would have a better score than (or win over) a control participant, to analyze endoscopy data from UC and CD trials. Specifically, we will use the win probability to compare the existing advanced treatments for IBD, including tumor necrosis factor antagonists, vedolizumab, ustekinumab, tofacitinib, filgotinib, and ozanimod. The results of this proposal will provide a direct answer to the question most relevant for patients and physicians: what is the chance that a patient will do better if given the treatment?

Scientific Abstract:

Background:
Endoscopic evaluation is a critical component of assessing disease activity in patients with UC and CD. The Mayo Endoscopic Subscore (MES) is the most commonly used instrument to measure endoscopic activity in UC, and is an ordinal, 4-point score (ranging from 0 [normal] to 3 [severe]). The Simple Endoscopic Score for Crohn’s Disease (SES-CD) is the most commonly used instrument to measure endoscopic activity in CD, and similarly, consists of multiple component items (ulcer presence and size, ulcerated and affected area, presence of stenosis) across multiple bowel segments. While historically, clinical trials of advanced therapies, including biologic agents and oral small molecules, have analyzed endoscopic data by dichotomizing into binary endoscopic response/remission endpoints or by comparing mean changes in MES/SES-CD (treating the data as

continuous), both approaches are suboptimal, not true to the nature of endoscopic data, and preclude accurate comparisons of relative endoscopic efficacy.

Objective:
We propose to compare existing advanced treatments for UC and CD for improving endoscopic disease activity, as expressed using the ordinal win probability (WinP).

Study Design:
This is a post-hoc analysis of phase 3 placebo-controlled trials of infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib, filgotinib, and ozanimod using data available in VIVLI. We propose recalculating endoscopic efficacy at the end of induction and at the end of maintenance in each respective trial, using the WinP. The WinP is calculated using individual patient endoscopy data to estimate the probability that a patient receiving active treatment will have an endoscopic response compared to a patient receiving placebo. We will then conduct a meta-analysis of WinP, comparing different classes of biologic/small molecule intervention, stratified by disease type. The methods for meta-analysis of WinP have also been developed by our group (2).

Participants:
All participants from phase 3 placebo-controlled randomized trials for advanced therapies for moderate-to-severely active UC or CD, who have undergone endoscopic evaluation will be included.

Primary and Secondary Outcome Measures:
The primary outcome measure will be the WinP, as calculated above for each therapy.

Statistical Analysis:
Point estimate and 95% confidence interval for a WinP entails two steps. Specifically, MES and SES-CD scores need to be converted to “win fractions” (with values ranging from 0 to 1), followed by applying conventional methods such as t-test or analysis of covariance (ANCOVA) for continuous outcomes.
Suppose we have n1 patients in the treatment group and n0 patients in the control group. Win fractions are obtained as follows:
1) Start with patient number 1 in the treatment group. We will compare the MES/SES-CD score of this patient with every patient in the control group, one at a time, with all n0 patients. Each time we count a ‘win’ (1) if the score of this patient (n1) is better than the control patient, ‘tie’ (0.5) if they have the same score, or ‘loss’ (0) if the patient had a worse score than the control patient. The win fraction is the calculated as the sum of all these scores, divided by n0 to calculate the win fraction.
2) We then use the same approach to get the win fraction for all n1 patients.
3) We then move to patient 1 in the control group. We will compare this patient with every patient in the treatment group, one at a time with all n1 patients in the treatment group. Each time again, we count a ‘win’ (1), ‘tie’ (0.5), or ‘loss’ (0) by comparing the MES/SES-CD score of the control patient with each patient in the treatment group. We sum up these win scores and divide by n1 to obtain the win fraction for this patent.
4) We move to the second, third, etc., patient in the control group until we get the win fraction for every patient in the control group.
This process can be simplified by ranks of the raw scores, as shown elsewhere (1, 2). Please refer to these articles for details and justifications, as well as the validity of the methods. For meta-analysis, the estimated WinP will be used for pooling using both fixed effect model and random effect models (1, 2).

Brief Project Background and Statement of Project Significance:

The Mayo endoscopic subscore (MES) is the gold standard instrument used in ulcerative colitis (UC) randomized controlled trials (RCTs) (3). It is a 4-point ordinal score, ranging from 0 (normal) to 3 (severe). In Crohn’s disease (CD), the Simple Endoscopic Score for Crohn’s Disease (SES-CD) is the most commonly used instrument to evaluate endoscopic activity and is comprised of ordinal evaluations of ulcer presence/size, ulcerated surface area, affected surface area, and stenosis, scored across 5 bowel segments (ileum, right colon, transverse colon, left colon, and rectum) (4). Endoscopic data in RCTs are generally analyzed by 1) dichotomizing the outcome to endoscopic

improvement (MES=0/1 or 50% reduction in SES-CD) or remission (MES=0, SES-CD < 4 but variable thresholds used in the literature) (5, 6) and comparing the proportions between groups; or 2) evaluating the difference in the mean change scores between groups. Both approaches are suboptimal. Dichotomizing results in a loss of power and efficiency for detecting treatment effects because much of the endoscopic data are discarded. Analyzing difference in mean changes incorrectly assumes the data are continuous rather than ordinal, and invariably leads to challenges in interpretation because non-integer values of the MES/SES-CD have no defined meaning. Historically, the Wilcoxon-Mann-Whitney (WMW) test has been used to compare the distribution of ordinal data (e.g., MES/SES-CD scores) to obtain a p-value, without providing an estimate of treatment effect.(7) However, the isolated p-value from the WMW test does not answer the question patients are mostly likely to ask: what is the likelihood that I will respond to treatment? (8) We propose using an alternative ordinal approach to the analysis of endoscopic data in UC and CD for quantifying the treatment effect, as the probability that a patient in the comparator arm will have a better endoscopic response than a patient in the control arm. This probability is referred to as the win probability (WinP) favoring the treatment.
Incorporation of the WinP could represent a substantial paradigm shift in the analysis of UC and CD trials. This analysis is true to the ordinal nature of the MES and SES-CD. All endoscopic data contribute to the WinP; there is no over- or underuse, and no data are discarded. The approach is easily extended to meta-analysis using the weighted average of the WinP from each trial (2). The proportion of patients achieving a dichotomous outcome varies based on the outcome definition that is applied (e.g., using an MES=0 vs. MES=1 as the cutoff for endoscopic remission), whereas the WinP uses the distribution of all endoscopic scores after treatment and is therefore robust to heterogeneous endpoint definitions.
Multiple classes of advanced therapy are now available for the treatment of moderate-to-severely active UC and CD, including tumor necrosis factor (TNF) antagonists, vedolizumab, ustekinumab, tofacitinib, and in some jurisdictions, filgotinib, ozanimod, risankizumab, and upadacitinib. Endoscopic efficacy is a key operating property of these therapies when patients and physicians choose therapy. To date, the efficacy of these therapies has always been expressed using dichotomous methods. In this proposal, we aim to express endoscopic efficacy using the WinP: this will help clinicians better communicate to patients what the likelihood is of achieving endoscopic response and help make more valid comparisons between agents for endoscopic efficacy.

Specific Aims of the Project:

(1) To quantify the endoscopic treatment effect of advanced agents approved for the treatment of moderate-to-severe UC and CD using the WinP
(2) To compare the endoscopic treatment effect as quantified by the WinP between classes of therapy that are approved for the treatment of moderate-to-severe UC and CD

Study Design:

Meta-analysis (analysis of multiple trials together)

Study Design Explanation:

This study will be conducted in two parts: (1) recalculate endoscopic efficacy using WinP in individual trials and (2) meta-analysis of endoscopic efficacy

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

Confirm or validate previously conducted research on treatment effectiveness

Summary-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Develop or refine statistical methods

Research Methods

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

We will include all adult patients receiving active treatment or placebo in phase 3 placebo-controlled trials of approved advanced therapies for UC and CD as available (including infliximab, adalimumab, golimumab, ustekinumab, vedolizumab, tofacitinib, and ozanimod). The eligibility of patients enrolling in these trials has been included in the original studies. We will include only patients who had a baseline MES=2/3 or baseline SES-CD ≥3 to ensure consistent moderate-to-severe endoscopic disease at baseline. Preferentially, we will aim to evaluate endoscopic endpoints at week 8-12 for induction trials and at week 52 for maintenance trials. All patients enrolling in these studies had moderate-to-severely active UC or CD.
We will conduct two separate analyses for patients who did not have an endoscopic evaluation at the follow-up time point because missing data impacts the calculation of the WinP (see Statistical methods). One analysis will exclude all patients without follow-up endoscopy; a sensitivity analysis imputing the worst endoscopic score possible (MES=3 for UC or 3-points for each SES-CD item for CD) for patients with missing outcome endoscopy data will also be performed.

In addition to the data requested through the YODA platform, we have requested the following studies through Vivli: NCT00853099, NCT00385736, NCT00348283, NCT02914522, NCT01458951, NCT01458574, NCT02039505, NCT00783718, NCT00408629. All analyses will be conducted in the secure research environment provided through Vivli.

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

The primary outcome measure will be endoscopic efficacy expressed as the WinP. To calculate the WinP, we will use the MES or SES-CD subscore. Each level of the MES (i.e., MES=0/1/2/3) will be treated as “ranks”, which is true to the ordinal nature of the instrument. Similarly, each level of the SES-CD will be treated as “ranks”.

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

The primary independent variable will be treatment exposure for calculating the WinP (i.e., expressed as the probability of having a better endoscopic response in the treatment group as compared to the placebo group). For meta-analysis, our primary independent variable for subgroup testing will be class of therapy (i.e., TNF antagonists vs. vedolizumab vs. ustekinumab vs. tofacitinib vs. ozanimod) (as the data allows). Meta-analysis in CD and UC will be conducted separately.

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

The following covariables at trial baseline will also be requested (and defined according to the original trials):
• Age, sex
• Mayo Clinic Score components for UC (stool frequency subscore, rectal bleeding subscore, baseline endoscopic subscore, physician global assessment)
• Crohn’s Disease Activity Index and its components for CD
• Disease duration
• Previous and concomitant treatment exposures (5-ASA, corticosteroids, immunosuppressants, previous biologic treatment failure)
• Disease extent UC (left sided vs. extensive/pancolitis for UC)

• Disease extent CD (ileal vs. ileocolonic vs. colonic disease for CD, as defined by the involved segments on the SES-CD)

Statistical Analysis Plan:

Study selection: Placebo-controlled phase 3 trials of advanced therapies for UC and CD. We will limit the analysis to patients with MES=2/3 or SES-CD >=3 at baseline. All trials used the Mayo Clinic Score and the MES for disease activity in UC, and the Crohn's Disease Activity Index and SES-CD for assessment in CD. Descriptive analysis: Analysis population will be patients with baseline MES=2 or MES=3 for UC and SES-CD >=3 for CD. We will provide summary demographic characteristics using descriptive statistics.
Effect Measure of Interest (WinP): Point estimate and 95% confidence interval for a WinP entails two steps. MES scores are converted to "win fractions" (0 to 1), followed by applying conventional methods such as t-test or ANCOVA for continuous outcomes (1, 2). For n1 patients in the treatment group and n0 patients in the control group: 1) Start with patient 1 in the treatment group and compare the MES/SES-CD score with every patient in control, with all n0 patients. Count a 'win' (1) if the score of this patient (n1) is better than the control, 'tie' (0.5) if have the same score, or 'loss' (0) if a worse score. The win fraction is the sum of all these scores, divided by n0 to calculate the win fraction. 2) Use the same approach to get the win fraction for all n1 patients. 3) Move to patient 1 in the control group. Compare this patient with every patient in the treatment group, one at a time with all n1 patients in the treatment group. Count a win, tie, or loss by comparing the MES/SES-CD score of the control with each patient in the treatment group. We sum up these win scores and divide by n1 to obtain the win fraction for this patient.4) We move to the second, third, etc., patient in the control group until we get the win fraction for every patient in the control group. This process can be simplified by using ranks of the raw scores.
For meta-analysis, the estimated WinP will be used for pooling using fixed effect model and random effect models (1, 2). The WinP can be benchmarked against Cohen's effect size (0.0=null, 0.2=small, 0.5=medium, and 0.8=large effect size, equivalent to WinP of 0.50, 0.56, 0.64, and 0.71, respectively). The WinP will be calculated separately for subgroups of interest. Treatment effects as estimated by the WinP will also be contrasted against those derived from a likelihood-based mixed effects model for repeated measures (MMRM), to assess mean change in MES/SES-CD from baseline to end of induction. Analysis using the MMRM will include fixed categorical effects of treatment assignment and continuous baseline MES/SES-CD. An unstructured covariance structure will be applied to model within-subject errors, and we will evaluate for effect modification by important covariates (e.g., disease location).
Meta-Analysis: a meta-analysis of endoscopic efficacy will be conducted using the WinP and done separately for UC and CD. A random effects model will be used given the potential heterogeneity of trial designs and patient populations. No heterogeneity will be introduced due to differential definitions of endoscopic response, as we will use the ordinally derived WinP which is robust to differences in outcome definitions. Differences in WinP between subgroups will be tested. Heterogeneity in estimates of endoscopic efficacy will be evaluated using the I2. Stratified analyses will be conducted according to: Induction vs. maintenance trials, baseline MES or SES-CD, presence/absence of central reading of endoscopy, prior biologic failure baseline corticosteroid us, disease extent, baseline disease duration.
Missing Data: For primary analysis, we will exclude patients with missing endpoint endoscopy data. In the sensitivity analysis, we will impute the worst possible endoscopy score (MES=3 for UC, 3-points for SES-CD item) which treats as non-responders and is the most conservative estimate.

Software Used:

I am not analyzing participant-level data / plan to use another secure data sharing platform

Please clarify software used:

We will be using the Vivli platform - this submission is being submitted in parallel

Project Timeline:

01 Feb 2024 – 01 Nov 2026
- Project start date: 01 Feb 2024
- Analysis completion date: 01 Feb 2025
- Abstract & Manuscript drafted: 1 Jul 2025
- Abstract submitted to congress: 1 Sep 2025
- Manuscript submitted for publication: 1 Feb 2026
- Results reported back to the YODA project: 1 Aug 2026
- Project completion date: 01 Nov 2026

Dissemination Plan:

We anticipate that the analysis will result in a manuscript in a clinical gastroenterology journal. We will plan to share the resulting information through presentation at relevant international GI conferences (e.g., Digestive Disease Week, European Crohn's and Colitis Organization Congress). The results of the study will impact key stakeholders including clinical trialists, researchers, physicians, and patients when choosing therapeutic agents in UC.

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