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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?: Other

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2016/01/yoda_coi_cma.pdf
https://yoda.yale.edu/wp-content/uploads/2018/12/yoda_coi_gzhong.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. 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)
2. 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)
3. 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

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

Research Proposal

Project Title

Correlation Between Symptoms and Objective Measures of Disease Activity in Patients with Moderate to Severe Ulcerative Colitis and Crohn?s Disease

Narrative Summary:

Symptoms and objective measures of disease activity (endoscopy, microscopy, and blood biomarkers) are used to assess inflammatory bowel disease activity.1, 2 Clinical decisions are often driven by symptoms, although symptoms may not correlate with objective measures of disease and bowel healing. Using individual patient-level data from completed clinical trials, this study will determine the correlation between symptoms and objective disease measures and the speed of symptom resolution compared to bowel healing with different therapies. The results of this study

could help inform clinical decision-making by providing timelines for symptom resolution and bowel healing for different therapies.

Scientific Abstract:

Background: CD (Crohn?s disease) and UC (ulcerative colitis) are chronic inflammatory bowel diseases (IBD) which carry a substantial burden on quality of life. Assessing disease activity in patients with IBD has traditionally included patient-reported symptoms, endoscopic and histologic evidence of inflammation, and evaluating levels of inflammatory biomarkers in blood and stool (C-reactive protein [CRP] and fecal calprotectin [FCP], respectively). While symptom resolution is an important therapeutic goal, the correlation between patient-reported outcomes (PROs) and objective disease measures (endoscopy, histology, and biomarkers) are poor. Understanding the relationship between symptoms and objective disease measures may help in evaluating the efficacy of novel therapies that rely on PROs and to inform clinical decisions by physicians.
Objective: The objectives of this study are to 1) Determine the correlation between PROs and objective measures of healing, 2) Assess treatment effect sizes based on historical and contemporary definitions of disease remission, and for the different PROs and objective disease measures, and 3) determine the speed of symptom resolution and objective bowel healing with treatment.
Study Design & Participants: The study will include data from randomized, placebo-controlled trials of biological drugs and advanced oral small molecules (i.e., infliximab, adalimumab, vedolizumab, ustekinumab, and tofacitinib) in moderately to severely active CD and UC. Anonymized individual participant-level clinical (including patient-reported symptom subscores), PRO, endoscopic, and histologic data will be used for this study. Statistical analyses will consist of a pooled analysis of the intent-to-treat population. The impact of covariates known to affect disease improvement will be assessed and adjusted for.
Main Outcome Measure(s): The following data will be collected at baseline and all time points through to the end of the maintenance period for both CD and UC trials: patient-reported symptoms, heath-related quality of life, clinical, endoscopic, and histologic disease activity scores, and CRP and FCP levels. Historical and contemporary definitions of clinical remission will be assessed at each study?s induction endpoint visit.
Statistical Analysis: For all analyses, multiple drug dose arms will be pooled into a single active drug arm. All available data will be used, and no specific imputation strategy is planned. To determine the correlation between PROs and objective measures of disease activity, Spearman?s correlation estimates will be calculated. To compare the clinical remission definitions, treatment efficacy will be calculated as the ratio of clinical remission rates between placebo and active drug. Standardized effect size and distribution-free estimates will be calculated with treatment assignment as the criterion to define improvement. To determine the speed of onset of symptomatic and objective improvement, restricted maximum likelihood-based mixed-effect repeated-measures model will be estimated using an unstructured residual (co)variance matrix over time and using the Kenward-Roger degrees-of-freedom adjustment. Results will be presented as point estimates and 95% CIs of the linear combination for the point-per-week change of the treatment effect.

Brief Project Background and Statement of Project Significance:

Accurate assessment of disease activity in patients with IBD is important for informing treatment decisions in clinical practice and for demonstrating efficacy in clinical trials. Symptom-based measures may not be sufficiently sensitive or specific enough for assessing disease activity, which has resulted in a shift towards normalizing objective measures of disease, such as endoscopic and histologic disease activity, and inflammatory biomarkers. Accurately capturing the patient experience using PROs is a priority for patients and clinicians. Current guidelines of treatment targets in CD and UC recommend an early symptomatic response, normalization of biomarker levels in the intermediate-term, and endoscopic remission in the long-term.9
Correlation between PROs and objective measures is poor.5 In fact, previous studies have shown that only half of patients with CD in clinical remission (as defined by the Crohn?s Disease Activity Index [CDAI]), with infliximab and/or azathioprine therapy had normalized endoscopic disease or CRP

levels. Similarly, 49% of patients with UC treated with mesalamine had persistent abnormal stool frequency (SF) despite endoscopic healing.6 These studies highlight the potential issues of relying on symptom-based measures, although several questions remain unanswered.
First, although correlations between PROs and endoscopy have been evaluated cross-sectionally, the association between changes in symptoms and objective disease measures over time is less clear. Given that disease assessments in clinical care and trials are conducted longitudinally, quantifying the correlation between changes in PROs and changes in objective disease measures will better define treatment response thresholds.
Second, time to symptomatic and objective disease improvement for different classes of advanced therapies has not been studied, but could influence treatment choice. Although a recent systematic review found no difference in the speed of CDAI improvement between biologics, it was unable to account for individual patient characteristics.10 The heterogeneity of definitions, analytical approaches, and lack of patient-level data has limited the study of the speed of improvement in symptoms and objective disease activity and between-therapy comparisons. Patient-level data will enable these comparisons and adjustment for relevant confounders of response time, such as age, disease activity, smoking status, and prior drug exposure.11-15
Finally, there have been recent changes to primary endpoints in IBD trials, moving from the CDAI to a coprimary endpoint of SF and abdominal pain (AP) (2-item PRO) in CD and in UC, from the 12-point Mayo Clinic Score (MCS), consisting of SF, rectal bleeding [RB], endoscopic [MES], and physician?s global assessment (PGA) subscores, to the 9-point Adapted MCS (aMCS), which excludes the PGA subscore. Current treatments have been largely approved using the CDAI and MCS. To facilitate comparisons of efficacy with novel compounds in development, defining treatment effect sizes using both historical and current definitions of PRO, endoscopic, histologic, and biomarker disease remission are required.

Specific Aims of the Project:

It is hypothesized that different therapies will promote symptom resolution and bowel healing at different speeds and that the results of this study could help clinicians tailor therapies to individual patient preferences.
Primary Aim
Aim 1: To determine the correlation between individual PROs (SF, AP, RB)/ HRQoL [IBDQ]) and endoscopic, histologic, and inflammatory biomarker (CRP and FCP) measures of disease activity in moderately to severely active CD and UC and the correlations among their change score over time.
Secondary Aims
Aim 2: To compare the speed of symptomatic (defined by PROs [SF, AP, RB]) and objective improvement in moderately to severely active CD and UC within and between different types of biologics and small molecules and to identify covariates affecting the speed of improvement in IBD.
Aim 3: To compare treatment effect sizes between active drug and placebo groups, defined by historical measures (CDAI for CD and 12-point MCS for UC) versus contemporary measures (2-item PRO [SF and AP] for CD and 9-point aMCS for UC). The difference in effect sizes for the PROs, endoscopic, histologic, and biomarker outcome measures will also be determined at the end of induction and maintenance periods for each clinical trial.

Study Design:

Meta-analysis (analysis of multiple trials together)

Research Methods

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

The study will include randomized controlled trials of patients with moderate-to-severe CD or UC, who are undergoing treatment with one of the following drugs: infliximab, adalimumab, vedolizumab, ustekinumab, and tofacitinib. Trials in perianal fistulizing CD, post-operative CD, and trials in acute severe UC will be excluded.

The data from the YODA Platform will be combined with the studies from the Vivli Platform and the analysis will be completed in the Vivli secure research environment. Please see the rest of the studies that we will be including in the analysis below;
NCT01465763, NCT01458951, NCT00783718, NCT02497469, NCT02611830, NCT00783692, and NCT00348283.

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

Clinical remission outcomes will be defined at each study?s induction endpoint visit resulting in a dichotomous outcome.
For CD trials, the following definitions of remission will be used:
1) Historical: CDAI < 150 points
2) Contemporary: SF ? 3.0 and AP ? 1.0, with neither score worse than baseline
For UC trials, the following definitions of remission will be used:
1) Historical: 12-point MCS ? 2 with no individual subscore > 1
2) Contemporary (based on the 9-point adapted MCS [SF, RB, MES]): 1) SF = 0, RB = 0, and an MES = 0 or 1; and 2) ? 1-point improvement in SF from baseline with a final score ? 1, RB = 0, and an MES = 0 or 1

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

The following variables will be assessed for their impact on the correlation between symptoms and objective disease measures, and on the speed of symptomatic and objective disease improvement:
- Patient age (years, continuous)
- CRP and FCP at baseline
- Previous IBD-related surgery (yes/no)
- Previous exposure to biologic drugs (yes/no)
- Concomitant corticosteroid treatment (yes/no)
- Concomitant immunomodulator treatment (yes/no)
- Smoking status (current, former, never)
- Disease duration (years, continuous)
- Isolated ileal disease versus other disease locations (CD only) (yes/no)
- Presence of perianal disease (CD only) (yes/no)

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

NA

Statistical Analysis Plan:

For all analyses, multiple drug dose arms will be pooled into a single active drug arm. All available data will be used, and no specific imputation strategy is planned.
Objective 1:Determine the correlation between PROs and objective measures of disease activity.
Due to uncertainty regarding distributions of the raw data, Spearman?s correlation estimates will be calculated with associated 95% confidence intervals (CIs) obtained using Fisher?s z-transformation. Comparisons between correlations will be conducted using CIs as previously described.16
Objective 2: Speed of onset of symptomatic and objective improvement.
Study results will be analyzed in terms of the average rate of change in each of the symptom (PRO), and objective measures. A restricted maximum likelihood-based mixed-effect repeated-measures model17 will be estimated using an unstructured residual (co)variance matrix over time and using the Kenward-Roger degrees-of-freedom adjustment. The outcome vector will be baseline and follow-up score vectors. Fixed-effects to be modeled include treatment arm (binary), timepoint, and the treatment arm-by-time interaction. Results will be presented as point estimates and 95% CIs of the linear combination for the point-per-week change of the treatment effect (i.e., the between-arm difference in mean changes from baseline at each timepoint divided by the study week).

Where multiple studies exist for the same drug, all data will be pooled using a metaregression approach, allowing for a fixed-effect of study. Contrasts between drugs on the speed of response at specific times can be formed based on the linear contrasts from each respective model, as described above.18 Speed of treatment response will be compared across drugs at the end of the respective induction periods, and after half of the induction period. Comparisons may also be made after a fixed amount of treatment time.
A graphical method will be used to aid interpretation. To explore the impact of baseline demographic or clinical characteristics on speed of response, these factors may be adjusted for in the model as simple main-effects.
Objective 3: Comparison of clinical remission definitions
Treatment efficacy will be calculated as the ratio of clinical remission rates between placebo and active drug, with associated 2-sided 95% CIs. Treatment efficacy will be reported separately for each study, drug, and by disease. Comparisons between historical and contemporary remission definitions will be made using methods appropriate for risk ratios for correlated proportions.19 Nonresponse imputation will for missing data at the induction endpoint.
Treatment effect sizes for the PROs and objective outcomes will be determined with treatment assignment as the criterion to define improvement, where the active drug arm is considered improved and the placebo arm is considered not improved. Treatment effect sizes will be assessed using 2 approaches. The first method assumes normality for each effect measure at endpoint. Estimates of the standardized effect size (SES) will be obtained as previously described,20 with comparisons and associated 95% CIs made using the approach described by Zou and Donner.18 Interpretation of SES will be based on Cohen?s benchmarks of 0.2, 0.5, and 0.8 representing small, moderate, and large effects, respectively.21 The second method will use distribution-free estimates of effect size for each measure and will be quantified using the probability that change in 1 index for a subject in the improved group would be at least as large as that for a subject in the not improved group. This probability is commonly known as the Mann-Whitney probability,22 also equivalent to the area under the receiver operating characteristic curve.23, 24 Methods described by Zou and Yue will be used to determine 95% CIs for the effect sizes and their differences.25 Results will be interpreted according to benchmarks that are equivalent to Cohen?s effect size for SES.

Project Timeline:

Please see the important milestones below:
- Analysis start date: 1 Feb 2023
- Analysis completion date: 1 Aug 2023
- Abstract submitted to congress: 1 Nov 2023
- Manuscript submitted for publication: 1 Aug 2024

Dissemination Plan:

We plan to publish the results in a gastroenterology journal, as well as to present the results at relevant international conferences (e.g., Digestive Disease Week [DDW], European Crohn?s and Colitis Organization [ECCO] Congress). The results from this study will interest several stakeholders, such as clinicians, payors, and those involved in the design of clinical trials for IBD (researchers, investigators, and pharmaceutical companies).
Please see the important milestones below:
- Analysis start date: 1 Feb 2023
- Analysis completion date: 1 Aug 2023
- Abstract submitted to congress: 1 Nov 2023
- Manuscript submitted for publication: 1 Aug 2024

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