Principal Investigator

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General Information

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SCOPUS ID: 57210187757  
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


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 - 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 - 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. NCT02407236 - 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

Outcomes from induction using ustekinumab or vedolizumab among patients who have prior biologic intolerance vs biologic failure in UC and CD

Narrative Summary:

Ulcerative colitis (UC) and Crohn’s disease (CD) both fall under the category of inflammatory bowel diseases (IBD). UC primarily targets the large intestine and manifests through symptoms such as diarrhea, rectal bleeding, abdominal pain, a constant urge for bowel movements, and tenesmus (a sensation of needing to defecate even when the bowels are empty). CD, on the other hand, can impact any part of the gastrointestinal tract, although it often affects the ileum and colon. CD patients typically experience symptoms like abdominal pain, weight loss, and diarrhea. In cases where the disease proves severe or unresponsive to conventional therapies, such as corticosteroids, healthcare professionals may explore the potential benefits of employing biologic agents and small molecule treatments as alternative therapeutic strategies.

Biologic agents, also known as biologic therapies, are a category of treatments, typically proteins or antibodies, designed to target specific components of the immune system involved in the inflammatory process of IBD. They are used to modulate the immune response and reduce inflammation in the gut. Two notable biologic therapies, ustekinumab and vedolizumab, have gained approval for the treatment of both UC and CD. Their efficacy and ability to maintain a positive response have been substantiated through various placebo-controlled trials, including GEMINI 1 (NCT00783718), UNITI 1 (NCT01369329), UNITI 2 (NCT01369342), and UNIFI (NCT02407236).

Clinical remission is a critical outcome measure in assessing the effectiveness of treatments. It refers to a state in which the patient experiences a significant reduction or complete absence of symptoms related to the disease. In the case of IBD, it means the patient is no longer experiencing symptoms like abdominal pain, diarrhea, rectal bleeding, or the constant urge for bowel movements. It has been observed within these trials that patients who have previously used biologics have lower rates of clinical and endoscopic response compared to biologic-naïve patients. This ‘previous use’ includes those patients who did not have symptomatic improvement but also encompasses those who may have had adverse events to prior therapy. This is what we refer to as biologic intolerance.

The primary objective of this study is to assess whether IBD patients with prior biologic intolerance have similar achievement of clinical remission and response to ustekinumab and vedolizumab as those who have had a prior failure of one biologic treatment.

Scientific Abstract:

Background: Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn’s disease (CD), pose persistent challenges in healthcare, necessitating innovative therapeutic approaches. Ustekinumab and vedolizumab, prominent biologic agents, have demonstrated efficacy in treating both UC and CD through various clinical trials. Notably, clinical trials have revealed a lower response rate in patients with prior biologic exposure, inclusive of those with intolerance and adverse events.

Objective: This study aims to elucidate the clinical outcomes of IBD patients with a history of biologic intolerance compared to those with previous biologic failure when treated with ustekinumab and vedolizumab. Through a comprehensive assessment of clinical remission and response, we seek to discern potential similarities or differences in treatment outcomes between these two distinct patient cohorts.
Study Design: Patient level data will be acquired from several clinical trials of UC and CD through VIVLI and YODA. The data will be grouped to form cohorts to be analyzed on a secure platform using VIVLI.

Participants: CD and UC patients from several clinical trials who have prior intolerance to one biologic treatment, prior failure of one biologic treatment, or those who are naïve to biologic treatment will be included in the study. Patients who do not have these criteria will be excluded.

Primary and Secondary Outcome Measure(s): Primary outcomes of interest are clinical response and clinical remission at weeks 6 (vedolizumab trials) or 8 (ustekinumab trials). For UC patients, clinical response is characterized by a reduction in the total Mayo Score by at least 3 points and by 30% or more compared to the baseline. This reduction must be accompanied by a decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. For CD patients, clinical response is defined as a decrease in the Crohn's Disease Activity Index (CDAI) of at least 100 points compared to the baseline. For clinical remission, it is defined as achieving a Mayo score of 2 points or less, with no individual subscore exceeding 1 point for UC. Conversely, for CD, clinical remission is defined as achieving a CDAI score of 150 or lower. Secondary outcome includes mucosal healing for UC patients is defined as achieving a Mayo endoscopy subscore of 1 or lower by week 6/8.

Statistical Analysis: 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. Variables such as gender, age, and UC and CD disease characteristics at baseline will be assessed across trials. Week 6 was the time of evaluation post-induction for the vedolizumab studies and week 8 was the time of evaluation for the ustekinumab studies. 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 characteristics, disease characteristics, and outcomes of interest such as clinical response and remission, between groups. Differences between groups will be compared using chi-squared test or using the Mann-Whitney U test. Data will be analyzed using Stata, which is available on the Vivli secure platform.

The significance of this investigation lies in its potential to inform clinical decision-making by elucidating the therapeutic efficacy of ustekinumab and vedolizumab in the context of prior biologic intolerance. Insights derived from this study could optimize treatment strategies, enhance patient outcomes, and contribute to the broader understanding of IBD treatment dynamics. This research holds promise for refining therapeutic paradigms and addressing the unique challenges faced by a subset of IBD patients with a history of biologic intolerance.

Brief Project Background and Statement of Project Significance:

This study addresses a critical gap in our understanding of the treatment dynamics for IBD patients, specifically those who have encountered intolerance to biologics. Given the increasing reliance on ustekinumab and vedolizumab in clinical practice, it becomes imperative to discern whether patients with prior biologic intolerance achieve comparable clinical remission and response as those with previous failure of a biologic treatment.

The outcomes of this research will have far-reaching implications for both healthcare providers and patients. Understanding the efficacy of these biologics in the context of prior intolerance will guide clinicians in making informed treatment decisions, potentially improving outcomes and minimizing adverse events. Furthermore, this study contributes to the broader scientific understanding of IBD, shedding light on the nuanced factors influencing treatment response and offering insights that may pave the way for more personalized and effective therapeutic approaches in the future. Ultimately, the significance of this project lies in its potential to optimize treatment strategies for a subset of IBD patients who face distinct challenges in managing their condition.

Specific Aims of the Project:
The study seeks to assess how previous experiences with biologic treatments might influence clinical outcomes. Our hypothesis posits that patients who have experienced biologic intolerance in the past are likely to exhibit higher rates of clinical and endoscopic improvement compared to those who have previously encountered true biologic treatment failure.

**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
- Summary-level data meta-analysis
- Meta-analysis using data from the YODA Project and other data sources

**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 the data analysis: GEMINI 1 (NCT00783718), UNITI 1 (NCT01369329), UNITI 2 (NCT01369342), and UNIFI (NCT02407236). The studies will be obtained from YODA and VIVLI. The data analysis will be conducted using STATA on the VIVLI secure platform.

Patients who have prior intolerance to one biologic treatment, prior failure of one biologic treatment, or those who are biologic naïve in both UC and CD. Patients who do not have these criteria will be excluded.

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

Primary outcomes of interest are clinical response and clinical remission at weeks 6 (vedolizumab trials) or 8 (ustekinumab trials). For UC patients, clinical response is characterized by a reduction in the total Mayo Score by at least 3 points and by 30% or more compared to the baseline. This reduction must be accompanied by a decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. For CD patients, clinical response is defined as a decrease in the Crohn's Disease Activity Index (CDAI) of at least 100 points compared to the baseline.

For clinical remission, it is defined as achieving a Mayo score of 2 points or less, with no individual subscore exceeding 1 point for UC. Conversely, for CD, clinical remission is defined as achieving a CDAI score of 150 or lower.

Secondary outcome: Mucosal healing for UC patients is defined as achieving a Mayo endoscopy subscore of 1 or lower by week 6/8.

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

The independent variable is prior intolerance to one biologic treatment, prior failure of one biologic treatment, or those who are biologic naive in both UC and CD.

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

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:

Data from the clinical trials will be assessed based on the disease type (UC or CD) for patients treated with ustekinumab or vedolizumab, and will be stratified into three categories: prior failure of 1 biologic, prior intolerance of 1 biologic, and biologic naive. Vedolizumab and ustekinumab-treated patients will be analyzed separately to determine if there are differences in patterns of response for biologic failure and intolerant patients for the different biologics. Clinical response, clinical remission, and mucosal healing will be assessed and compared for each category in both disease types. 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. Variables such as gender, age, and UC and CD disease characteristics at baseline will be assessed across trials. Week 6 was the time of evaluation post-induction for the vedolizumab studies and week 8 was the time of evaluation for the ustekinumab studies. 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 characteristics, disease characteristics, and outcomes of interest such as clinical response and remission, between groups. Differences between groups will be compared using chi-squared test or using the Mann-Whitney U test. Data will be analyzed using Stata, which is available on the Vivli secure platform.

Software Used:

STATA

Project Timeline:

Anticipated project start date: as soon as the access is granted
Analysis completion date: within a year of data access
Manuscript and publication date: within a year of the project start, might be before depending on how fast the analysis proceeds
Results reported back to the YODA project: as soon as the results are available from the analysis (within one year)

Dissemination Plan:

Anticipated products include abstracts, posters, and discussions in scientific conferences/events including the Canadian IBD Nurses Annual Conference, 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, Gut, American Journal of Gastroenterology, Journal of the Canadian Association of Gastroenterology, and Clinical Gastroenterology and Hepatology. Target audiences include clinicians and researchers with an appeal towards inflammatory bowel diseases. Those with an interest in research synthesis methods may also be targeted.

Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2024/02/2023-5300-Amendment.docx