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General Information

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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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_coi_-_uniti_bmi_aruljothy.pdf

https://yoda.yale.edu/system/files/yoda_bmi_uniti_ravi.pdf

https://yoda.yale.edu/system/files/coi_narula_bmi.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. [NCT01369329 - CTO1275CRD3001 - 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 - CTO1275CRD3002 - 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 - CTO1275CRD3003 - 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

The Impact of Body Mass Index on the Efficacy of Ustekinumab in the IM-UNITI Trial

Narrative Summary:

The effect of body mass index on the efficacy of thiopurines, anti-TNF agents and surgery has been assessed with varying outcomes. Most recently, data has been presented on the effect of BMI on the safety and efficacy of tofacitinib as seen in OCTAVE 1,2 and SUSTAIN studies. The results revealed that patients with an elevated BMI did not demonstrate lower rates of clinical remission or mucosal healing and that BMI was not a significant predictor for any efficacy endpoint. The proposed study will evaluate, based on data from the UNITI maintenance study, whether BMI influences the effect of standard dosing Ustekinumab therapy in Crohns disease.

Scientific Abstract:

Background: Obesity has been reported as a predictor of poor response to anti-TNF agents in autoimmune disease. Despite recent meta analysis data suggesting that the effect of BMI is variable, there have been pharmacokinetic studies that reported underdosing, increased drug clearance and lower trough levels in obese patients. The effect of Ustekinumab (UST) has not been established.

Objectives: To establish the association of BMI on the efficacy of UST.

Study Design: UNITI 1/ 2 trials were 2 multicentre, double blinded, placebo-controlled trials that randomized patients to UST or placebo. and were then followed by the 44-week IM-UNITI trial for those who responded. This post-hoc study will assess BMI and UST efficacy.

Population:Patients will be those enrolled in the IM-UNITI trial.

Outcomes:Patients will be stratified into BMI groups as follows; BMI<25, 25-<30 and >30. The primary end point will be clinical remission at week 44 (CDAI score <150). Major secondary end points at week 44 will be clinical response (decrease in CDAI score of ?100 points from week 0 of induction or clinical remission), remission maintenance among patients in remission at week 0 of IM-UNITI, and glucocorticoid-free remission, and remission in patients who meet the criteria for nonresponse or who had unacceptable side effects when treated with a TNF antagonist (UNITI-1 population).

Statistical Analysis: Descriptive statistics will be used to summarize baseline patient and disease related data. Regression analyses will be used to assess associations between BMI and efficacy outcomes.

Brief Project Background and Statement of Project Significance:

The incidence and prevalence of obesity has increased worldwide with a concomitant rise in the incidence of inflammatory bowel disease (IBD) (1–3). Contrary to belief, approximately 15-40% of IBD patients have elevated body mass index (BMIs) (2). Observational as well as population based pharmacokinetic studies have provided insights on obesity and its effect on tumor necrosis factor (TNF) antagonists (1–3). Patients who have an elevated BMI, particularly those who are morbidly obese, are less likely to receive optimal weight-appropriate therapy. Additionally, BMI may have an impact on increased drug clearance, resulting in short half-life and low trough drug concentrations. This effect might be related to rapid proteolysis and to a ‘TNF sink’ phenomenon in patients with obesity, whereby increased levels of adipose-secreted TNF sequester anti-TNF agents (1–3).

Recently, unpublished data has been presented with regards to the Janus kinase (JAK) inhibitor, Tofacitinib, and its relationship to BMI. This post hoc analysis of the OCTAVE studies revealed no relationship of BMI or weight on drug efficacy and safety and there were not significant predictors for mucosal healing, endpoints of remission and clinical response (4,5).

Ustekinumab (UST) is a monoclonal antibody that targets the standard p40 subunit of the cytokines IL-12 and IL-23 (IL12/23p40), which are involved in the pathogenesis of Crohn's disease (CD). UST was shown to be effective in inducing and maintaining clinical remission in CD patients with moderate to severe CD (6,7,8)

To our knowledge, there are no studies that have assessed the effect of weight or BMI on the efficacy of maintenance ustekinumab in Crohn's disease.

Specific Aims of the Project:

This project aims to determine whether weight or BMI has an effect on the efficacy of ustekinumab based on data from the IM-UNITI study, i.e the maintenance phase of the UNITI trials.

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

Research Methods

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

Data Source will be obtained from the UNITI-1, UNITI-2 induction trials and UNITI-IM maintenance trial.

Inclusion Criteria

Participants must meet all of the following criteria to be eligible for study inclusion:

- ?18 years of age
- CD for a minimum duration of 3 months
- Moderate-to-severe CD (defined as a Crohn's Disease Activity Index [CDAI] score 220-450)
- Patients with response to ustekinumab in the UNITI 1 and 2 trials at 8 weeks

Exclusion Criteria

- Participants who meet any of the following criteria are not eligible for study inclusion:
- Bowel resection within 6 months
- Received infliximab, adalimumab or certolizumab pegol ?8 weeks before receiving study drug
- Ongoing chronic or recurrent infectious disease
- Previously received a biologic agent targeting IL-12 or IL-23

Main Outcome Measure and how it will be categorized/defined for your study:

In IM-UNITI, the primary endpoint was clinical remission at week 44 (CDAI score <150). Major secondary end points at week 44 were clinical response (decrease in CDAI score of ?100 points from week 0 of induction or clinical remission), maintenance of remission among patients in remission at week 0 of the maintenance trial, glucocorticoid-free remission, and remission in patients who met the criteria for primary or secondary nonresponse or who had unacceptable side effects when treated with a TNF antagonist.

Primary Outcome

The primary outcomes of this study are to establish the efficacy of standard dosing of ustekinumab when adjusted for stratified weight/BMI. Efficacy was assessed in the original trial every 4 weeks with CDAI scores, adverse events, concomitant medications, and CRP levels. Fecal calprotectin levels were evaluated at weeks 8, 24, and 44 during maintenance. Serum ustekinumab levels were also evaluated at every 4 weeks during maintenance.

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

Body mass index (BMI) will be the main predictor variable. Patients will be stratified into BMI groups as follows; BMI<25, 25-<30 and >30.

Statistical Analysis Plan:

Baseline data, such as patient demographics and disease characteristics, will be summarized using descriptive statistics. Continuous variables will be reported as means or medians with corresponding standard deviations or interquartile ranges, respectively.

Univariate and multivariate regression analyses will be used to evaluate possible associations between BMI (as a continuous or categorical variable) or weight, and efficacy outcomes of remission, mucosal healing, clinical response as in IM-UNITI.

Data from the YODA project will be accessed remotely in a secure environment by designated study investigators. Analyses with data provided by the YODA project will be conducted using the software available on the remote platform.

Software Used:

STATA

Project Timeline:

Date to Start Project: November – January 2020.

Date to Complete Analysis: January 2020 – February 2020.

Date to Draft Manuscript: February 2020 – March 2020.

Date to Submit Manuscript: March 2020 – April 2020.

Dissemination Plan:

Results from the study may be communicated to target audiences through posters, abstracts, and presentations. These may be submitted to conferences such as Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organisation. Further, a manuscript may be completed and submitted for publication in a relevant peer-reviewed journal. The investigators will acknowledge use of data from the YODA Project on all study products, which will be shared at the time of submission.

Bibliography:

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