

Principal Investigator

First Name: Neeraj
Last Name: Narula
Degree: MD, MPH, FRCPC
Primary Affiliation: McMaster University
E-mail: wong12@mcmaster.ca
Phone number: 9055259140 x73884
Address: 1280 Main Street West
1280 Main Street West
City: Hamilton
State or Province: Ontario
Zip or Postal Code: L8S4L8
Country: Canada

General Information

Key Personnel (in addition to PI):

First Name: Emily
Last name: Wong
Degree: BHSc
Primary Affiliation: McMaster University
SCOPUS ID:

First Name: Neeraj
Last name: Narula
Degree: MD MPH FRCPC
Primary Affiliation: McMaster University
SCOPUS ID:

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_-_narula.pdf

https://yoda.yale.edu/system/files/yoda_coi_-_wong.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 - 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

Comparative Efficacy of Ustekinumab and Infliximab on Clinical and Endoscopic Outcomes in Crohn's Disease

Narrative Summary:

Ustekinumab and infliximab are currently approved treatments for patients with Crohn's disease (CD). Ustekinumab is a monoclonal antibody targeted against the p40 subunit of the proinflammatory cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23), which have been implicated in the pathogenesis of CD. Infliximab, which is an antibody that targets tumor necrosis factor alpha, and infliximab biosimilar CT-P13, were compared in the phase three trial NCT02096861. Data from the UNITI trials is being requested to conduct a comparative efficacy analysis with data from the NCT02096861 trial.

Scientific Abstract:

Background and Rationale

Head to head comparisons are required to understand how ustekinumab and infliximab compare in their ability to achieve clinical and endoscopic outcomes among patients with CD.

Objectives

This study aims to evaluate if differences exist between patients who received ustekinumab or infliximab and ability to achieve clinical and endoscopic outcomes. as well as objective markers of disease activity.

Study Design

This will be a post-hoc analysis of NCT02096861, UNITI-1, UNITI-2 and IM-UNITI, which were multicentre, randomized, double-blind trials. UNITI-1 and 2 were 8-week induction trials and patients were offered to continue in IM-UNITI, depending on their treatment response. This post-hoc analysis aims to compare if differences in treatment impact the ability to achieve clinical and endoscopic disease improvement at week 6 and 52.

Study Population

Patients were eligible for UNITI 1 and 2 if they had moderate-to-severe CD and if they failed conventional therapies or anti-TNF therapy. In the main analysis, only those who receive ustekinumab at a weight-based dose of 6mg/kg will be included.

Outcomes

The primary outcome of the proposed study will be clinical remission at week 6 and 52, defined as CDAI<150. Secondary outcomes of interest includes clinical response, change in fecal calprotectin, change in C-reactive protein and endoscopic improvement at week 6 and 52.

Statistical Analysis

Descriptive statistics will be used to summarize the proportion of patients achieving clinical and endoscopic outcomes.

Brief Project Background and Statement of Project Significance:

Ustekinumab is a monoclonal antibody targeted against the p40 subunit of the proinflammatory cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23), which have been implicated in the pathogenesis of Crohn's disease (CD).¹ UNITI-1 (ClinicalTrials.gov number: NCT01369329) and UNITI-2 (ClinicalTrials.gov number: NCT01369342) were pivotal phase three double-blinded, placebo-controlled induction trials which randomized patients with moderate to severe Crohn's disease (CD) to receive placebo, weight-based ustekinumab 6mg/kg or standard dose ustekinumab for 8 weeks. Patients who did not respond were offered to continue with open label ustekinumab in IM-UNITI (ClinicalTrials.gov number: NCT01369355) and those who responded were re-randomized to placebo or continued to receive ustekinumab.

Infliximab, which is an antibody that targets tumor necrosis factor alpha, and infliximab biosimilar CT-P13 were compared in the phase three trial NCT02096861.⁽²⁾ Patients were randomized in a 1:1:1:1 ratio to receive CT-P13 then infliximab, infliximab then CT-P13, infliximab throughout or CT-P13 throughout, with switching occurring at week 30. For the purposes of this analysis, infliximab and CT-P13 biosimilar will both be classified as infliximab. Despite the extensive clinical trial data available on individual treatments for CD, there is a need to better understand how these treatments compare. Unfortunately, these comparisons are relatively limited in the literature due in part to varying outcome time points across different trials and differences in trial populations. The UNITI trials and NCT02096861 provide a unique opportunity to compare ustekinumab and infliximab as outcome evaluations occurred at common time points, including week 6 and 52.

Specific Aims of the Project:

This study proposes to compare the effectiveness of ustekinumab and infliximab on achieving clinical and endoscopic outcomes with patients from NCT02096861, UNITI-1 (ClinicalTrials.gov number: NCT01369329), UNITI-2 (ClinicalTrials.gov number: NCT01369342) and IM-UNITI (ClinicalTrials.gov number: NCT01369355). We hypothesize that both treatments are equally as effective in achieving clinical remission.

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

Research Methods

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

Study Design

Participants must meet all of the following criteria to be eligible for study inclusion³:

1. ≥18 years of age
2. CD for a minimum duration of 3 months
3. Moderate-to-severe CD (defined as a Crohn's Disease Activity Index [CDAI] score 220-450)
4. Nonresponse to anti-TNF therapy (UNITI-1) or treatment failure or intolerance to immunomodulators and/or glucocorticoids (UNITI-2)

Exclusion Criteria

Participants who meet any of the following criteria are not eligible for study inclusion¹:

1. Bowel resection within 6 months
2. Received infliximab, adalimumab or certolizumab pegol ≥8 weeks before receiving study drug (UNITI)
3. Ongoing chronic or recurrent infectious disease
4. Previously received a biologic agent targeting IL-12 or IL-23 (UNITI)

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

The primary outcome of this study, clinical remission, is defined as CDAI score < 150. The CDAI is comprised of 8

items assessing CD activity, including weight, sex, number of liquid/soft stools, abdominal pain, general well-being, use of anti-diarrheal drugs, presence of abdominal mass and hematocrit percentage. The total score ranges from 0 to 600, with a higher score indicating more severe disease activity.⁴ In this study, CDAI scores at baseline, week 6 and week 52 will be reported and used to determine if clinical response (decrease in CDAI from baseline of at least 100) and clinical remission (CDAI less than 150) was achieved. Secondary outcomes include change in objective markers of disease activity at week 6 (e.g. C-reactive protein and fecal calprotectin) and endoscopic remission at one year, which is defined as SES-CD score < 3. The SES-CD is an endoscopic scoring system of disease activity and extent, which is based on four endoscopic parameters: presence and size of ulcers, surface involvement of ulcerations, surface affected by ulcerations and the presence and severity of stenosis. The rectum, sigmoid/left colon, transverse colon, right colon, and ileum are individual

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

The type of treatment received (i.e. ustekinumab or infliximab) will be the independent variable in this study.

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

N/A

Statistical Analysis Plan:

Descriptive statistics will be used to summarize baseline characteristics (e.g. disease activity and patient demographics) and dichotomous variables will be presented as proportions or percentages. Continuous variables will be reported as means or medians with corresponding standard deviations or interquartile ranges, respectively.

In the main analysis, only those who receive ustekinumab at a weight-based dose of 6mg/kg (which is the currently approved dosage) will be included. If the primary analysis lacks sufficient power, all patients randomized to ustekinumab may be included. In recognition of the possibility that both baseline populations may not be similar, we will employ propensity score matching in a 1:1 ratio with matching on relevant baseline covariates, such as smoking status. Logistic regression will be used to model the likelihood of achieving outcomes. Models will be adjusted for baseline covariates with a p-value < 0.10 on univariate analysis.

Software Used:

STATA

Project Timeline:

Date to Start Project: September – October 2020.

Date to Complete Analysis: October – November 2020.

Date to Draft Manuscript: November – December 2020.

Date to Submit Manuscript: December – January 2021.

Dissemination Plan:

Analyses from this study may be shared to target audiences through presentations and abstracts. These may be submitted to conferences such as Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organisation. A manuscript may also be submitted for publication. The YODA Project will be acknowledged in all study products, which will be shared at the time of submission.

Bibliography:

1. Feagan, B. G. et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N. Engl. J. Med.* (2016) doi:10.1056/NEJMoa1602773.
2. Ye, B. D. et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. *Lancet* (2019) doi:10.1016/S0140-6736(18)32196-2.
3. Feagan, B. G. et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N. Engl. J. Med.* (2016) doi:10.1056/NEJMoa1602773.
4. Irvine, E. J. et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology* (1994).

5. Daperno, M. et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: The SES-CD. *Gastrointest. Endosc.* (2004) doi:10.1016/S0016-5107(04)01878-4.