

Principal Investigator

First Name: Neeraj
Last Name: Narula
Degree: MD, MPH, FRCPC
Primary Affiliation: Hamilton Health Sciences
E-mail: emchulee@gmail.com
Phone number: 9055212100
Address:

City: Hamilton
State or Province: Ontario
Zip or Postal Code: L8S 4L8
Country: Canada

General Information

Key Personnel (in addition to PI):

First Name: Emily
Last name: Wong
Degree: BHSc
Primary Affiliation: Hamilton Health Sciences

First Name: Neeraj
Last name: Narula
Degree: MD, MPH, FRCPC
Primary Affiliation: Hamilton Health Sciences

First Name: Cristina
Last name: Monaco
Degree: BSc
Primary Affiliation: Hamilton Health Sciences

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_-_2022-5037.pdf

https://yoda.yale.edu/system/files/yoda_coi_wong_-_2022-5037.pdf

https://yoda.yale.edu/system/files/yoda_-_cristina.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. [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. [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](#)
4. [NCT02407236 - CNT01275UCO3001 - 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

Estimating Differences in the Comparison of Outcomes in Clinical Trials for UC Patients using Patient-Level Data and Aggregated Data: Network Meta-Analysis

Narrative Summary:

The primary objective of this study is to evaluate whether differences exist in the estimations of clinical outcomes between two types of network meta-analyses. This will be facilitated by comparing a network-meta-analysis using individual patient-level data and an aggregated network meta-analysis using risk estimates from previously published clinical trial data.

Patient-level data from ULTRA 1, ULTRA 2, GEMINI 1, VARSITY and OCTAVE 1 is being requested from Vivli. Patient-level data from ACT 1, ACT 2, PURSUIT and UNIFI is being requested from the YODA project.

Scientific Abstract:

Background

Ulcerative colitis (UC) is a chronic inflammatory bowel disorder that disrupts the normal functioning of the colon [1]. Patients with UC encounter periods of asymptomatic remission and symptomatic relapse, including symptoms such as diarrhea, abdominal cramping, and rectal bleeding [2]. The many therapeutics that exist for UC should exhibit efficacy and safety, and these outcomes are assessed often in placebo-controlled clinical trials. Analyzing and comparing clinical outcomes between these trials can inform clinical decisions on the basis of comparing and ranking the effectiveness offered by UC therapeutics.

Objective

To compare aggregate/IPD NMA.

Participants

Infliximab, adalimumab and vedolizumab have shown to be effective biologic therapeutic options for patients with moderate-to-severe UC, suggesting success in ability to maintain clinical remission in placebo-controlled trials, including ACT 1 (NCT00036439) and ACT 2 (NCT00096655), ULTRA 1 (NCT00385736) and ULTRA 2 (NCT00408629), and GEMINI 1 (NCT00783718) [3-6]. The head-to-head VARSITY trial (NCT02497469) depicted vedolizumab was more effective in comparison to adalimumab, in achieving clinical remission in moderate-to-severe UC patients [7]. Golimumab is another therapeutic for treatment of moderate-to-severe active UC and has demonstrated efficacy and safety in the placebo-controlled study PURSUIT (NCT00488631) [8]. Induction and maintenance therapy in patients with moderate-to-severe UC has been depicted with ustekinumab on the strength of the UNIFI placebo-controlled trials (NCT02407236). More recently, small molecule biologics such as tofacitinib have recently evolved as an effective therapeutic on the strength of data from the placebo-controlled OCTAVE trials (NCT01465763) [10].

Primary and Secondary Outcome Measures

The primary objective of this study is to evaluate whether differences exist in the estimations of clinical outcomes between two types of network meta-analyses. This will be facilitated by comparing a network-meta-analysis using individual patient-level data and an aggregated network meta-analysis using risk estimates from previously published clinical trial data.

Patient-level data from ULTRA 1, ULTRA 2, GEMINI 1, VARSITY and OCTAVE 1 is being requested from Vivli.

Patient-level data from ACT 1, ACT 2, PURSUIT and UNIFI is being requested from the YODA project.

Statistical Analysis

In the aggregated NMA, patients assessed for clinical response at weeks 6/8 (ACT 1 & 2, ULTRA 1 & 2, GEMINI 1, PURSUIT, UNIFI, OCTAVE 1) will be aggregated to form a cohort of participants. For this NMA, comparisons between groups will elicit estimates on ranking therapies superior to inducing clinical response and remission. For clinical trials assessing different dosages of therapeutics, these will be combined into one subgroup. Infliximab 5mg/kg from ACT trials, golimumab 100mg from the PURSUIT trial, ustekinumab 6mg/kg from the UNIFI trial, and tofacitinib 10mg from the OCTAVE trial will be used as these are all approved induction doses [6, 8, 9, 10]. In the patient-level NMA, propensity score matching will be used to create cohorts of matched participants with similar distribution in baseline characteristics. The method of propensity score matching is used for purposes of creating more evenly distributed characteristics, to account for differences in baseline characteristics between patients [16].

Study Design

Meta-analysis

Brief Project Background and Statement of Project Significance:

Though a meta-analysis can investigate estimations of one effect between two treatments, the potential of a network meta-analysis offers more than one estimate involved in measuring the effects between multiple treatments simultaneously [11]. An aggregate network meta-analysis and an individual patient level meta-analysis can both yield estimates of the effects between clinical trials. However, the advantage of IPD meta-analyses can enhance the quality and information available in studies, by allowing us to adjust for differences in patient-level covariates [12]. This can allow us to conduct more reliable, precise, and informative estimations on ranking interventions and inform clinical-based decisions in the realm of UC disease [12]. While meta-analyses have been extensively performed in inflammatory bowel disease research, what is not entirely certain is whether the use of individual patient-level data makes a difference in the estimates obtained from network meta-analyses. Burr et.al. recently performed a network meta-analysis to compare the efficacy of biologic and small molecule therapeutics utilized in UC treatment, ranking upadacitinib as most effective in achieving clinical remission, and infliximab ranking superior in achieving endoscopic improvement [13]. Bonovas et.al. performed a systematic review investigating the efficacy of biologics such as tofacitinib, infliximab, adalimumab, golimumab and vedolizumab, suggesting infliximab was superior in attaining clinical response and endoscopic improvement [14]. An updated network-meta-analysis conducted by Singh et.al. discovered infliximab was ranked first in clinical remission and endoscopic improvement [15].

Although previous network meta-analyses have compared current biologics in respect to their ability to induce and maintain clinical response and remission, many have not explored treatment effect estimates using individual patient-level data.

The primary objective of this study is to evaluate whether differences exist in the estimations of clinical outcomes between two types of network meta-analyses. This will be facilitated by comparing a network-meta-analysis using individual patient-level data and an aggregated network meta-analysis using risk estimates from previously published clinical trial data.

Patient-level data from ULTRA 1, ULTRA 2, GEMINI 1, VARSITY and OCTAVE 1 is being requested from Vivli.

Patient-level data from ACT 1, ACT 2, PURSUIT and UNIFI is being requested from the YODA project.

Specific Aims of the Project:

The proposed study aims: 1) to perform a network meta-analysis using individual patient-level data, 2) to perform an aggregate network meta-analysis, using published risk estimates from previously completed clinical trials, 3) to evaluate whether differences exist in the estimates obtained from the two network meta-analyses. This will be achieved by comparing the results from both analyses and observing any potential differences in the estimates obtained using statistical analyses. The null hypothesis to be tested is that there is no difference in the estimates obtained from an individual patient-level NMA and an aggregate NMA.

What is the purpose of the analysis being proposed? Please select all that apply.

Summary-level data meta-analysis

Summary-level data meta-analysis using only data from YODA Project

Meta-analysis using data from the YODA Project and other data sources
Participant-level data meta-analysis
Summary-level data meta-analysis using only data from YODA Project
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:

In the aggregated NMA, patients assessed for clinical response at weeks 6/8 (ACT 1 & 2, ULTRA 1 & 2, GEMINI 1, PURSUIT, UNIFI, OCTAVE 1) will be aggregated to form a cohort of participants. For this NMA, comparisons between groups will elicit estimates on ranking therapies superior to inducing clinical response and remission. For clinical trials assessing different dosages of therapeutics, these will be combined into one subgroup. Infliximab 5mg/kg from ACT trials, golimumab 100mg from the PURSUIT trial, ustekinumab 6mg/kg from the UNIFI trial, and tofacitinib 10mg from the OCTAVE trial will be used as these are all approved induction doses [6, 8, 9, 10].

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

The primary outcome(s) of interest are evaluating clinical response from weeks 6/8, defined as a decrease in the total Mayo Score of ≥ 3 and $\geq 30\%$ from baseline, with a decrease in the rectal bleeding subscore of ≥ 1 , or absolute rectal bleeding subscore of 0 or 1. OCTAVE 1 defined remission with identical criteria as other trials but also included a rectal bleeding subscore of 0 as an additional component. In the individual patient-level analysis, remission will be defined using a common definition given the availability of Mayo scores at the patient-level. Weeks 6/8 of both clinical response and remission were common timepoints and endpoints in all trials, respectively. Secondary outcomes include endoscopic improvement (defined as a Mayo endoscopy subscore ≥ 1) at the post-induction period (week 6/8).

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

The independent variable is the type of treatment, these treatments including infliximab, adalimumab, vedolizumab, golimumab, ustekinumab, and tofacitinib.

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

One variable of interest is endoscopic improvement at induction (week 6/8). Although safety (quantified through frequency of adverse events/infections) was a common endpoint in all trials, assessments for these parameters were made at various timepoints throughout all trials, and therefore will not be considered as a variable of interest.

Statistical Analysis Plan:

In the aggregated NMA, patients assessed for clinical response at weeks 6/8 (ACT 1 & 2, ULTRA 1 & 2, GEMINI 1, PURSUIT, UNIFI, OCTAVE 1) will be aggregated to form a cohort of participants. For this NMA, comparisons between groups will elicit estimates on ranking therapies superior to inducing clinical response and remission. For clinical trials assessing different dosages of therapeutics, these will be combined into one subgroup. Infliximab 5mg/kg from ACT trials, golimumab 100mg from the PURSUIT trial, ustekinumab 6mg/kg from the UNIFI trial, and tofacitinib 10mg from the OCTAVE trial will be used as these are all approved induction doses [6, 8, 9, 10]. In the patient-level NMA, propensity score matching will be used to create cohorts of matched participants with similar distribution in baseline characteristics. The method of propensity score matching is used for purposes of creating more evenly distributed characteristics, to account for differences in baseline characteristics between patients [16]. Variables such as gender, age, and UC disease characteristics at baseline will be assessed across trials. Weeks 6/8 were common timepoints across all trials. An indicator variable will be utilized to differentiate between trials.

The ACT trials showed a higher percentage of patients achieving clinical response to infliximab compared to placebo, at week 8 [6]. OCTAVE 1 and ULTRA trials have similar clinical remission results, with patients receiving adalimumab and tofacitinib, respectively, achieving remission at week 8 assessments [3-4, 10]. GEMINI 1 and PURSUIT demonstrated patients who were on active therapy achieved clinical remission in one-year assessments [5,8]. VARSITY trial showed a higher percentage of patients in vedolizumab achieved clinical remission at week 52

assessment, compared to adalimumab [7]. The UNIFI trial showed higher percentage of patients in clinical remission at week 8 to ustekinumab, compared to placebo [9].

Sensitivity analyses will be performed to minimize heterogeneity. With either previously biologic-exposed and biologic-naïve patients in all trials, data will be stratified by conducting separate analyses to create subgroups for comparisons. Sensitivity analyses will be performed to exclude participants with any missing outcome data from the primary analysis.

A fixed-effect (FE) model will be used to assess clinical response and clinical remission, for comparisons between all trials [17]. A Bayesian model will be used to report effect estimates together to a) perform direct comparisons between outcomes between trials via pairwise comparisons between therapies or placebo, b) indirectly compare outcomes between trials [18, 19]. This combines the direct and indirect effect estimates together, and this will be represented as probabilities (Pr) [18, 19]. Probability statements can represent the effectiveness of each treatment, which can be further calculated to rank treatments. Univariate and multivariable logistic regression will be used to produce odds ratios (OR), to identify treatment effects on the outcome of interest [20].

Descriptive statistics will be used to explain baseline characteristics, disease characteristics, and outcomes of interest such as clinical response and remission, between groups [21]. Differences between groups will be compared using chi-squared test or using the Mann-Whitney U test [22]. Data will be analyzed using Stata, which is available on the Vivli secure platform.

Software Used:

STATA

Project Timeline:

Start date: Nov 1, 2022

Completion date: Jan 1, 2023

Draft manuscript date: June 1, 2023

Result reported: August 1, 2023

Dissemination Plan:

Dissemination and Publication 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.

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/research_proposal_v3_0.docx