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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/yale_university_open_data_access_yoda_project.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. NCT00487539 - C0524T17 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis
4. NCT01863771 - CNTO148UCO3001 - A Safety and Effectiveness Study of Golimumab in Japanese

What type of data are you looking for?: Full CSR

Research Proposal

Project Title

Early clinical response to biologics and small molecules for moderate-to-severe ulcerative colitis: a network meta-analysis

Narrative Summary:

To describe and compare the clinical response at two weeks after the initiation of induction therapy with FDA-approved biologics and/or small molecules on moderate-to-severe ulcerative colitis patients. This comparison would provide useful information on how fast clinical response is observed upon the initiation of different approved therapeutic alternatives for this condition and also would help to determine which of the approved medical treatments for moderate-to-severe ulcerative colitis would exhibit a more meaningful clinical effect at an early point during induction therapy.

Scientific Abstract:

BACKGROUND: Rapid response to medications in the setting of moderate-to-severe ulcerative colitis has been associated with improved quality of life. There is evidence reported on the rapid induction of clinical improvement during the first 2 weeks of induction therapy with FDA-approved biologics and small molecules. However, indirect comparisons are still lacking
OBJECTIVE: To describe the changes in stool frequency and rectal bleeding scores at week 2 of induction treatment with approved biologics and small molecules and perform an indirect comparison of them
STUDY DESIGN: A systematic review with network meta-analysis will be performed.
PARTICIPANTS: Adult patients with moderate-to-severe ulcerative colitis. Phase 3 clinical trials comparing an FDA-approved biologic and/or small molecule versus placebo will be included.
OUTCOME MEASURES: Post hoc analyses will be searched to determine the mean change of both stool frequency and rectal bleeding scores at week 2 of induction therapy versus placebo.
STATISTICAL ANALYSIS: Network meta-analysis will be performed using a frequentist approach. SUCRA values wil be estimated for indirect comparison.

Brief Project Background and Statement of Project Significance:

Ulcerative colitis (UC) is a chronic immune-mediated condition that is associated with a significant burden in terms of morbidity(1). A significant proportion of patients with moderate-to-severe UC will need treatment with biologics and/or small molecules, such as tofacitinib (2).
Even though anti-TNF agents such as infliximab or adalimumab have made a profound change in the natural history of UC (3,4), a non-neglectable proportion of patients would have a primary failure to anti-TNF (5). This led to the development of alternatives with different therapeutic targets, such as vedolizumab (6), or ustekinumab (7). In addition, small molecules such as Janus kinase inhibitors are being developed. Recently, tofacitinib was approved by the Federal Drug Administration (FDA) for the treatment of moderate-to-severe UC patients (8).
There is a need for clinical predictors of early response to the abovementioned medications (9). Prediction of the initial response would help to avoid unnecessary treatments. Additionally, rapid response to biologics and small molecules has been associated with improved quality of life (10). As a consequence, post hoc analyses from phase 3 trials assessing the efficacy of infliximab, golimumab (11), adalimumab (12), vedolizumab (13) and tofacitinib (14) have been published. Most of these post hoc analyses have focused on the change from baseline of patient-reported items of partial mayo score - that is, stool frequency and rectal bleeding scores. Most of them have shown that as early as two weeks after the first dose of the aforementioned drugs, an improvement in terms of stool frequency and rectal bleeding versus placebo was observed.
To our knowledge, there is no evidence of which of the FDA-approved treatments for moderate-to-severe UC would be associated with a higher proportion of early clinical response. An inidirect comparison through network meta-

analysis of post hoc analyses of phase 3 trials could suggest which alternative induces a more rapid clinical response. This information could be very valuable for the initiation of treament of very symptomatic UC patients.

Specific Aims of the Project:

1) To describe the mean change from baseline of both stool frequency score and rectal bleeding score at 2 weeks from biologic/small molecule induction treatment initiation
2) To make an indirect comparison of the mean change from baseline of both stool frequency score and rectal bleeding score at 2 weeks from FDA-approved biologics and small molecules

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
Research on clinical prediction or risk prediction

Research Methods

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

Eligibility criteria
Type of studies to be included: randomized controlled studies. We will consider all articles irrespective of publication type. Hence, articles published as short reports or conference abstracts will not be excluded. In the case of multiple studies involving the same population, data from the most recent or most comprehensive one will be included.
Population: adult patients (>90% of subjects over the age of 18 years) with moderate-to-severe UC as defined by the Mayo Score.
Intervention: We will focus on previoulsy approved biologics and small molecules for the treatment of UC in their approved dosages: infliximab, adalimumab, golimumab, vedolizumab, ustekinumab and tofacitinib.
Comparator: Placebo.
DATA SOURCE: We will look for other phase 3 studies assessing the efficacy of vedolizumab, tofacitinib and adalimumab on the same population. Published manuscripts of these drugs will be reviewed, as well as their corresponding supplementary materials. If required data is missing, we will contact main authors to request the necessary information.

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

Primary outcome is a composite of two items:
• Mean change from baseline of stool frequency score 2 weeks after initiation of induction treatment
• Mean change from baseline of rectal bleeding score 2 weeks after initiation of incudtion treatment

Secondary outcomes are the following:
a) Mean change from baseline of stool frequency score and rectal bleeding score 4 weeks after initiation of induction treatment
b) Mean change from baseline of stool frequency score and rectal bleeding score 6 weeks after initiation of induction treatment

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

1)Mean change from baseline of stool frequency score (a subitem of the partial Mayo score) at week 2 = this is defined as the difference between mean stool frequency score at baseline and mean stool frequency score at week 2 after first dose of induction treatment
2) Mean change from baseline rectal bleeding score (a subitem of the partial Mayo score) at week 2= this is defined as the difference between mean rectal bleeding score at baseline and mean rectal bleeding score at week 2 after first dose of induction treatment

Statistical Analysis Plan:

Information sources

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Published studies will be identified using MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from January 1 1990 until May 22 2021. Major congresses databases (European Crohn's and Colitis Organization, Digestive Disease Week, and United European Gastroenterology Week in the period 2018-2021 will also be reviewed manually.

Search strategy

Search algorithms will include the following terms: ["biologics" OR "anti-TNF" OR "infliximab" OR "adalimumab" OR ("golimumab" OR "CNTO-148") OR "anti-integrin" OR ("vedolizumab" OR "MLN-0002") OR ("ustekinumab" OR "CNTO-1275") OR "JAK inhibitor" OR ("tofacitinib" OR "CP-690550") AND ["efficacy" OR "safety" OR "adverse events" OR "early response"].

Selection process

Two authors will independently review titles/abstracts of studies identified in the search, and exclude those that are clearly irrelevant. The full text of the selected articles will be read to determine whether it contains information on the topic of interest. Their reference lists (and those of relevant systematic reviews and meta-analyses) will be hand-searched to identify further relevant publications.

Data extraction

The following information from each study will be abstracted into a specially designed data extraction form: citation data, first author's last name, study design, number of patients, study duration, population characteristics (age, sex, disease duration, prior biologic use), exposure definition (drug, dose, duration), and reported outcomes. Any differences in data extraction will be settled by consensus, referring back to the original article.
The following outcomes will be analyzed: mean change in both stool frequency and rectal bleeding scores at week 2 of induction therapy.

Risk-of-bias in individual studies

Two authors will independently assess the risk-of-bias in included studies. The Cochrane Risk of Bias tool will be used. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author.

Data synthesis and statistical analysis

A descriptive qualitative analysis of the efficacy and safety of the aforementioned drugs will be presented. Meta-analysis as well as network meta-analysis comparing biologics and small molecules for moderate-to-severe UC will be performed and described. Pooled odds ratios (OR) and 95% CIs will be calculated using the Mantel–Haenszel fixed-effects model with sensitivity analysis using the DerSimonian–Liard random-effects model. We will assess statistical heterogeneity using the I2 statistic, with values greater than 50% suggesting substantial heterogeneity. Publication bias will be assessed by evaluating small study effects by examining funnel plot asymmetry. First of all we will conduct a meta-analysis using R software. We will then conduct a network meta-analysis using a consistency model of multivariate, random-effects meta-regression as described by White et al (15) using R. This frequentist approach provides a point estimate from the network along with 95% CIs from the frequency distribution of the estimate.
We will calculate the relative ranking of agents for induction of clinical remission as their surface under the cumulative ranking (SUCRA), which represents the percentage of efficacy or safety achieved by an agent compared with an imaginary agent that is always the
best without uncertainty (ie, SUCRA ¼ 100%).
Software Used:
R
Project Timeline:

Data collection: May 2021
Data analysis: June-July 2021
Draft ellaboration with results: August 2021
Results Report to YODA: September 2021
Manuscript publication: September 2021

Dissemination Plan:

We intend to publish the results of our network meta-analysis in a scientific journal which would be indexed in the National Library of Medicine. We also intend to show our results in a major gastroenterology congress, such as the

2022 Digestive Disease Week.

Bibliography:

1) Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis. Lancet [Internet]. 2017 Apr 30;389(10080):1756–70. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673616321262

2) Olivera P, Danese S, Peyrin-Biroulet L. Next generation of small molecules in inflammatory bowel disease. Gut [Internet]. 2017 Feb;66(2):199–209. Available from: http://gut.bmj.com/lookup/doi/10.1136/gutjnl-2016-312912

3) Cohen RD, Yu AP, Wu EQ, Xie J, Mulani PM, Chao J. Systematic review: the costs of ulcerative colitis in Western countries. Aliment Pharmacol Ther [Internet]. 2010 Apr;31(7):693–707. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20064142

4) Paschos P, Katsoula A, Salanti G, Giouleme O, Athanasiadou E, Tsapas A. Systematic review with network meta-analysis: the impact of medical interventions for moderate-to-severe ulcerative colitis on health-related quality of life. Aliment Pharmacol Ther [Internet]. 2018;48(11–12):1174–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30378141

5) Danese S, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med [Internet]. 2014 May 20;160(10):704–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24842416

6) Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel J-F, Sandborn WJ, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2013;369(8):699–710.

7) Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019;381(13):1201–14.

8) Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2017;376(18):1723–36.

9) Peyrin-Biroulet L, Van Assche G, Sturm A, et al. Treatment satisfaction, preferences and perception gaps between patients and physicians in the ulcerative colitis CARES study: A real world-based study. Dig Liver Dis 2016;48:601–607.

10) Gray JR, Leung E, Scales J. Treatment of ulcerative colitis from the patient's perspective: a survey of preferences and satisfaction with therapy. Aliment Pharmacol Ther 2009;29:1114–1120.

11) Singh S, Proudfoot JA, Dulai PS et al. Efficacy and speed of induction of remission of infliximab vs golimumab for patients with ulcerative colitis, based on data from clinical trials. Clin Gastroenterol Hepatol 2020;18(2):424-431

12) Hanauer S, Sandborn WJ, Colombel JF et al. Rapid changes in laboratory parameters and early response to adalimumab: a pooled analysis from patients with ulcerative colitis in two clinical trials. J Crohns Colitis 2019, 1227-1233

13) Feagan BG, Lasch K, Lissoos T et al. Rapid response to vedolizumab therapy in biologic-naive patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2019;17:130-138

14) Hanauer S, Panaccione R, Danese S et al. Tofacitinib induction therapy reduces symptoms within 3 days for patients with ulcerative colitis. Clin Gastroenterol Hepatol 2019;17:139-147

15) White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods 2012; 3:111–125.

Supplementary Material:

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