Oct 11, 2022

Protocol of An Indirect Comparison of Efficacy including Histologic Assessment and Safety in Biologic Agents in Ulcerative Colitis: Systematic Review and Network Meta-analysis

ksun.chae[1], Yeon Sook Seo[1], Yun Mi Yu[2], Min Jung Chang[2], Junjeong Choi[2]

[1]1Graduate program of Industrial Pharmaceutical Sciences;

[2]1Graduate program of Industrial Pharmaceutical Sciences, 2Department of Pharmacy and Yonsei In stitute of Pharmaceutical Sciences, College of Pharmacy, Yonsei University

This protocol is published without a DOI.

College of Pharmacy, Yonsei University

ksun.chae

ABSTRACT

Currently, treatment targets of ulcerative colitis (UC) are defined as clinical remission and endoscopic improvement. However, there is debate over whether histologic target should also be considered as an additional treatment target. Multiple studies indicate histologic target as an important prognostic factor andsupport the inclusion of histologic target as treatment target. In addition, the U.S Food and Drug Administration (FDA) recommended histologic response and remission as the exploratory endpoints in clinical trials for drugs being developed for treating UC in April 2022.

Except for only 1 head-to-head VARSITY trial, there is no randomized controlled trial studies to compare in terms of histologic remission between FDA-approved biologics for UC, although the importance of histologic remission as a treatment target of UC continues to grow bigger.

The aim of the study is to compare biologic therapy for UC in terms of efficacy including histologic remission and safety to present a confident evidence that can be considered when selecting biologics with a therapeutic target for histologic remission through systematic literature search and newtwork meta-analysis.

PROTOCOL CITATION

ksun.chae, Yeon Sook Seo, Yun Mi Yu, Min Jung Chang, Junjeong Choi 2022. Protocol of An Indirect Comparison of Efficacy including Histologic Assessment and Safety in Biologic Agents in Ulcerative Colitis: Systematic Review and Network Meta-analysis. **protocols.io** https://protocols.io/view/protocol-of-an-indirect-comparison-of-efficacy-inc-chqtt5wn

CREATED

Oct 11, 2022

LAST MODIFIED

Oct 11, 2022

PROTOCOL INTEGER ID

71155

Backgroud

1 Currently, treatment targets of ulcerative colitis (UC) are defined as clinical remission and endoscopic improvement. However, there is debate over whether histologic target should also be considered as an additional treatment target. Multiple studies indicate histologic target as an important prognostic factor andsupport the inclusion of histologic target as treatment target.[1-5] In addition, the U.S Food and Drug Administration (FDA) recommended histologic response and remission as the exploratory endpoints in clinical trials for drugs being developed for treating UC in April 2022.[6]

Except for only 1 head-to-head VARSITY trial, there is no randomized controlled trial studies to compare in terms of histologic remission between FDA-approved biologics for UC, although the importance of histologic remission as a treatment target of UC continues to grow bigger. [7]

The aim of the review proposed here is to compare biologic therapy for UC in terms of efficacy including histologic remission and safety to present a confident evidence that can be considered when selecting biologics with a therapeutic target for histologic remission.

Method

2 ***Search strategy***

This study will be conducted according to the Preferred Reporting Items for Systematic

Review and Network Meta-analysis (PRISMA NMA)[8] checklist, which is an extension of traditional pairwise meta-analysis.

For efficient evidence collection, the research question will be set based on the PICO-SD (P: Population, I: Intervention, C: Comparator, O: Outcome, SD: Study Design) framework.[9] In this study, 'Is there a difference in the efficacy including histological assessment, and safety between biologic therapy in UC?' was selected as a key question, and the subject was set as an adult patient with moderately to severely UC. Intervention drugs were set as FDA-approved biologics for moderately to severely UC until September 2022, and comparative drugs were defined as drugs including intervention drugs and placebo.The efficacy endpoints were set as follows: 1) Clinical remission, 2) Corticosteroid-free remission, 3) Endoscopic improvement, and 4) Histologic remission. As safety endpoints, all safety assessments results were included for a comprehensive search. The study design was set as the randomized controlled trial.

The literature search will be conducted using 4 electronic databases, including the major literature search databases Pubmed, EMBASE, The Cochrane Library, and the ClinicalTrials.gov site providing clinical information. The search will be conducted on literature published until September 2022, and there is no restriction on the year of publication of the literature.

Literature selection will be conducted by two researchers independently based on the collected literature. First, literatures requiring full-text review will be selected through titles and abstracts, and full-text reviews will be conducted to select the literatures to be included in the analysis. If there is a discrepancy in the literature selection review process, the final decision will be made through discussion.

3 *Eligibility criteria*

The literatures for analysis will be selected based on the following criteria through full-text reviews.

The inclusion criteria are: 1) A study of adult patients with moderately to severely UC, 2) A study including biologic therapy with the same regimen as FDA-approved regimen, 3) A study that includes the efficacy and/or safety results of induction and/or maintenance phase after administration of biologics, and 4) A randomized controlled trial.

The exclusion criteria are: 1) A study using biologics that do not have any histologic assessment result, 2) Review studies, observational studies, case studies, academic abstracts, correspondence, or ongoing studies with no reported results, and 3) A study written in other languages than English.

4 *Data analysis*

Efficacy and safety results at each time point will be extracted from selected clinical trials and summarized in a separate excel file.

4.1 Bayesian Network Meta-analysis

To compare the effects of each of the biologics at the same time, NMA based on the Bayesian framework by integrated all available study results

will be conducted.[10]All NMA will be analyzed using the GEMTC package in R software version 4.2.0 (R foundation for Statistical Computing, Vienna, Austria).

4.2 Sensitivity analysis

If needed, sensitivity analysis will be conducted to evaluate the effect of special parameter. Sensitivity analysis will also be conducted with the same simulation settings as the main analysis using the GEMTC package in R software version 4.2.0.

5 *Risk of bias*

To assess the risk of bias, the Cochrane groups risk of bias assessment tool, Risk of Bias (RoB) 2, which was developed for use with randomized controlled trials will be used. The RoB 2 tool is consist of 5 domains, 1) bias arising from the randomization process, 2) bias due to deviations from intended interventions, 3) bias due to missing outcome data, 4) bias in measurement of the outcome, and 5) bias in selection of the reported result. Risk of bias judgement will be conducted through 3 level: Low risk of bias, Some concerns, or High risk of bias.[11]

Reference

6 *Reference*

1. Peyrin-Biroulet, L., Sandborn, W., Sands, B. E., Reinisch, W., Bemelman, W., Bryant, R. V., ... & Colombel, J. F. (2015). Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Official journal of the American College of Gastroenterology| ACG*, *110*(9), 1324-1338.
2. Rubin, D. T., Ananthakrishnan, A. N., Siegel, C. A., Sauer, B. G., & Long, M. D. (2019). ACG clinical guideline: ulcerative colitis in adults. *Official journal of the American College of Gastroenterology| ACG*, *114*(3), 384-413.
3. Feuerstein, J. D., Isaacs, K. L., Schneider, Y., Siddique, S. M., Falck-Ytter, Y., Singh, S., ... & Terdiman, J. (2020). AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*, *158*(5), 1450-1461.
4. Lamb, C. A., Kennedy, N. A., Raine, T., Hendy, P. A., Smith, P. J., Limdi, J. K., ... & Hawthorne, A. B. (2019). British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*, *68*(Suppl 3), s1-s106.
5. Turner, D., Ricciuto, A., Lewis, A., D'amico, F., Dhaliwal, J., Griffiths, A. M., ... & Dignass, A. (2021). STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology*, *160*(5), 1570-1583.
6. U.S Food and Drug Administration (2022). Ulcerative Colitis: Developing Drugs for Treatment Guidance for Industry https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ulcerative-colitis-developing-drugs-treatment

7. Sands, B. E., Peyrin-Biroulet, L., Loftus Jr, E. V., Danese, S., Colombel, J. F., Törüner, M., ... & Schreiber, S. (2019). Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *New England Journal of Medicine*, *381*(13), 1215-1226.
8. PRISMA (2015). PRISMA for Network Meta-Analyses http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis
9. Eriksen, M. B., & Frandsen, T. F. (2018). The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. *Journal of the Medical Library Association: JMLA*, *106*(4), 420.
10. Hu, D., O'Connor, A. M., Wang, C., Sargeant, J. M., & Winder, C. B. (2020). How to conduct a Bayesian network meta-analysis. *Frontiers in veterinary science*, *7*, 271.
11. Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... & Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj*, *366*.