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Protocol of An Indirect Comparison of Efficacy including Histologic Assessment and Safety in Biologic Agents in Ulcerative Colitis: Systematic Review and Network Meta-analysis V.2

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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.

Troubleshooting

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.

2.1 *Definition of Endpoints*

[Clinical remission]

Clinical remission was defined as total Mayo score of less than or equal to 2 with no individual subscore greater than 1. The Mayo score is composed of 4 categories (stool frequency, rectal bleeding, endoscopic appearance and PGA) rated from 0 to 3 that are summed to give a total score that range from 0 to 12. It is the most commonly used disease activity index in clinical trials for UC.

[Corticosteroid free remission]

Corticosteroid free remission was defined as clinical remission (defined as total Mayo score of less than or equal to 2 with no individual subscore greater than 1) without concomitant corticosteroids at the end of the maintenance phase in patients who were using corticosteroids at baseline.

[Endoscopic improvement]

Endoscopic improvement (previously known as Mucosal healing) was defined as endoscopic subscore of Mayo score (MES) of less than or equal to 1 point. The MES evaluates the degree of endoscopic rectal inflammation based on a 4-point scale according to flexible proctosigmoidoscopy findings.

[Histologic remission]

Currently, there is no standard definition for histologic remission, so both the definitions and terms of histologic assessment set for each study were slightly different. It was assessed by the Nancy Historical Index (NHI) in HIBISCUS1 and 2 studies, and by the Geboes score and Robarts Histopathology Index (RHI) in UNIFI, VARSITY, and VISIBLE1 studies. The RHI and the NHI are the only two index recommended by the ECCO for use in patients with UC. Among the results of the UNIFI, VARITY, and VISIBLE1 studies, the results of the histologic remission which defined by RHI that most matches the definition by NHI used in HIBISCUS 1 and 2 studies were included in this analysis, and the definition are as follows.

Histologic remission is defined as RHI of less than or equal to 3 point in UINIFI study and less than 3 point in VARITY and VISIBLE1 studies. The RHI is composed of 4 categories (1: lamina propria chronic inflammation; 2: lamina propria neutrophils; 3: epithelial neutrophils; 4: surface epithelial injury) rated from 1-4 that are summed with different weights to give a total score ranges from 0 to 33.

Histologic remission is defined as NHI of less than or equal to 1 point in in HIBISCUS1, 2 studies. The NHI score ranges from 0 to 4, with the following definitions for each

grade: 0 is no histologically significant disease; 1 is chronic inflammatory infiltrate with no acute inflammatory infiltrate; and 2, 3, and 4 are mildly, moderately, and severely active disease, respectively.

[*Treatment emergent adverse event*]

A TEAE was defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug, regardless of its causal relationship to study drug.

[*Treatment emergent serious adverse event*]

A TESAE was defined as any event considered serious by the investigator or that meet serious adverse event criteria of each clinical trial, not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug, regardless of its causal relationship to study drug.

[*Infection*]

Infection is defined as an adverse event classified as 'infections and infestations' by system organ class of Medical Dictionary for Regulatory Activities (MedDRA), regardless of its causal relationship to study drug.

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]

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