

BMJ Open Impact of biological agents and tofacitinib for moderate-to-severe ulcerative colitis on health-related quality of life: a protocol for a network meta-analysis

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ABSTRACT

Introduction In the past few years, several options have been proposed as alternative and more effective therapeutic drugs for moderate-to-severe ulcerative colitis (UC), such as biological agents and tofacitinib. Most of the clinical studies related to UC aimed to evaluate the efficacy of the drugs on clinical outcomes such as disease activity and side effects. This review aims to compare the impact of infliximab, adalimumab, golimumab, ustekinumab, vedolizumab and tofacitinib for moderate-to-severe UC on health-related quality of life (HRQoL), thereby guiding clinical treatment and scientific research of this disease.

Methods and analysis We will search PubMed, Embase and Cochrane Library from inception until July 2021 for all randomised controlled trials (RCTs) reported in English as double-blind comparing infliximab, adalimumab, golimumab, ustekinumab, vedolizumab or tofacitinib as induction or maintenance therapies with another or with placebo in moderate-to-severe UC on HRQoL. The primary outcome of this study is changes in the mean difference in HRQoL scores. Data of each pairwise comparison will be synthesised to obtain summary standardised mean differences for continuous outcomes and ORs for dichotomous outcomes. Then, a network meta-analysis (NMA) will be performed, and a common-effects Mantel-Haenszel NMA will be conducted for dichotomous outcomes, while a random-effects NMA will be used for all other outcomes. Finally, we will follow the Grading of Recommendations, Assessment, Development and Evaluations approach to assess the confidence in estimates derived from NMA of the main outcomes.

Ethics and dissemination Only published secondary data will be used in this study, and therefore ethics approval is not required. The findings will be published in a peer-reviewed medical journal.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic and life-long condition characterised by inflammation and ulceration of the rectal and colonic mucosa. Patients with UC typically manifest recurring and episodic clinical symptoms,

Strengths and limitations of this study

- This network meta-analysis will provide a comprehensive summary of the direct and indirect evidence on the impact of biological agents and tofacitinib for moderate-to-severe ulcerative colitis on health-related quality of life (HRQoL).
- We will follow the Grading of Recommendations, Assessment, Development and Evaluations approach to assess the confidence in estimates derived from the network meta-analysis of the main outcomes.
- We will assess the HRQoL of individuals with moderate-to-severe ulcerative colitis who received biological agents or tofacitinib to inform clinicians and the development of guidelines for the management of those patients.
- It is expected that this systematic review will encourage further research to be conducted for which systematic review evidence of high quality is currently insufficient or lacking.
- Possible limitations of this review include the diverse outcome measurements, the possible role of confounding factors in biasing finding estimates and the limited data available for some interventions.

including rectal bleeding, bloody diarrhoea, urgency, tenesmus and abdominal pain.¹ In recent decades, many studies have reported that the incidence and prevalence of UC increased in Asia, making it a kind of global disease.²⁻³ The physical health and mental health of patients with UC are poorer than those of healthy subjects, posing a great direct and indirect burden on the patient and society.⁴ Therefore, given that the physical and emotional impact of UC causes a huge burden on patients' daily functioning and well-being, their health-related quality of life (HRQoL) is severely compromised.⁵ Recently, the US Food and Drug Administration (FDA) and the European Medicines

Agency (EMA) have suggested that HRQoL can be an important measure in drug development clinical trials.^{6,7}

Conventional treatments of UC, including 5-aminosalicylate, glucocorticoids and immunomodulators, have high rates of relapse.⁸ In the past few years, several options have been proposed as alternative and more effective therapeutic drugs for moderate-to-severe UC, such as anti-tumour necrosis factor α (anti-TNF- α) and anti-integrin antibodies.^{9–13} The efficacy and safety of infliximab, adalimumab, golimumab, ustekinumab, vedolizumab and tofacitinib in patients with moderate-to-severe active UC have been evaluated in recent studies.^{14,15} In the clinical trials of inflammatory bowel disease, outcomes reported by patients are mainly focused on the efficacy of drugs such as disease activity and side effects. However, as a useful index for guiding future clinical decision-making and healthcare policy, the HRQoL of patients with UC is less presented. The generic HRQoL measures contain the Short-Form 36 questionnaire (SF-36) and European Quality of Life-5 Dimensions (EQ-5D), while the Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease-specific questionnaire.¹⁶ A network meta-analysis (NMA) suggested that compared with placebo, induction treatment with infliximab, golimumab, adalimumab, vedolizumab and tofacitinib improves patients' quality of life.¹⁷ However, ustekinumab, a human IgG1 monoclonal antibody, has been approved for treating many diseases, such as psoriasis, psoriatic arthritis,¹⁸ Crohn's disease¹⁹ and UC recently.²⁰ Moreover, the efficacy and safety of ustekinumab in patients with moderate-to-severe UC have been evaluated in a phase III, randomised, double-blinded, placebo-controlled study.²⁰ Although a head-to-head clinical trial has been conducted to compare vedolizumab versus adalimumab in patients with moderate-to-severe UC, the lack of head-to-head trials renders that the existing evidence cannot provide a basis for a more effective comprehensive decision-making.²¹ Given the availability of a new drug, ustekinumab, for the treatment of UC and the publication of a head-to-head pilot study, a new NMA is warranted to further provide a comprehensive basis for biological agents and tofacitinib in the treatment of UC.

Therefore, we will conduct a systematic review and NMA to compare the impact of infliximab, adalimumab, golimumab, ustekinumab, vedolizumab and tofacitinib for moderate-to-severe UC on HRQoL, thereby guiding for clinical treatment and scientific research of this disease.

METHODS AND ANALYSIS

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO). We will adhere to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) and the guideline for systematic review and meta-analysis protocols (PRISMA-P), as well as the extension statement for NMA (PRISMA-NMA).^{22,23}

Data source and search strategy

We will search the PubMed, Embase and Cochrane Library from inception until July 2021 for all randomised controlled trials (RCTs) reported as double-blind to compare infliximab, adalimumab, golimumab, ustekinumab, vedolizumab and tofacitinib as induction or maintenance therapies with another or with placebo in moderate-to-severe UC on HRQoL. ClinicalTrials.gov and the websites of the EMA and the FDA for ongoing or completed clinical trials will also be searched. Our search will be limited to papers published in international scientific journals and English. The databases will be searched using search terms related to ulcerative colitis, proctitis, IBD, anti-TNF, infliximab, adalimumab, golimumab, tofacitinib, ustekinumab, anti-alpha4, Janus Kinases and RCTs. The search strategy is listed in online supplemental file 1. Furthermore, we will search for additional RCTs in the reference lists of included studies.

Eligibility criteria

Population

Adults (aged >18 years) with moderate-to-severe UC (Mayo Clinic score of 6–12, with an endoscopic subscore of 2 or 3) who were either treatment-naïve (first-line) or previously exposed to TNF- α antagonists (second-line) will be included in this study.

Interventions and comparisons

This review will include interventions including infliximab, adalimumab, golimumab, vedolizumab, ustekinumab or tofacitinib, and the treatment courses of greater than 2 weeks. Comparisons may include another intervention as mentioned above or placebo.

Outcomes

The primary outcome of this study is changes in the mean difference in HRQoL scores. We will measure the primary outcome at the end of induction therapy (6–8 weeks) and the end of maintenance therapy (approximately 1 year). The HRQoL measures considered in this study are SF-36, EQ-5D and IBDQ. Secondary outcomes are the proportion of patients who achieved clinically significant improvement in the HRQoL (as defined by the investigators of each study) and the proportion of patients with an IBDQ total score ≥ 170 points.

Study designs

We will include RCTs that provide at least one comparison between two interventions of interest. In addition, we will not limit study inclusion by publication status and period in which the study has been conducted.

Study selection

Literature search records will be imported into EndNote V.X9 (Thomson Reuters, New York, NY, USA) literature management software. Two reviewers will independently read the titles and abstracts of retrieved studies according to the inclusion criteria to identify potentially eligible RCTs for inclusion. The same two reviewers will obtain

the full-text reports of potentially eligible studies and independently assess those studies for inclusion or exclusion. Disagreements will be resolved by a third reviewer.

Data extraction

Data will be extracted using a prespecified Microsoft Excel collection form. Two reviewers will independently extract detailed information from those included articles. Discrepancies will be resolved through team discussion or consulting a third investigator. The following information will be extracted from each study: study characteristics, participants' baseline characteristics and HRQoL outcomes. Data from different reports for the same study will be collated.

Risk of bias assessment among included studies

To evaluate the risk of bias, we will use the Cochrane Collaboration revised tool to assess risk of bias in randomised trials (RoB V.2.0).^{24 25} Two independent reviewers will perform the evaluation using the provided Microsoft Excel form. If disagreements occur, the final result will be made by consensus with the involvement of another member of the review group. Studies reporting at least one primary outcome will be evaluated in the following domains: sequence for random allocation, allocation concealment, blinding of study personnel and participants, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases such as sponsorship bias. Studies that meet all the criteria were rated as 'low' risk, while studies with insufficient procedures in at least one domain were rated as 'high' risk. In all other cases, studies were rated to be at 'unclear' risk of bias.²⁵

Statistical synthesis of study data

Pairwise meta-analyses

The characteristics of the included RCTs will be summarised. We will synthesise data of each pairwise comparison to obtain summary standardised mean differences for continuous outcomes and ORs for dichotomous outcomes, both with 95% CIs. Statistical heterogeneity across trials will be evaluated by I^2 statistics and Cochran's Q test. I^2 statistic with values $>50\%$ or $p < 0.10$ for Cochran's Q test suggested significant heterogeneity.²⁶ Data from all included trials were pooled to assess the overall effect on HRQoL of any active treatment compared with placebo.

Network meta-analysis

R V.4.0.4 and STATA V.15.1 (Stata Corp, College Station, TX, USA) were used for NMA. For dichotomous outcomes, we will perform a common-effects Mantel-Haenszel NMA.²⁷ For all other outcomes, we will employ a random-effects NMA given a single heterogeneity parameter for different comparisons in each network. Each node represents a treatment option, and the size of nodes is relevant to the sample size of each treatment in network diagrams, and the line between two certain nodes indicates that a direct comparison between the two treatment regimens exists; also the width of lines is related to the

number of studies.¹⁴ For each outcome, we will use the rankogram plots and the surface under the cumulative ranking curves (SUCRA) to figure out the hierarchy of different therapies. The probabilities of therapies will be presented by the rankogram plots supposing any of the possible ranks. Furthermore, SUCRA curves will be shown as percentages, 100% for the best treatment and 0% for the worst treatment.²⁸

Sensitivity analyses

To understand how the following factors influence the effect estimates, we will perform sensitivity analysis by excluding studies with a high risk of bias in each assessed item. In addition, we will conduct a sensitivity analysis by excluding those studies where very high/low dosages were used for off-label medications.

Assessment of inconsistency

The consistency assumption will be assessed for each comparison where there is direct and indirect evidence and the two will be compared. Furthermore, 'design-by-treatment interaction' models will be used to examine the consistency across the whole network, which carry out an overall significance test for inconsistency.

Assessment of publication bias

For the primary outcome, we will use Egger's test and funnel plots to assess the publication bias of the included studies. We will try to explain funnel plot asymmetry if the funnel plots are found to be asymmetrical.²⁹

Grading the quality of evidence

We will follow the Grading of Recommendations, Assessment, Development and Evaluations approach to assess the confidence in estimates derived from the NMA of the main outcomes. In this method, direct evidence from RCTs will be rated as high confidence and can be downgraded according to the following five domains—risk of bias, indirectness, imprecision, inconsistency and publication bias—to levels of moderate, low and very low confidence.^{30 31}

Patient and public involvement

There was no patient or public involvement in the design of this study, or conduct, or reporting or dissemination plans of this manuscript.

Ethics and dissemination

This work relies on published data and therefore does not require an ethical approval. The findings will be published in a scientific peer-reviewed journal.

Contributors XM and DZ conceived the idea for this study; DZ designed the meta-analysis; XM and HX provided statistical advice and input; XM drafted the protocol. DZ and HX reviewed the protocol and provided critical feedback. All authors approved the manuscript in its final form.

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Competing interests None declared.

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