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# Etrolizumab as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis: a protocol of systematic review and meta-analysis of placebo-controlled, randomised clinical trials

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## ABSTRACT

**Introduction** Etrolizumab is a gut-targeted, anti-β7 integrin, monoclonal antibody. Recently, data from phase 2 and 3 trials presented different results in patients with moderately to severely active ulcerative colitis. The aim of this study is to summarise the latest published trials to analysis the role of etrolizumab in treatment of moderately to severely active ulcerative colitis during induction and maintenance phases.

**Methods** Eligible randomised controlled trials (RCTs) will be retrieved from following databases: PubMed, Web of Science and the Cochrane Library. The last search time is May 2023. Two reviewers will independently identify RCTs according to inclusion and exclusion criteria. The primary outcome is clinical remission. The second outcomes are clinical response, endoscopic remission, endoscopic improvement, histological remission, any adverse event. The Grades of Recommendations, Assessment, Development and Evaluation tool will be established to estimate the evidence level of each outcome. All compute will be accomplished with Stata V.17.0 software.

**Ethics and dissemination** This systematic review and meta-analysis will be disseminated through peer-reviewed journals. No ethical approval requirements are required because the results presented in this study are conducted based on published data.

**PROSPERO registration number** CRD42023415369.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will be conducted with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.
⇒ Induction and maintenance phases will be separately analysed.
⇒ Included studies will be strictly restricted as placebo-controlled, randomised clinical trials.
⇒ Grades of Recommendations, Assessment, Development and Evaluation is employed to assess evidence level of outcomes.
⇒ One potential limitation of this study is that substantial heterogeneity will exist among included studies.

## INTRODUCTION

### Description of the condition

Ulcerative colitis (UC), a subtype of inflammatory bowel disease (IBD), is characterised by chronic, disabling, inflammatory disease of the colon that has a perennial detrimental influence on patient's quality of life.[1–4] Immunomodulators (such as azathioprine, mercaptopurine and tumour necrosis factor inhibitors), corticosteroids and targeted therapies are used for patients active UC; however, numerous patients do not retain an enduring response to these treatment, especially among patients with moderately to severely active UC.[4–6] Hence, feasible, valuable and safe targeted therapy that possesses ability to implement clinical remission is warranted for these patients.

Etrolizumab is the first biologic, dual-action, anti-β7 monoclonal, IgG1-humanised antibody in the gut that specifically targets the β7 subunit of both the α4β7 and α4Eβ7 integrins, which regulate trafficking and retention of leucocyte/lymphocyte subsets, respectively, in the intestinal mucosa. Rutgeerts *et al* conducted the phase I, randomised trial in 2013 with 33 patients (26 in etrolizumab and 7 in placebo) and verified etrolizumab is well tolerated among patients with moderate-to-severe UC.[7] In 2014, Vermeire *et al* published a first phase II, placebo-controlled, randomised clinical trial and demonstrated that etrolizumab is superior to placebo as regard achieving clinical remission in the

Table 1 Search strategy

| | |
|---|---|
| #1 | Etrolizumab[Title/Abstract] |
| #2 | rhuMAb Beta7[Title/Abstract] |
| #3 | ANTI-BETA7[Title/Abstract] |
| #4 | PRO145223[Title/Abstract] |
| #5 | #1 OR #2 OR #3 OR #4 |
| #6 | Colitis, Ulcerative[Mesh terms] |
| #7 | Ulcerative Colitis[Title/Abstract] |
| #8 | Idiopathic Proctocolitis[Title/Abstract] |
| #9 | Colitis Gravis[Title/Abstract] |
| #10 | #6 OR #7 OR #8 OR #9 |
| #11 | Inflammatory bowel diseases[Mesh terms] |
| #12 | Inflammatory Bowel Diseases[Title/Abstract] |
| #13 | Bowel Diseases, Inflammatory[Title/Abstract] |
| #14 | #11 OR #12 OR #13 |
| #15 | #5 AND (#10 OR #14) |

induction therapy process.[8] However, evidence-based data is still insufficient.[9] The aim of this systematic review and meta-analysis of RCTs is to collect newest evidence on application of etrolizumab for patients with UC.

## METHODS

### Literature search

This protocol was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines.[10] Meanwhile, the systematic review will be conducted by following PRISMA guidelines.[11] Here, we will perform literature search to collect relevant studies from PubMed, Embase and the Cochrane Library databases by using predefined key words (table 1) from inception until 1 July 2023. Furthermore, to broaden the search, previous published reviews and reference lists of relevant articles will be screened.

### Eligibility criteria

#### Types of studies

Here, to generate high level evidence for this topic, we only included placebo-controlled RCTs. Also, to broaden the search, no restriction on geographical region or year of publication.

#### Types of participants

Patients, age>18, with moderately to severely active UC (Mayo Clinic total score of 6–12 with an endoscopic subscore of≥2, a rectal bleeding subscore of≥1, and a stool frequency subscore of ≥1), possess a definite diagnosis of UC for a duration of 3 months or more, as evidenced by clinical and endoscopic findings, along with evidence of disease extending to 20 cm or beyond from the anal margin, will be enrolled in present analysis.[12]

#### Types of interventions

Patients in intervention group will receive etrolizumab for induction or maintenance therapy. Simultaneously, patients also receive matching placebo, such as subcutaneous dummy adalimumab saline placebo.

#### Types of control group

For this group, patients will only receive matching placebo.

### Outcomes

The primary outcomes are clinical remission, clinical response, while second outcomes are endoscopic remission, endoscopic improvement, histological remission and any adverse event.

### Exclusion criteria

An article will be excluded if meets the one of the following exclusion criteria:

1. Pharmacokinetics, pharmacodynamics analysis.
2. Other subtype IBD, such as Crohn's disease.
3. Case reports, case series, letters to editor, reviews, comments, animal studies or cost-effective studies.
4. Incomplete research data.
5. Articles that were written in non-English languages.

### Study selection and data extraction

After downloading all identified records from PubMed, Embase and the Cochrane Library databases, according to pre-established eligibility and exclusion criteria, two trained investigators (XQ, MW) will independently identify eligible RCTs. During study selection, any divergences or other issues will be settled down by advisement with a third investigator (XX). The process of study selection is presented in figure 1.

For eligible RCTs, available information will be independently recorded by using a standardised Microsoft Excel file by two investigators (XQ, MW). Analogously, a third investigator (XX) will umpire in case of arising any divergences or other issues. The following items are regarded as valuable for readers to comprehend context of study: the name of RCT, year of publish, multicentre (yes or no), study period, therapy phase, sample size of each group, etrolizumab regime, the definitions of outcomes and follow-up. An email will be sent to author if valuable data missing. With respect to republished studies, we only collect the newest one.

### Quality assessment

As the current systematic review merely including RCTs, the Cochrane Collaboration's tool, Risk of Bias V.2.0 tool[13] will be used to assess methodological quality of the included RCTs by two trained investigators (XQ, MW). Risk of Bias V.2.0 tool contains six sections: 'randomization process', 'deviations from intended interventions', 'missing outcome data', 'measurement of the outcome', 'selection of the reported result' and 'overall'. In this process, intraclass correlation coefficient will be computed to detect consistency in the data obtained by

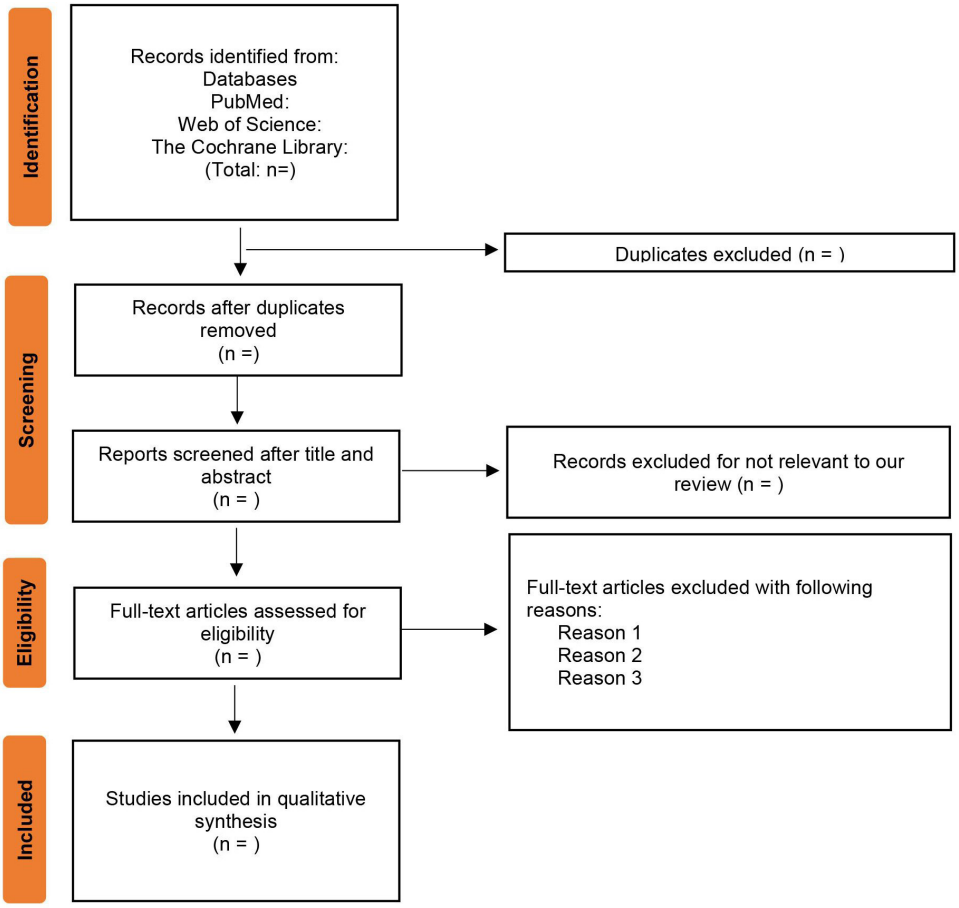


**Figure 1** Process of study selection.

the two investigators (XQ, MW) and a third investigator (XX) will redress evaluated results if necessary. The risk bias of included RCTs will be divided into the following three levels: 'low risk', 'some concerns' or 'high risk'.

## Measures of treatment effect

The Stata V.17.0 (Cambridge, UK) will be used to calculate statistics data. Here, for dichotomous data, risk ratio with its 95% CI will be estimated. For continuous data, weighted mean difference or standardised mean differences with its 95% CI will be estimated. Heterogeneity across RCTs is assessed by the Cochran Q statistic ($\chi^2$ test),[14] and $I^2$ are employed to depict the level of inter-study heterogeneity.[15] In case of $I^2$ more than 50%, or p value of $\chi^2$ test, data will be synthesised by using random-effect model with the Der Simonian-Laired method; otherwise, fix-effect model with the Mantel-Haenszel method will be used. A p value of less than 0.05 is considered as statistical significance, except for a p value of less than 0.10 for $\chi^2$ test.

## Subgroup analysis and sensitivity analysis

For all outcomes, subgroup analyses are conducted according to therapy phase (induction therapy, maintenance therapy), publish year, sample size. Also, for all outcomes, sensitivity analyses are performed to check the stability and consistency of pooled results with leave one out method.

## Assessment of publication bias

Publication bias will be visualised with funnel plot, and a p value of Egger'test will be calculated to estimate potential publication bias.[16]

## Quality of evidence

For this systematic review and meta-analysis, the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) tool will be used to divide evidence level of each outcome into four grades: 'high level', 'moderate level', 'low level' and 'critically low level'.[17]

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