

Efficacy and safety of etrolizumab in the treatment of inflammatory bowel disease: a meta-analysis

Yong gang Dai^{1,2}, Dajuan Sun¹, Jiahui Liu¹, Xiunan Wei¹, Lili Chi¹ and Hongya Wang²

¹ Shandong University of Traditional Chinese Medicine, Shandong, China

² Shandong Provincial Third Hospital, Shandong, China

ABSTRACT

Background. To explore the efficacy and safety of etrolizumab in treating inflammatory bowel disease (IBD) through meta-analysis.

Method. A comprehensive exploration encompassed randomized controlled trials examining the efficacy of etrolizumab in treating IBD across PubMed, Embase, Cochrane library, and Web of Science, with a search deadline of 1 December 2023. Quality assessment leaned on the Cochrane manual's risk-of-bias evaluation, while Stata 15 undertook the data analysis.

Result. Five randomized controlled studies involving 1682 individuals were finally included, Meta-analysis results suggested that compared with placebo, etrolizumab could improve clinical response (RR = 1.26, 95% CI [1.04–1.51]), clinical remission (RR = 1.26, 95% CI [1.04–1.51]) in IBD patients. Endoscopic alleviate (RR = 2.10, 95% CI [1.56–2.82]), endoscopic improvement (RR = 2.10, 95% CI [1.56–2.82]), endoscopic remission (RR = 2.10, 95% CI [1.56–2.82]), Endoscopic improvement (RR = 1.56, 95% CI [1.30–1.89]), histological remission (RR = 1.62, 95% CI [1.26–2.08]), and did not increase any adverse events (RR = 0.95, 95% CI [0.90–1.01]) and serious adverse events (RR = 0.94, 95% CI [0.68–1.31]).

Conclusion. According to our current study, etrolizumab is a promising drug in IBD.

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Corresponding authors

Lili Chi, chililiyl@163.com

Hongya Wang,

wangya828qing@163.com

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Additional Information and Declarations can be found on page 11

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, idiopathic inflammatory condition that can affect all parts of the digestive tract, characterized by mucosal immune dysregulation and recurrent bouts of intestinal inflammation ([Bisgaard et al., 2022](#); [Sasson et al., 2021](#)). Ulcerative colitis (UC) and Crohn's disease (CD) represent the two expression types of this condition, distinguished by the location and depth of inflammation, closely associated with genetic, immune, lifestyle, and environmental factors ([Agrawal et al., 2021](#); [Plevris & Lees, 2022](#); [Welz & Aden, 2023](#)). Although CD and UC are different diseases, from the point of view of disease occurrence, both UC and CD belong to autoimmune diseases, and their clinical manifestations are similar, so we can analyze them together. Epidemiological

studies reveal the highest prevalence of IBD in Europe and North America, with a rapid rise in incidence in emerging industrialized nations (Xu *et al.*, 2021). Individuals and their descendants migrating from regions with low IBD prevalence (such as the Middle East and South Asia) to areas with high prevalence exhibit increased susceptibility to IBD. However, the precise causes and mechanisms underlying IBD remain unclear. Inflammation and oxidative stress are generally perceived as key mechanisms in IBD pathogenesis (Barbieri, 2021; Zhao *et al.*, 2021). Clinically, treatments for IBD mainly include drugs like 5-aminosalicylic acid, corticosteroids, immunosuppressants (such as azathioprine), and biologics (like anti-TNF-[3] agents, anti-integrins, and anti-cytokine antibodies) (Baumgart & Le Berre, 2021). Unfortunately, these medications merely offer symptomatic relief without curing the disease and often lead to noticeable adverse effects such as anemia, liver and kidney dysfunction, leukopenia, cataracts, osteoporosis, malignancies, immunosuppression, and an increased risk of opportunistic infections (Hadji & Bouchemal, 2022). Some of these adverse effects are irreversible. Moreover, research indicates that early surgery and the use of immunosuppressants fail to prevent the tendency for reoperation and disease disability in Crohn's disease patients (Ouyang, Zhao & Wang, 2023). Hence, there is an urgent need to discover safe and effective therapies for IBD.

In recent years, anti-integrins have been used in therapy and have shown promise (Solitano *et al.*, 2021). Natalizumab, Vedolizumab and etrolizumab are part of this class of drugs. Natalizumab is a monoclonal antibody targeting the $\alpha 4$ integrin, which is rarely used nowadays due to safety concerns (Gordon *et al.*, 2002). Vedolizumab is a selective antibody targeting the $\alpha 4\beta 7$ integrin, which plays an important role in intestinal Leukocytes play an important role in the migration of leukocytes to the intestine (Pouillon, Vermeire & Bossuyt, 2019). Etrolizumab is a humanized monoclonal IgG1 antibody directed against the $\beta 7$ subunit of the heterodimeric integrins $\alpha 4\beta 7$ and $\alpha E\beta 7$. $\alpha 4\beta 7$ integrin is a key mediator of leukocyte infiltration in the gastrointestinal tract by interacting with MAdCAM-1 on the vascular endothelium of mucosal tissues (Lichnog *et al.*, 2019; Makker & Hommes, 2016). However, the efficacy and safety of etrolizumab for IBD are still controversial (Fiorino, Gilardi & Danese, 2016), so we hope to resolve these controversies with this study and provide new options for clinical patient treatment.

METHOD

The systematic review described herein was accepted by the online PROSPERO international prospective register of systematic reviews (Page *et al.*, 2021) of the National Institute for Health Research (CRD42023494132).

Inclusion and exclusion criteria

The included population met the diagnostic criteria for inflammatory bowel disease (Watermeyer *et al.*, 2022). Etrolizumab was used in the experimental group and placebo was used in the control group, and the primary outcome were clinical remission (defined as (Mayo Clinic Score) MCS of ≤ 2); clinical response (3-point decrease and 30% reduction in MCS and 1-point decrease); endoscopic remission (defined as Mayo endoscopic sub score of 0); endoscopic improvement (defined as Mayo endoscopic sub score of ≤ 1); and

the secondary outcome were histological remission (defined as Nancy histological index [NHI] of ≤ 1 among patients with histological inflammation at baseline); adverse events, the randomized controlled trial was included in this study.

Conference abstracts, meta-analyses, systematic reviews, animal experiments, Full text is not available and case reports will be considered for exclusion.

Literature retrieval

Randomized controlled trials on etrolizumab for inflammatory bowel disease were searched in PubMed, Embase, Cochrane Library, Web of science, with a search deadline of 1 December 2023, using the mesh word combined with a free word: etrolizumab inflammatory bowel disease. Detailed search strategies are provided in [Supplemental Information 1](#).

Data extract

Two authors (DYG and SDJ) rigorously screened the literature based on predetermined inclusion and exclusion criteria. In case of any disagreement, they resolved it through discussion or sought the opinion of a third person (WHY) to negotiate and reach consensus. Information extracted from the included studies included the following key details: authors, year, country, sample size, gender, mean age, Type of disease, intervention, and outcome.

Grade of evidence

To determine the quality of our results, we selected the Graded Recommendations Assessment Development and Evaluation (GRADE) system to evaluate the evidence ([Atkins et al., 2004](#)) for methodological quality. We considered five factors that could reduce the quality of the evidence, including study limitations, inconsistent findings, inconclusive direct evidence, inaccurate or wide confidence intervals, and publication bias. In addition, three factors that could reduce the quality of evidence were reviewed, namely effect size, possible confounding factors, and dose–effect relationships. A comprehensive description of the quality of evidence for each parameter data is provided ([Table S1](#)).

Included studies' risk of bias

Two investigators (DYG and SDJ) independently assessed the risk of bias as low, unclear, or high using the Cochrane Collaboration's tools ([Higgins et al., 2011](#)). If there was any disagreement, a third person (WHY) was consulted to reach consensus. The assessment included seven areas: generation of randomized sequences, allocation concealment, blinding of implementers and participants, blinding of outcome assessors, completeness of outcome data, selective reporting of study results, and other potential sources of bias.

Data analysis

The collected data were statistically analyzed using Stata 15.0 software (Stata Corp, College Station, TX, USA). Heterogeneity between included studies was assessed using I² values or Q-statistics. I² values of 0%, 25%, 50%, and 75% indicated no heterogeneity, low heterogeneity, moderate heterogeneity, and high heterogeneity, respectively. If the I² value was equal to or greater than 50%, a sensitivity analysis was performed to explore potential sources of heterogeneity. If heterogeneity was less than 50 per cent, analyses were

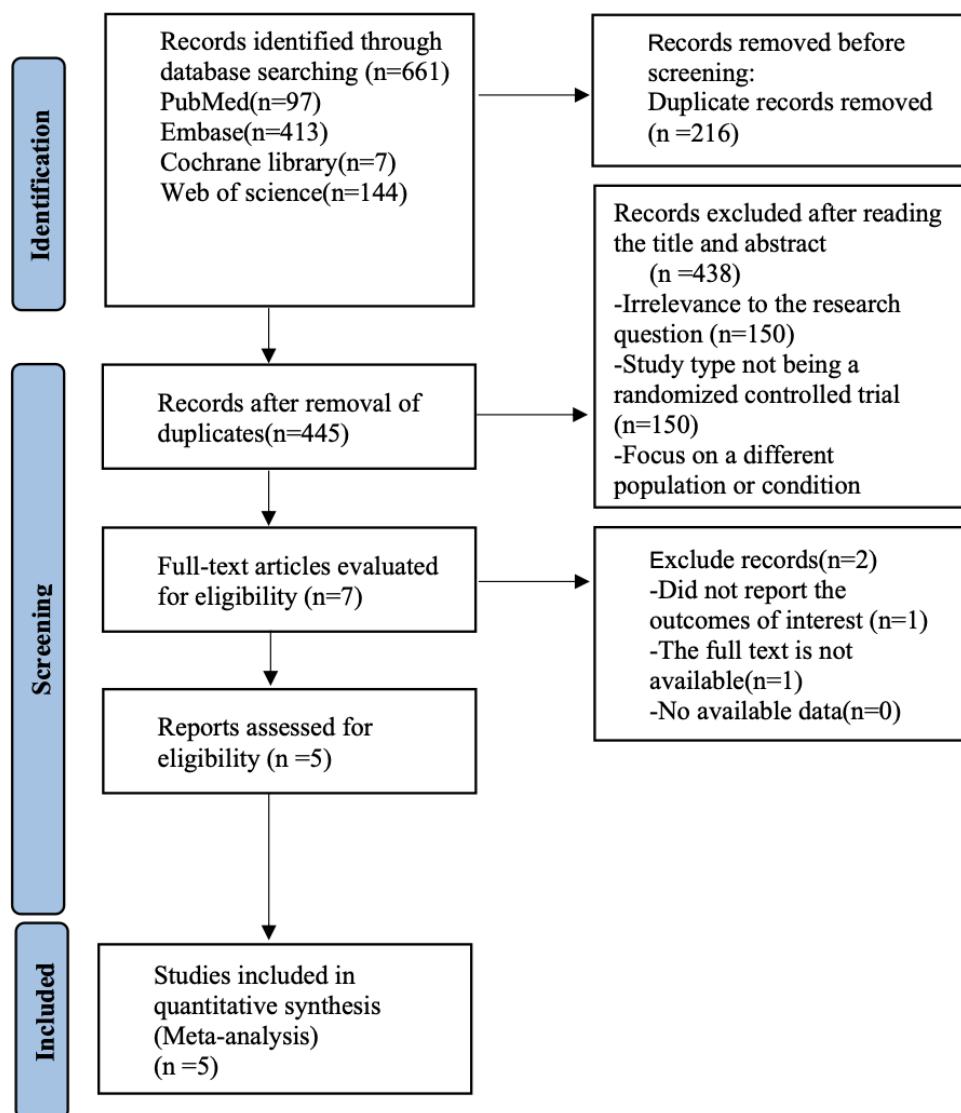


Figure 1 PRISMA flow chart.

Full-size DOI: 10.7717/peerj.17945/fig-1

conducted using a fixed-effects model. Risk ratio (RR) and 95% confidence interval (CI) for dichotomous variables. In addition, random effects model and Egger's test were used to assess publication bias.

RESULT

Study selection

Figure 1 shows our literature search process, which initially retrieved 661 documents, removed 216 duplicates, removed 438 articles by reading titles and abstracts, removed two papers by reading the full text, and finally included five ([Peyrin-Biroulet et al., 2022](#); [Rubin et al., 2022](#); [Sandborn et al., 2023](#); [Vermeire et al., 2022](#); [Vermeire et al., 2014](#)) randomized controlled trials for analysis.

Basic characteristics and risk of bias of the included studies

Five randomized controlled studies involving 1,682 individuals were finally included, in four articles ([Peyrin-Biroulet et al., 2022](#); [Rubin et al., 2022](#); [Vermeire et al., 2022](#); [Vermeire et al., 2014](#)) for ulcerative colitis and one ([Sandborn et al., 2023](#)) for Crohn's disease, doses of etrolizumab ranged from 100 to 300 mg. Baseline characteristics are shown in [Table 1](#). The five included studies clearly accounted for the method of randomization used, and the risk of bias results are shown in [Figures S2–S3](#).

Result of meta-analysis

Clinical response

Five articles were divided into seven trials mentioning clinical response and the test of heterogeneity was ($I^2 = 26.1\%$, $P = 0.247$), so the data were analyzed by using the fixed effect model and the analysis results ([Fig. 2](#)) suggested that compared with placebo, etrolizumab was able to improve IBD patients' clinical response ($RR = 1.26$, 95% CI [1.04–1.51]), and the difference was statistically significant.

Clinical remission

Three articles were divided into five trials mentioning clinical remission and the test of heterogeneity was ($I^2 = 26.1\%$, $P = 0.247$), so the data were analyzed by using the fixed effect model and the analysis results ([Fig. 3](#)) suggested that compared with placebo, etrolizumab was able to improve IBD patients' clinical remission ($RR = 1.26$, 95% CI [1.04–1.51]), and the difference was statistically significant.

Endoscopic remission

Five articles were divided into seven trials mentioning endoscopic remission and the test of heterogeneity was ($I^2 = 0\%$, $P = 0.826$), so the data were analyzed by using the fixed effect model and the analysis results ([Fig. 4](#)) suggested that compared with placebo, etrolizumab was able to improve IBD patients' endoscopic remission ($RR = 2.10$, 95% CI [1.56–2.82]), and the difference was statistically significant.

Endoscopic improvement

Four articles were divided into five trials mentioning endoscopic improvement and the test of heterogeneity was ($I^2 = 0\%$, $P = 0.556$), so the data were analyzed by using the fixed effect model and the analysis results ([Fig. 5](#)) suggested that compared with placebo, etrolizumab was able to improve IBD patients' endoscopic improvement ($RR = 1.56$, 95% CI [1.30–1.89]), and the difference was statistically significant.

Adverse event

Five articles were divided into seven trials mentioned adverse events (including any adverse events and serious adverse events), for any adverse events, the heterogeneity test ($I^2 = 43.2\%$, $P = 0.103$), so the data were analyzed by using the fixed effect model, and the results of the analysis ([Fig. 6](#)) suggested that compared with placebo Compared with placebo, etrolizumab was not statistically significant for any adverse events ($RR = 0.95$, 95% CI [0.90–1.01]); for serious adverse events, heterogeneity test ($I^2 = 0\%$, $P = 0.886$), so the

Table 1 Baseline characteristics.

Study	Year	Country	Race	Sample size		Gender (M/F)	Mean age (years)		Types of disease	Disease severity	Comorbidity	Medications	Intervention		Outcome
				EG	CG		EG	CG					EG	CG	
Peyrin	2022	France	White and Asian	384	95	278/201	39	36	ulcerative colitis	moderately to severely	NR	Corticosteroid and immunosuppressant use	Subcutaneous etrolizumab 105 mg once every 4 weeks	Placebo	F1; F2; F3; F4; F5; F6
Rubin	2022	USA	NR	144	72	113/103 (HIBISCUS I)	36.5	36	Ulcerative colitis	Moderately to severely	NR	Corticosteroid and Immunosuppressant use	Subcutaneous etrolizumab 105 mg once every 4 weeks	Placebo	F1; F2; F3; F4; F5; F6
				143	72	122/93 (HIBISCUS II)	39	36.5		Moderately to severely	NR	Corticosteroid and immunosuppressant use			
Sandborn	2023	USA	White	217	217	218/216	38.8	37.9	Crohn's disease	Moderately to severely	NR	Corticosteroid and immunosuppressant and anti-TNF use	Subcutaneous etrolizumab 105 mg once every 4 weeks	Placebo	F1; F3; F4; F5;
Vermeire	2022	Belgium	White	108	106	112/102	36	38	Ulcerative colitis	Moderately to severely	NR	Corticosteroid and immunosuppressant use	Subcutaneous etrolizumab 105 mg once every 4 weeks	Placebo	F1; F3; F4; F5; F6
Vermeire	2014	Belgium	White	81	43	71/63	42	37.5	Ulcerative colitis	Moderately to severely	NR	Corticosteroid and Immunosuppressant use	Subcutaneous etrolizumab 100/300 mg once every 4 weeks	Placebo	F1; F2; F3; F5

Notes.

EG, experimental group; CG, Control group; M/F, Male/Female; F1, clinical response; F2, clinical remission; F3, endoscopic remission; F4, endoscopic improvement; F5, adverse events; F6, Histological remission.

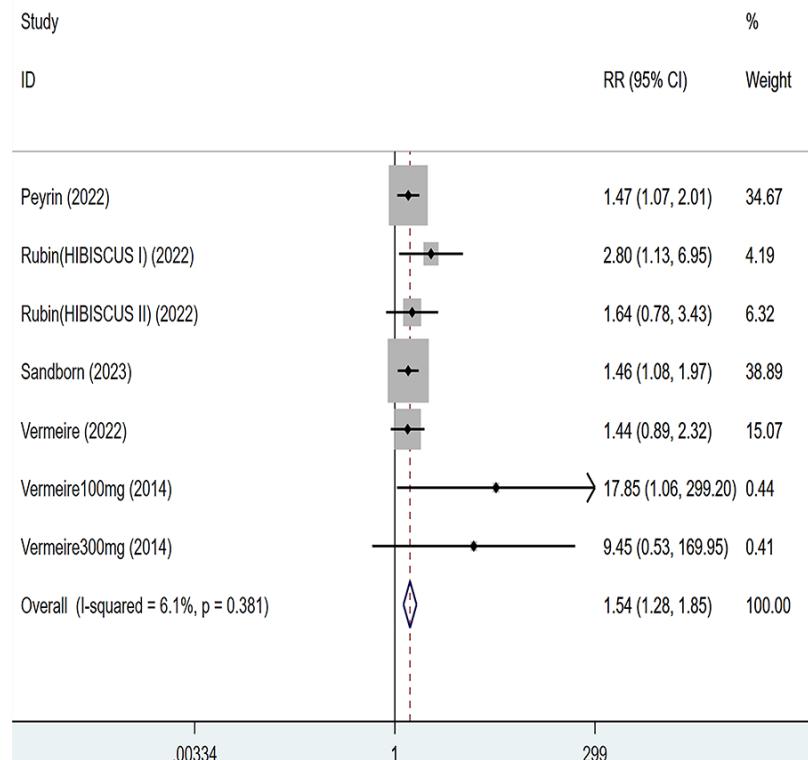


Figure 2 Forest plot of meta-analysis of clinical response.

[Full-size](#) DOI: 10.7717/peerj.17945/fig-2

data were analyzed using fixed effect model. The results (Fig. 7) suggested that etrolizumab was not statistically significant for serious adverse events compared to placebo (RR = 0.94, 95% CI (0.68–1.31]).

Histological remission

Three articles were divided into five trials mentioning histological remission and the test of heterogeneity was ($I^2 = 43.4\%$, $P = 0.151$), so the data were analyzed by using the fixed effect model and the analysis results (Fig. 8) suggested that compared with placebo, etrolizumab was able to improve IBD patients' histological remission (RR = 1.62, 95% CI [1.26–2.08]), and the difference was statistically significant.

Published bias

Publication bias was assessed by an Egger's test for clinical remission, clinical response, endoscopic remission, histologic–endoscopic mucosal improvement, adverse events. Which showed no publication bias (Figures S3–S8) for clinical remission ($P = 0.435$), endoscopic improvement ($p = 0.095$), adverse events ($P = 0.937$), histological remission ($P = 0.230$), However, publication bias was detected in clinical response ($P = 0.003$) and endoscopic remission ($P = 0.001$).

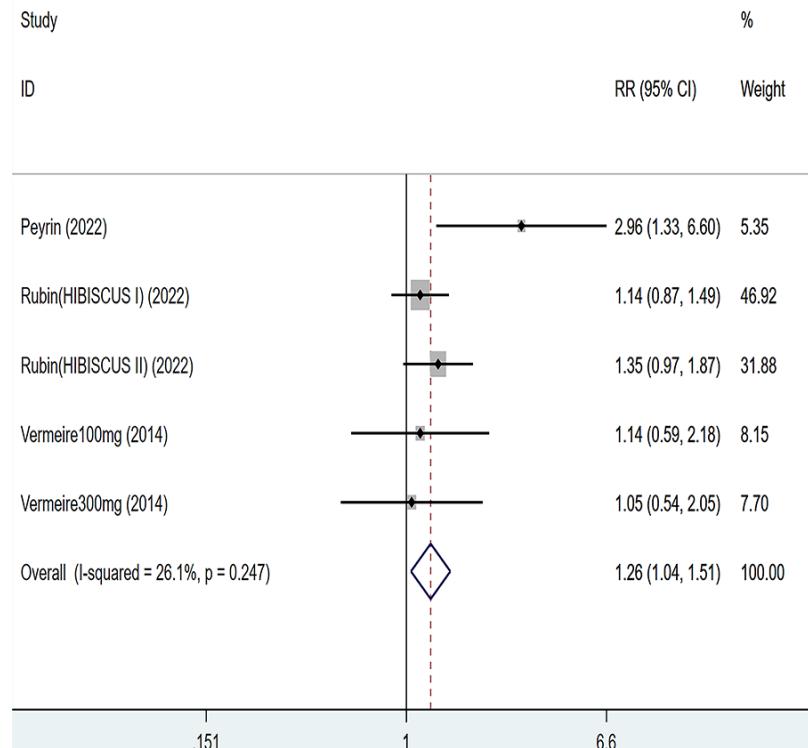


Figure 3 Forest plot of meta-analysis of clinical remission.

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DISCUSSION

As far as we are concerned, this is not the first time etrolizumab treatment for IBD has been evaluated, but a previous Cochrane study (*Rosenfeld et al., 2015*) included only two original studies. A 2019 meta-analysis (*Motaghi, Ghasemi-Pirbaluti & Zabih, 2019*) compared an indirect comparison of etrolizumab and infliximab. This is not consistent with our current meta-analysis inclusion metrics. Therefore, the current study included more high-quality studies and the conclusions are more credible.

In this study, we found that etrolizumab improved clinical response, clinical remission, endoscopic remission, endoscopic improvement, and histological remission in patients with IBD without increasing adverse events. The results of our study are further supported by the finding of *Rutgeerts et al. (2013)*. That etrolizumab is safe and well tolerated in patients with moderately to severely active UC. Consistent with these *in vitro* data, preclinical rodent studies demonstrated that blockade of $\beta 7$ integrins prevented T-cell recruitment to the inflammatory colon in a mouse model of IBD, whereas in a mouse model of multiple sclerosis, blockade of $\beta 7$ integrins had no effect on lymphocyte homing to the brain. The anti- $\alpha 4\beta 7$ antibody vedolizumab (vedolizumab) has also demonstrated clinical efficacy in UC and CD (*Feagan et al., 2008; Feagan et al., 2005*). Like vedolizumab, etrolizumab binds to $\alpha 4\beta 7$, but is unique in that it also blocks the binding of $\alpha E\beta 7$ to its ligand,

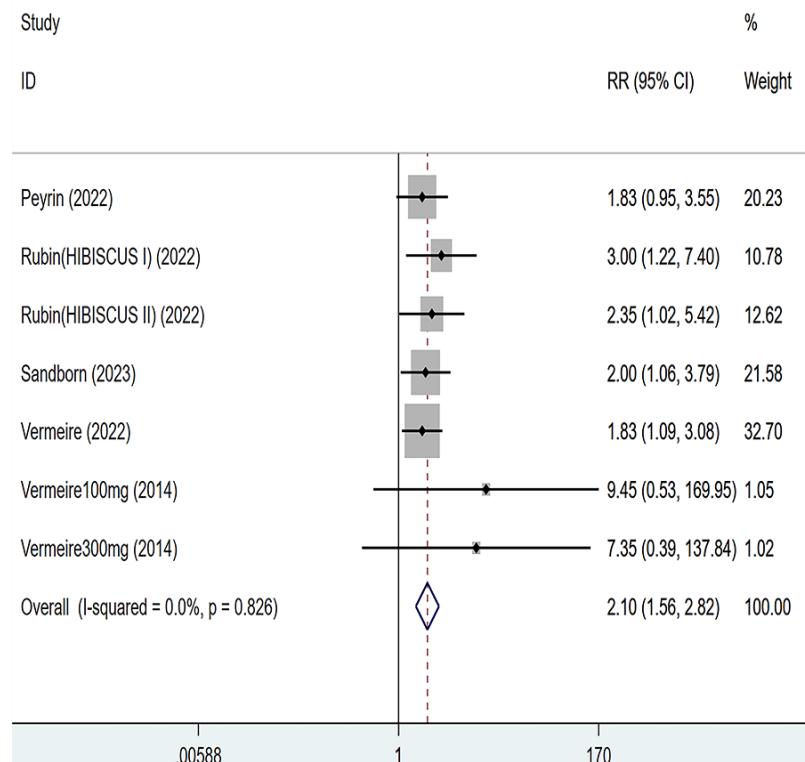


Figure 4 Forest plot of meta-analysis of endoscopic remission.

Full-size DOI: [10.7717/peerj.17945/fig-4](https://doi.org/10.7717/peerj.17945/fig-4)

e-calmodulin ([Tang et al., 2018](#)). Thus, etrolizumab can affect leukocyte composition within the intestinal mucosa through several mechanisms. First, as previously described, it can block entry of $\alpha 4\beta 7$ -expressing leukocytes into the intestine by inhibiting extravasation of mucosal endothelial microveins expressing madcam-1 ([Solitano et al., 2021](#); [Verstockt et al., 2018](#)). Notably, MADCAM-1 expression is increased in patients with UC and CD. In animal models, anti- $\beta 7$ or $\alpha 4\beta 7$ antibodies are effective in blocking lymphocyte migration into the inflamed intestinal mucosa ([Pérez-Jeldres et al., 2019](#)). Second, by inhibiting the interaction of $\alpha E\beta 7$ with E-cadherin, $\alpha E\beta 7$ can directly affect the retention of leukocytes in the intestinal mucosa ([Müsselwitz et al., 2020](#)). αE integrins are expressed at very low levels in peripheral blood, and are found predominantly on intestinal resident cells, including intraepithelial lymphocytes and dendritic cells ([Jaansson et al., 2008](#)). In the lamina propria of the human intestinal mucosa, more than 90% of intraepithelial lymphocytes and 50% of T cells expressed $\alpha E\beta 7$ integrin, suggesting a unique role in mucosal immunity. In addition, $\alpha E\beta 7$ is expressed on intestinal dendritic cells, which are associated with the production of pro-intestinal effector T cells ([Johansson-Lindbom et al., 2005](#)). Importantly, intraepithelial lymphocytes may exhibit cytotoxic activity against epithelial cells, and cells expressing $\alpha E\beta 7$ integrins have been shown to be pathogenic in mouse models of colitis and acute graft-versus-host disease ([Sandborn, 2012](#)). Etolizumab does not increase adverse

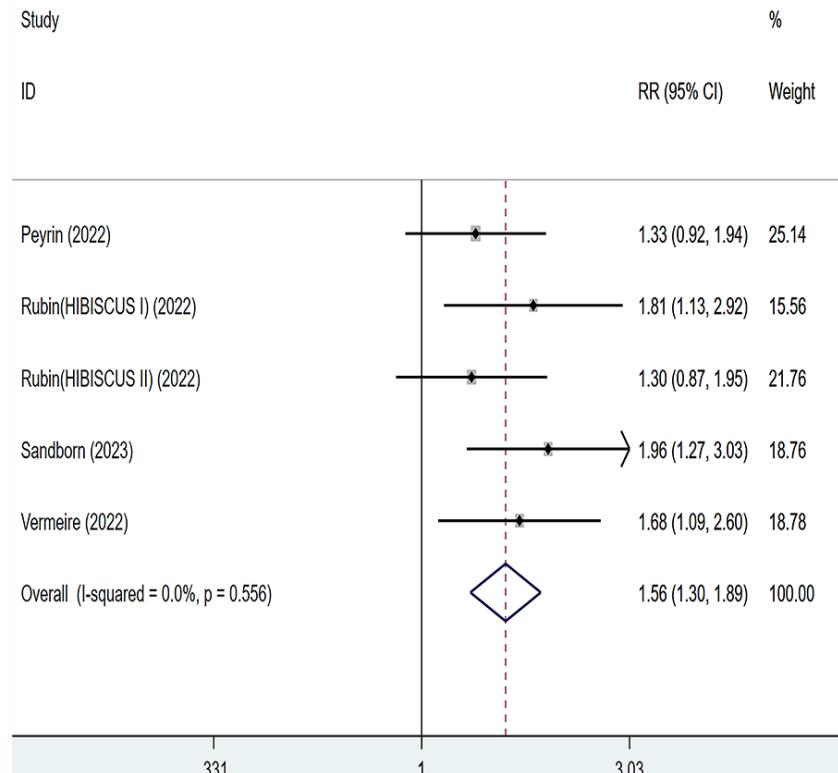


Figure 5 Forest plot of meta-analysis of endoscopic improvement.

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reactions. This may be because etrolizumab is a monoclonal antibody that acts on the $\alpha 4\beta 7$: MAdCAM-1 and α E β 7, Ecadherin complexes, which are primarily found in the intestinal epithelium ([Ungar & Kopylov, 2016](#)). The most common adverse reactions to etolizumab include exacerbation of ulcerative colitis, headache, nausea, abdominal pain, dizziness, malaise, nasopharyngitis, arthralgia, and urinary tract infections ([Gubatan et al., 2021](#)). Serious adverse reactions to etolizumab include bacterial peritonitis and worsening of ulcerative colitis. Although etolizumab has demonstrated an acceptable safety profile in previous trials, its safety could not be evaluated due to the small number of patients tested ([Weisskopf et al., 2018](#)). Although etrolizumab demonstrated an acceptable safety profile in previous trials, rare adverse events could not be observed due to the small number of patients tested. In addition, due to the small sample size of the trial, we were only able to detect a main effect of etrolizumab. It is expected that additional data from large-volume centers or population studies will provide more information on the safety and efficacy of etrolizumab ([Zundler et al., 2017](#)).

The risk of bias was low for all included studies. However, the GRADE analysis showed that the overall quality of evidence from etrolizumab trials was moderate or low due to small sample sizes. This means that further trials may change the estimates and improve their accuracy.

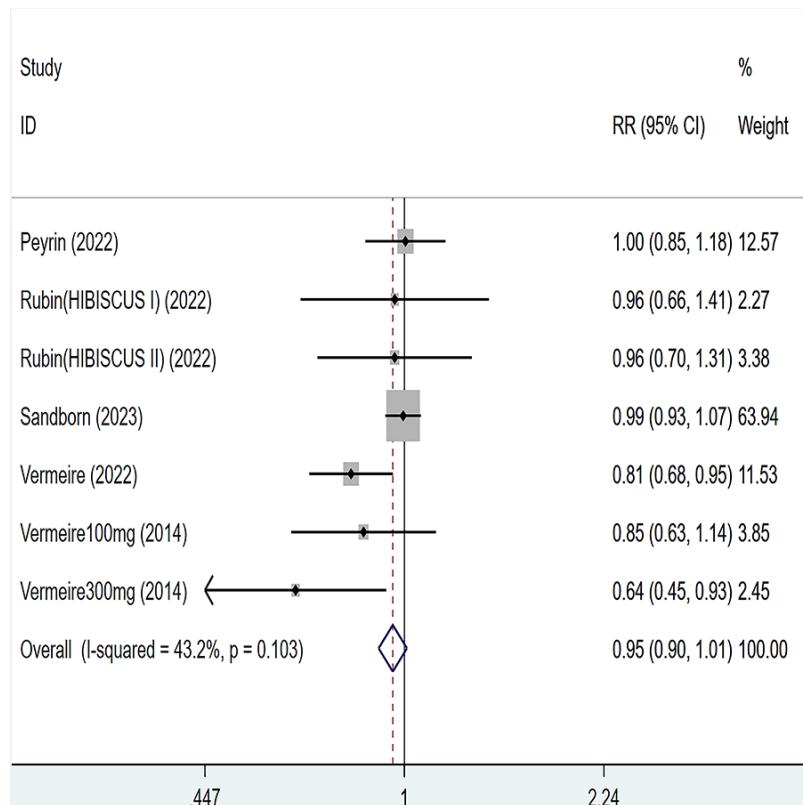


Figure 6 Forest plot of meta-analysis of any adverse events.

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Our study still has several limitations: firstly, due to the small number of studies we included, the number of people involved was small, which may affect the extrapolation of our findings. Secondly, due to the limitation of the number of included studies, we were not able to perform subgroup analyses for outcomes with large heterogeneity. Finally, the dose and duration of time used for etrolizumab were also inconsistent, which may also contribute to the source of heterogeneity.

CONCLUSION

According to our current study, etrolizumab is a promising drug in IBD, but due to the limitations of the study, we look forward to more high-quality, multicenter, large sample, randomized controlled studies to further support our view.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

The authors received no funding for this work.

Competing Interests

The authors declare there are no competing interests.

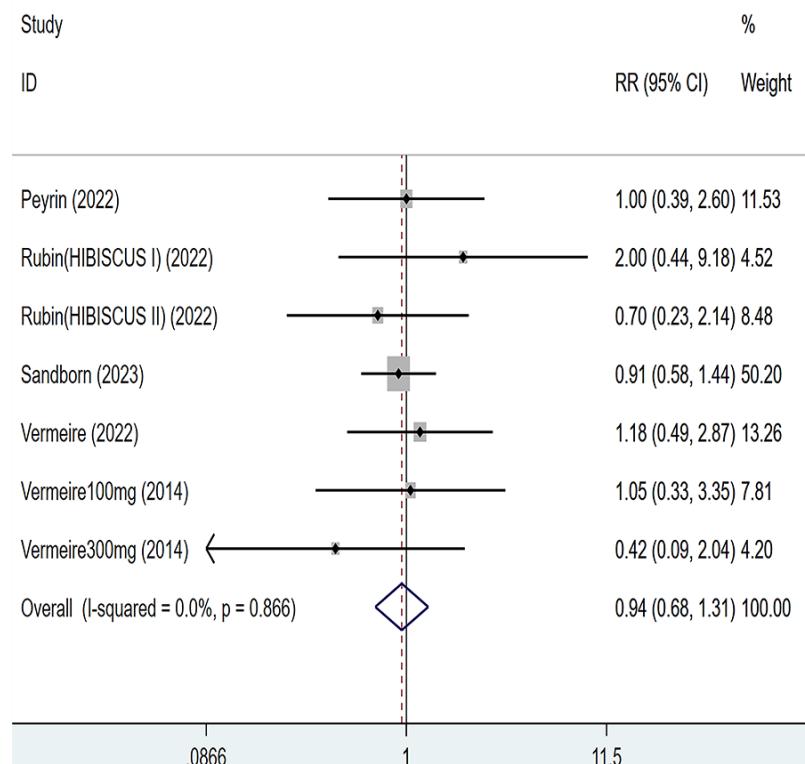


Figure 7 Forest plot of meta-analysis of serious adverse events.

Full-size DOI: 10.7717/peerj.17945/fig-7

Author Contributions

- Yong gang Dai conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Dajuan Sun conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Jiahui Liu conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Xiunan Wei conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Lili Chi conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.

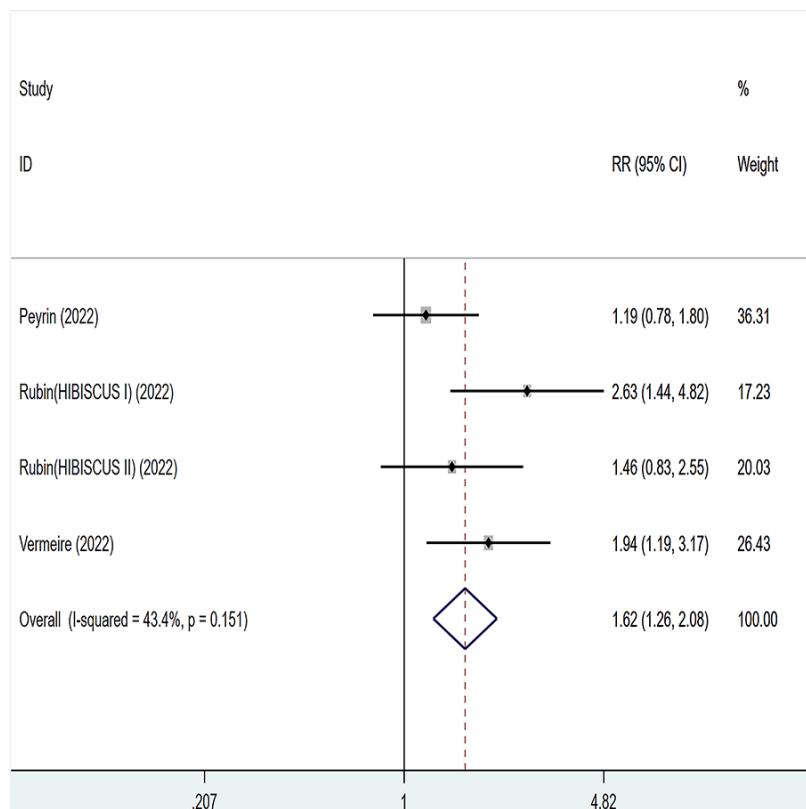


Figure 8 Forest plot of meta-analysis of histological remission.

[Full-size](#) DOI: 10.7717/peerj.17945/fig-8

- Hongya Wang conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

This is a systematic review / meta-analysis.

Supplemental Information

Supplemental information for this article can be found online at <http://dx.doi.org/10.7717/peerj.17945#supplemental-information>.

REFERENCES

Agrawal M, Spencer EA, Colombel JF, Ungaro RC. 2021. Approach to the management of recently diagnosed inflammatory bowel disease patients: a user's guide for adult and pediatric gastroenterologists. *Gastroenterology* **161**:47–65 DOI 10.1053/j.gastro.2021.04.063.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N,

Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams Jr JW, Zaza S. 2004. Grading quality of evidence and strength of recommendations. *BMJ* 328:1490 DOI 10.1136/bmj.328.7454.1490.

Barbieri JS. 2021. Isotretinoin and risk of inflammatory bowel disease: more data to support lack of meaningful risk. *Journal of the American Academy of Dermatology* 84:228–229 DOI 10.1016/j.jaad.2020.07.041.

Baumgart DC, Le Berre C. 2021. Newer biologic and small-molecule therapies for inflammatory bowel disease. *New England Journal of Medicine* 385:1302–1315 DOI 10.1056/NEJMra1907607.

Bisgaard TH, Allin KH, Keefer L, Ananthakrishnan AN, Jess T. 2022. Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment. *Nature Reviews Gastroenterology & Hepatology* 19:717–726 DOI 10.1038/s41575-022-00634-6.

Feagan BG, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JW, Cohen A, Bitton A, Baker J, Dubé R, Landau SB, Vandervoort MK, Parikh A. 2008. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. *Clinical Gastroenterology and Hepatology* 6:1370–1377 DOI 10.1016/j.cgh.2008.06.007.

Feagan BG, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JW, Dubé R, Cohen A, Steinhart AH, Landau S, Aguzzi RA, Fox IH, Vandervoort MK. 2005. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. *New England Journal of Medicine* 352:2499–2507 DOI 10.1056/NEJMoa042982.

Fiorino G, Gilardi D, Danese S. 2016. The clinical potential of etrolizumab in ulcerative colitis: hopes and hopes. *Therapeutic Advances in Gastroenterology* 9:503–512 DOI 10.1177/1756283x16647935.

Gordon FH, Hamilton MI, Donoghue S, Greenlees C, Palmer T, Rowley-Jones D, Dhillon AP, Amlot PL, Pounder RE. 2002. A pilot study of treatment of active ulcerative colitis with natalizumab, a humanized monoclonal antibody to alpha-4 integrin. *Alimentary Pharmacology and Therapeutics* 16:699–705 DOI 10.1046/j.1365-2036.2002.01205.x.

Gubatan J, Keyashian K, Rubin SJS, Wang J, Buckman CA, Sinha S. 2021. Anti-integrins for the treatment of inflammatory bowel disease: current evidence and perspectives. *Clinical and Experimental Gastroenterology* 14:333–342 DOI 10.2147/ceg.S293272.

Hadji H, Bouchemal K. 2022. Advances in the treatment of inflammatory bowel disease: focus on polysaccharide nanoparticulate drug delivery systems. *Advanced Drug Delivery Reviews* 181:114101 DOI 10.1016/j.addr.2021.114101.

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928 DOI 10.1136/bmj.d5928.

Jaensson E, Uronen-Hansson H, Pabst O, Eksteen B, Tian J, Coombes JL, Berg PL, Davidsson T, Powrie F, Johansson-Lindbom B, Agace WW. 2008. Small intestinal CD103+ dendritic cells display unique functional properties that are conserved

between mice and humans. *Journal of Experimental Medicine* 205:2139–2149
DOI 10.1084/jem.20080414.

Johansson-Lindbom B, Svensson M, Pabst O, Palmqvist C, Marquez G, Förster R, Agace WW. 2005. Functional specialization of gut CD103+ dendritic cells in the regulation of tissue-selective T cell homing. *Journal of Experimental Medicine* 202:1063–1073 DOI 10.1084/jem.20051100.

Lichnog C, Klabunde S, Becker E, Fuh F, Tripal P, Atreya R, Klenske E, Erickson R, Chiu H, Reed C, Chung S, Neufert C, Atreya I, McBride J, Neurath MF, Zundler S. 2019. Cellular mechanisms of etrolizumab treatment in inflammatory bowel disease. *Frontiers in Pharmacology* 10:39 DOI 10.3389/fphar.2019.00039.

Makker J, Hommes DW. 2016. Etrolizumab for ulcerative colitis: the new kid on the block? *Expert Opinion on Biological Therapy* 16:567–572
DOI 10.1517/14712598.2016.1158807.

Misselwitz B, Juillerat P, Sulz MC, Siegmund B, Brand S. 2020. Emerging treatment options in inflammatory bowel disease: janus kinases, stem cells, and more. *Digestion* 101(Suppl 1):69–82 DOI 10.1159/000507782.

Motaghi E, Ghasemi-Pirbaluti M, Zabihi M. 2019. Etrolizumab versus infliximab in the treatment of induction phase of ulcerative colitis: a systematic review and indirect comparison. *Pharmacological Research* 139:120–125 DOI 10.1016/j.phrs.2018.11.003.

Ouyang Y, Zhao J, Wang S. 2023. Multifunctional hydrogels based on chitosan, hyaluronic acid and other biological macromolecules for the treatment of inflammatory bowel disease: a review. *International Journal of Biological Macromolecules* 227:505–523 DOI 10.1016/j.ijbiomac.2022.12.032.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj* 372:n71 DOI 10.1136/bmj.n71.

Pérez-Jeldres T, Tyler CJ, Boyer JD, Karuppuchamy T, Bamias G, Dulai PS, Boland BS, Sandborn WJ, Patel DR, Rivera-Nieves J. 2019. Cell trafficking interference in inflammatory bowel disease: therapeutic interventions based on basic pathogenesis concepts. *Inflammatory Bowel Disease* 25:270–282 DOI 10.1093/ibd/izy269.

Peyrin-Biroulet L, Hart A, Bossuyt P, Long M, Allez M, Juillerat P, Armuzzi A, Loftus EV, Ostad-Saffari E, Scalori A, Oh YS, Tole S, Chai A, Pulley J, Lacey S, Sandborn WJ, Aguilar H, Ahmad T, Akriviadis E, Aldeguer Mante X, Altorki I, Ananthakrishnan A, Andersen V, Andreu Garcia M, Aumais G, Avni-Biron I, Axler J, Ayub K, Baert F, Bafutto M, Bamias G, Bassan I, Baum C, Beaugerie L, Behm B, Bekal P, Bennett M, Bermejo San Jose F, Bernstein C, Bettenworth D, Bhaskar S, Biancone L, Bilir B, Blaeker M, Bloom S, Bohman V, Bosques Padilla FJ, Bouchnik Y, Bouma G, Bourdages R, Brand S, Bressler B, Brückner M, Buening C, Carbonnel F, Caves T, Chapman J, Cheon JH, Chiba N, Chioncel C, Christodoulou D, Clodi M, Cohen A, Corazza GR, Corlin R, Cosintino R, Cummings F, Dalal R, Danese S, De Maeyer

M, De Magalhães Francesconi CF, De Silva A, Debinski H, Desreumaux P, Dewit O, D'Haens G, Di Felice Boratto S, Ding JN, Dixon T, Dryden G, Du Vall GA, Ebert M, Echarri Piudo A, Ehehalt R, Elkhashab M, Ennis C, Etzel J, Fallingborg J, Feagan B, Fejes R, Ferraz de Campos Mazo D, Ferreira de Almeida Borges V, Fischer A, Fixelle A, Fleisher M, Fowler S, Freilich B, Friedenberg K, Fries W, Fu-llop C, Fumery M, Fuster SG, Kiss G, Garcia Lopez S, Gassner S, Gill K, Gilletta de Saint Joseph C, Ginsburg P, Gionchetti P, Goldin E, Goldis AE, Gomez Jaramillo HA, Gonciarz M, Gordon G, Green D, Grimaud JC, Guajardo Rodriguez R, Gurzo Z, Gutierrez A, Gyökeres T, Hahm KB, Hanauer S, Hanson J, Harlan III W, Hasselblatt P, Hayee B, Hebuterne X, Hendy P, Heyman M, Higgins P, Hilal R, Hindryckx P, Hoentjen F, Hoffmann P, Holtkamp-Endemann F, Holtmann G, Horvat G, Howaldt S, Huber S, Ibegbu I, Iborra Colomino MI, Irving P, Isaacs K, Jagarlamudi K, Jain R, Jankiel Miszputen S, Jansen J, Jones J, Karagiannis J, Karyotakis N, Kaser A, Katz L, Katz S, Katz L, Kaur N, Kazenaite E, Khanna R, Khurana S, Kim JS, Kim YH, Kim SK, Kim D, Klaus J, Kleczkowski D, Kohout P, Korczowski B, Kouklakis G, Koutroubakis I, Krause R, Kristof T, Kronborg I, Krummenerl A, Kupcinskas L, Laborda Molteni J, Laharie D, Lahat-zok A, Lee J, Lee KM, Leong R, Levine H, Limdi J, Lindsay J, Lodhia N, Loftus E, Longman R, Lopez Serrano P, Louis E, Louzada Pereira MH, Lowe J, Lueth S, Lukas M, Maconi G, Macrae F, Madi-Szabo L, Mahadevan-Velayos U, Malluta EF, Mana F, Mannon P, Mantzaris G, Marin Jimenez I. 2022. Etrolizumab as induction and maintenance therapy for ulcerative colitis in patients previously treated with tumour necrosis factor inhibitors (HICKORY): a phase 3, randomised, controlled trial. *The Lancet Gastroenterology and Hepatology* 7:128–140 DOI [10.1016/S2468-1253\(21\)00298-3](https://doi.org/10.1016/S2468-1253(21)00298-3).

Plevris N, Lees CW. 2022. Disease monitoring in inflammatory bowel disease: evolving principles and possibilities. *Gastroenterology* 162:1456–1475 DOI [10.1053/j.gastro.2022.01.024](https://doi.org/10.1053/j.gastro.2022.01.024).

Pouillon L, Vermeire S, Bossuyt P. 2019. Vedolizumab trough level monitoring in inflammatory bowel disease: a state-of-the-art overview. *BMC Medicine* 17:89 DOI [10.1186/s12916-019-1323-8](https://doi.org/10.1186/s12916-019-1323-8).

Rosenfeld G, Parker CE, MacDonald JK, Bressler B. 2015. Etrolizumab for induction of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2015: Cd011661 DOI [10.1002/14651858.CD011661.pub2](https://doi.org/10.1002/14651858.CD011661.pub2).

Rubin DT, Dotan I, DuVall A, Bouhnik Y, Radford-Smith G, Higgins PDR, Mishkin DS, Arrisi P, Scalori A, Oh YS, Tole S, Chai A, Chamberlain-James K, Lacey S, McBride J, Panés J, Abdulkhakov R, Abu Bakar N, Aguilar H, Aizenberg D, Akpinar H, Akriviadis E, Alexeeva O, Alikhanov B, Alvarisqueta A, Ananthakrishnan A, Andrews J, Arlukowicz T, Atkinson N, Atug O, Bafutto M, Balaz J, Bamias G, Banic M, Baranovsky A, Barbalaco Neto G, Basaranoglu M, Baum C, Baydanov S, Bennetts W, Besisik F, Bhaskar S, Bielasik A, Biliantskyi L, Bilir B, Blaha P, Bohman V, Borissova J, Borzan V, Bosques-Padilla F, Brooker J, Budko T, Budzak I, Bunganic I, Chapman J, Che' Aun A, Chernykh T, Chiorean M, Chopey I, Christodoulou D, Chu PS, Chumakova G, Cummins A, Cunliffe R, Cvetkovic M,

Dagli U, Danilkiewicz WC, Datsenko O, De Magalhães Francesconi CF, Debinski H, Deminova E, Derova J, Ding JN, Dmitrieva J, Dolgikh O, Douda T, Drobinski P, Dryden G, Duarte Gaburri P, DuVall GA, Dvorkin M, Ennis C, Erzin Y, Fadieienko G, Fediv O, Fedorishina O, Fedurco M, Fejes R, Fernandez J, Fernandez ML, Flores L, Freilich B, Friedenberg K, Fuster S, Gawdis-Wojnarska B, Gil Parada FL, Gimenez ED, Golovchenko N, Golovchenko O, Gonciarz M, Gordon G, Gregus M, Grinevich V, Guajardo Rodriguez R, Hall S, Hanson J, Hartleb M, Hebuterne X, Hendy P, Herring R, Higgins P, Hilal R, Hilmı IN, Hlavaty T, Holman R, Holtmann G, Hong J, Horvath F, Hospodarskyy I, Hrstic I, Hulagu S, Ibarra Verdugo LA, Ibegbu I, Inns S, Ivashkin V, Izanec J, Jain R, Jamrozik-Kruk Z, Kamburov V, Karagiannis J, Karakan T, Karczewski M, Kasherininova I, Katz S, Kaufman B, Kazenaite E, Kholina I, Khurana S, Kiselevska A, Kleczkowski D, Klymenko V, Knezevic S, Kondusz-Szklarz M, Korablina N, Korczowski B, Kosturkov L, Kotzev I, Kouklakis G, Koutroubakis I, Krause R, Kronborg I, Krstic M, Krzmaric Z, Krzyzanowski M, Kulig G, Kull K, Kupcinskas L, Lamet M, Latinovic Radakovic T, Leong R, Leung WK, Levine H, Li MKK, Libanez Bessa Campelo Braga L, Livzan M, Lohdanidi T, Louzada Pereira MH, Lowe J, Luetic K, Lukas M, Lymar Y, Macrae F, Mäelt A, Maev I, Mamos A, Mantzaris G, Margus B, Marinova I, Markevych I, Markov M, Markovic S, Marquez Velasquez JR, Mazzoleni F, Mimidis K, Mitchell B, Moore G, Morales Garza LA, Moscatello S, Mostovoy Y, Mountfield R, Nagorni A, Neshta V, Obrezan A, Oliynyk O, Oliveira Santana Silva G, Orzeszko M, Pavlenko V, Pavlov D, Penkova M, Peric S. 2022. Etrolizumab versus adalimumab or placebo as induction therapy for moderately to severely active ulcerative colitis (HIBISCUS): two phase 3 randomised, controlled trials. *The Lancet Gastroenterology and Hepatology* 7:17–27 DOI [10.1016/S2468-1253\(21\)00338-1](https://doi.org/10.1016/S2468-1253(21)00338-1).

Rutgeerts PJ, Fedorak RN, Hommes DW, Sturm A, Baumgart DC, Bressler B, Schreiber S, Mansfield JC, Williams M, Tang M, Visich J, Wei X, Keir M, Luca D, Danilenko D, Egen J, O’Byrne S. 2013. A randomised phase I study of etrolizumab (rhuMAb β 7) in moderate to severe ulcerative colitis. *Gut* 62:1122–1130 DOI [10.1136/gutjnl-2011-301769](https://doi.org/10.1136/gutjnl-2011-301769).

Sandborn WJ. 2012. The future of inflammatory bowel disease therapy: where do we go from here? *Digestive Diseases* 30:140–144 DOI [10.1159/000342742](https://doi.org/10.1159/000342742).

Sandborn WJ, Panés J, Danese S, Sharafali Z, Hassanali A, Jacob-Moffatt R, Eden C, Daperno M, Valentine JF, Laharie D, Baía C, Atreya R, Panaccione R, Rydzewska G, Aguilar H, Vermeire S, Grp BS. 2023. Etrolizumab as induction and maintenance therapy in patients with moderately to severely active Crohn’s disease (BERG-AMOT): a randomised, placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterology & Hepatology* 8:43–55 DOI [10.1016/s2468-1253\(22\)00303-x](https://doi.org/10.1016/s2468-1253(22)00303-x).

Sasson AN, Ingram RJM, Zhang Z, Taylor LM, Ananthakrishnan AN, Kaplan GG, Ng SC, Ghosh S, Raman M. 2021. The role of precision nutrition in the modulation of microbial composition and function in people with inflammatory bowel disease. *The Lancet Gastroenterology and Hepatology* 6:754–769 DOI [10.1016/s2468-1253\(21\)00097-2](https://doi.org/10.1016/s2468-1253(21)00097-2).

Solitano V, Parigi TL, Ragagni E, Danese S. 2021. Anti-integrin drugs in clinical trials for inflammatory bowel disease (IBD): insights into promising agents. *Expert Opinion on Investigational Drugs* 30:1037–1046 DOI [10.1080/13543784.2021.1974396](https://doi.org/10.1080/13543784.2021.1974396).

Tang MT, Keir ME, Erickson R, Stefanich EG, Fuh FK, Ramirez-Montagut T, McBride JM, Danilenko DM. 2018. Review article: nonclinical and clinical pharmacology, pharmacokinetics and pharmacodynamics of etrolizumab, an anti- β 7 integrin therapy for inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 47:1440–1452 DOI [10.1111/apt.14631](https://doi.org/10.1111/apt.14631).

Ungar B, Kopylov U. 2016. Advances in the development of new biologics in inflammatory bowel disease. *Annals of Gastroenterology* 29:243–248 DOI [10.20524/aog.2016.0027](https://doi.org/10.20524/aog.2016.0027).

Vermeire S, Lakatos PL, Ritter T, Hanauer S, Bressler B, Khanna R, Isaacs K, Shah S, Kadva A, Tyrrell H, Oh YS, Tole S, Chai A, Pulley J, Eden C, Zhang W, Feagan BG, Abraham P, AcirCrippa Júnior M, Aguilar H, Ahmed T, Altorjay I, Andersen V, Arai R, Arnold H, Ausk K, Axler J, Ayub K, Balekuduru A, Barbalaco Neto G, Bassan I, Behm B, Bekal P, Bhatia S, Bod B, Brandão Mello CE, Brandeburova J, Breedt J, Chopey I, Connor M, Corlin R, Cortez Hernandez CA, De A, De Sá Rolim A, Di Felice Boratto S, Dixon T, Dourado Poli D, Dresner D, Du Vall GA, Ebert M, Ehehalt R, Ertan A, Escarcega Valencia R, Etzel J, Fallingborg J, Fedurco M, Fernandez Castro E, Ferreira de Almeida Borges V, Finklestein M, Fischer A, Fleisher M, Flores Rendon AR, Fogel R, Franceschi Junior O, Freedland C, Gatoof D, Gill K, Glerup H, Gokak V, Goldin E, Gomez Jaramillo HA, Gupta N, Gurzo Z, Gyrina O, Habeeb MA, Hardi R, Harlan W, Hemaidan A, Heyman M, Hoffmann P, Holderman W, Holtkamp-Endemann F, Horvat G, Israeli E, Jankiel Miszputen S, Jensen S, Johnson K, Jones J, Junior O, Kadleckova B, Kalla M, Kallo Z, Karyotakis N, Katz L, Katz L, Kaur N, Kohout P, Lakatos P, Larrivadelos Reyes E, Lee R, Leman B, Levchenko O, Levine H, Libanez Bessa Campelo Braga L, Loftus E, Lohdanidi T, Longman R, Lozano J, Maaser C, Madi-Szabo L, Malluta EF, Marshall J, Martinez Silva F, Maynard K, Meder A, Mehta C, Minarik P, Mueller J, Mukewar S, Nagy B, Neiko V, Neurath M, Nichol B, Novick J, Pai N, Pandak W, Panigrahi S, Pape UF, Paraná R, Parekh N, Patel B, Pecsi G, Peralta S, Pesta M, Peterfai E, Petruzzellis C, Petryka R, Pica R, Piniella C, Pratha V, Prochazka V, Prokopchuk S, Prystupa L, Puri A, Rainis T, Ramesh Kumar B, Ramos Júnior O, Rishko I, Robbins B, Rock E, Rodrigues Borba M, Rodriguez M, Rozciedla J, Ruiz Flores AY, Rydzewska G, Safadi R, Saibeni S, Schirbel A, Schmiegel W, Schnabel R, Schneider H, Segui A, Seidelin J, Seidler U, Sellin J, Shafran I, Sheikh A, Sherman A, Shirin H, Shukla A, Siddiqui F, Sike R, Sood A, Stallmach A, Stanislavchuk M, Staun M, Stein D, Steinberg A, Steinhart H, Stifft J, Tandon R, Tantry V, Thiwan S, Treiber M, Ulbrych J, Valentine J, Vasudeva R, Vaughn B, Velasco B, Vincze A, Volfova M, Waterman M, Weiss LM, Wiesner E, Williams A, Witthoeft T, Wohlman R, Wright J, Yamamoto Furusho JK, Younes Z. 2022. Etrolizumab for maintenance therapy in patients with moderately to severely active ulcerative colitis (LAUREL): a randomised, placebo-controlled, double-blind, phase 3 study. *The Lancet Gastroenterology and Hepatology* 7:28–37 DOI [10.1016/S2468-1253\(21\)00295-8](https://doi.org/10.1016/S2468-1253(21)00295-8).

Vermeire S, O'Byrne S, Keir M, Williams M, Lu TT, Mansfield JC, Lamb CA, Feagan BG, Panes J, Salas A, Baumgart DC, Schreiber S, Dotan I, Sandborn WJ, Tew GW, Luca D, Tang MT, Diehl L, Eastham-Anderson J, De Hertogh G, Perrier C, Egen JG, Kirby JA, Van Assche G, Rutgeerts P. 2014. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet* **384**:309–318
DOI [10.1016/s0140-6736\(14\)60661-9](https://doi.org/10.1016/s0140-6736(14)60661-9).

Verstockt B, Ferrante M, Vermeire S, Van Assche G. 2018. New treatment options for inflammatory bowel diseases. *Journal of Gastroenterology* **53**:585–590
DOI [10.1007/s00535-018-1449-z](https://doi.org/10.1007/s00535-018-1449-z).

Watermeyer G, Katsidzira L, Setshedi M, Devani S, Mudombi W, Kassianides C. 2022. Inflammatory bowel disease in sub-Saharan Africa: epidemiology, risk factors, and challenges in diagnosis. *The Lancet Gastroenterology and Hepatology* **7**:952–961
DOI [10.1016/s2468-1253\(22\)00047-4](https://doi.org/10.1016/s2468-1253(22)00047-4).

Weisshof R, El Jurdi K, Zmeter N, Rubin DT. 2018. Emerging therapies for inflammatory bowel disease. *Advances in Therapy* **35**:1746–1762
DOI [10.1007/s12325-018-0795-9](https://doi.org/10.1007/s12325-018-0795-9).

Welz L, Aden K. 2023. Fibrosis and inflammation in inflammatory bowel disease-more than 2 sides of the same coin? *Gastroenterology* **164**:19–21
DOI [10.1053/j.gastro.2022.10.024](https://doi.org/10.1053/j.gastro.2022.10.024).

Xu F, Carlson SA, Liu Y, Greenlund KJ. 2021. Prevalence of inflammatory bowel disease among medicare fee-for-service beneficiaries—United States, 2001–2018. *Morbidity and Mortality Weekly Report* **70**:698–701 DOI [10.15585/mmwr.mm7019a2](https://doi.org/10.15585/mmwr.mm7019a2).

Zhao M, Gönczi L, Lakatos PL, Burisch J. 2021. The burden of inflammatory bowel disease in Europe in 2020. *Journal of Crohn's and Colitis* **15**:1573–1587
DOI [10.1093/ecco-jcc/jjab029](https://doi.org/10.1093/ecco-jcc/jjab029).

Zundler S, Becker E, Weidinger C, Siegmund B. 2017. Anti-adhesion therapies in inflammatory bowel disease-molecular and clinical aspects. *Frontiers in Immunology* **8**:891 DOI [10.3389/fimmu.2017.00891](https://doi.org/10.3389/fimmu.2017.00891).