Annals of Gastroenterology (2025) **38,** 1-8

Effectiveness of upadacitinib in ulcerative colitis patients with prior tofacitinib exposure: a systematic review and meta-analysis

Fariha Hasan[a], Ayesha Liaquat[b], Ahmed Raza[c], Zain Ali Nadeem[d], Fatima Farooqi[b], Hassam Ali[e], Dushyant Singh Dahiya[f], Zeina Issa[g], Bhanu Siva Mohan Pinnam[f], Saqr Alsakarneh[h], Islam Mohamad[i], Gursimran S. Kocchar[j]

Cooper University Health Care, Camden, NJ, USA; Dow Medical College, Karachi, Pakistan; Services Institute of Medical Sciences, Pakistan; [d]Allama Iqbal Medical College, Lahore, Pakistan; ECU Health, Greenville, NC, USA; University of Kansas School of Medicine, Kansas City, KS, USA; Cooper Medical School of Rowan University, Camden, NJ, USA; Mayo Clinic, Rochester, MN, USA; University of Missouri, Columbia, MO, USA; Allegheny Health Network, Pittsburgh, PA, USA

Abstract

Background Upadacitinib, a selective Janus kinase (JAK) inhibitor, is a recently approved therapy for moderate-to-severe ulcerative colitis (UC). Limited data are available on its efficacy in patients previously exposed to tofacitinib, a non-selective JAK inhibitor. Therefore, we conducted a systematic review and meta-analysis to evaluate the efficacy of upadacitinib in UC patients with prior tofacitinib treatment.

Methods PubMed, Embase, Web of Science, and Cochrane Library were queried for studies evaluating the effectiveness of upadacitinib in UC patients with prior tofacitinib treatment. Primary outcomes included clinical remission, steroid-free clinical remission (SFCR), and clinical response. Secondary outcomes were the mean decrease in fecal calprotectin, and adverse events. Statistical analyses were performed using R, calculating pooled proportions with 95% confidence intervals (CI) for dichotomous outcomes and mean differences with 95%CI for continuous outcomes using a random-effects model.

Results Five studies, with 127 patients, were included in the final analysis. Upadacitinib increased pooled clinical remission rates by 57% (95%CI 0.32-0.80), SFCR rates by 52% (95%CI 0.26-0.78), and clinical response rates by 75% (95%CI 0.44-0.96). Upadacitinib reduced mean fecal calprotectin levels by 597.59% (95%CI 350.94-844.324). Adverse events, such as headache, acne vulgaris, rash, nasopharyngitis and infections, were reported in 34% of patients (95%CI 0.11-0.62).

Conclusions Our meta-analysis indicates that upadacitinib may be an effective treatment for patients with prior tofacitinib exposure, demonstrating significant clinical remission, SFCR, and clinical response. Larger clinical trials are needed to establish long-term outcomes.

Keywords Upadacitinib, tofacitinib, inflammatory bowel disease, ulcerative colitis

Ann Gastroenterol 2025; 38 (X): 1-8

Conflict of Interest: None

Correspondence to: Zeina Issa, Cooper Medical School of Rowan University, Camden, New Jersey, USA, e-mail: issaz2@rowan.edu

Received 28 April 2025; accepted 5 July 2025;
published online 14 August 2025

DOI: https://doi.org/10.20524/aog.2025.0991

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) of the large intestine characterized by diarrhea, abdominal pain, rectal bleeding, and weight loss [1]. Conventional therapies for UC, including aminosalicylates, corticosteroids, azathioprine, vedolizumab and anti-tumor necrosis factor agents, are often ineffective in providing sustained remission [2,3]. Over the past 2 decades, small-molecule therapies, such as Janus kinase (JAK) inhibitors, have proven revolutionary in managing UC, exhibiting significantly improved disease outcomes.

JAK/STAT is an intracellular tyrosine kinase signaling pathway that modulates and induces proinflammatory cytokines, such as interleukin (IL)-6, IL-12, IL-13, IL-17, IL-21, IL-23 and IL-33, implicated in the pathogenesis of UC. JAK inhibitors disrupt this signaling pathway by blocking the phosphorylation of JAK, resulting in the anti-inflammatory therapeutic effects seen in UC patients [4,5]. Tofacitinib, a first-generation, non-selective oral pan-JAK inhibitor, was approved by the United States Food and Drug Administration (FDA) for the treatment of UC in 2018. It has induced and maintained remission in patients who had failed treatment with conventional therapies and biologics [6-9]. However, it has been associated with primary and secondary non-response in a subset of patients, as well as adverse effects including hypercholesterolemia, malignancy, cardiovascular events and infections, with particular safety concerns regarding venous thromboembolism (VTE) and herpes zoster reactivation, prompting exploration of alternate options with increased selectivity, greater response rate, and fewer adverse events [10,11].

One such medication, upadacitinib, an oral selective JAK inhibitor associated with better disease-specific outcomes than tofacitinib [12-14], was approved by the FDA in March 2022 [15]. However, initial trials evaluating the effectiveness of upadacitinib in UC patients excluded patients with prior exposure to tofacitinib, leading to a significant knowledge gap and a lack of real-world data on upadacitinib efficacy in tofacitinib-refractory patients. To address this, we conducted a systematic review and meta-analysis to assess disease outcomes with upadacitinib use in patients who had previously failed treatment with tofacitinib, thereby providing evidence-based therapy options to patients who do not respond to non-selective JAK inhibitors.

Materials and methods

This meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1) [16,17]. Ethical approval was not required for this analysis.

[a]Cooper University Health Care, Camden, NJ, USA (Fariha Hasan); [b]Dow Medical College, Karachi, Pakistan (Ayesha Liaquat, Fatima Farooqi); [c]Services Institute of Medical Sciences, Pakistan (Ahmed Raza); [d]Allama Iqbal Medical College, Lahore, Pakistan (Zain Ali Nadeem); [e]ECU Health, Greenville, NC, USA (Hassam Ali); [f]University of Kansas School of Medicine, Kansas City, KS, USA (Dushyant Singh Dahiya, Bhanu Siva Mohan Pinnam); [g]Cooper Medical School of Rowan University, Camden, NJ, USA (Zeina Issa); [h]Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA (Saqr Alsakarneh); [i]Department of Gastroenterology and Hepatology, University of Missouri, Columbia, MO, USA (Islam Mohamad); [j]Department of Gastroenterology and Hepatology, Allegheny Health Network, Pittsburgh, PA, USA (Gursimran S. Kocchar)

Data sources and search strategy

A comprehensive electronic search was conducted across multiple databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase (Elsevier) and Web of Science, covering all records from inception until December 2024. We also manually screened the reference lists of included studies and relevant systematic reviews. The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms, specifically targeting "Upadacitinib," "Tofacitinib," and "Ulcerative colitis" (Supplementary Table 2).

Eligibility criteria

Eligible studies included randomized controlled trials, observational studies (case–control, retrospective, or prospective cohort), and case series that assessed disease outcomes with upadacitinib use in UC patients with prior exposure to tofacitinib. No restrictions were applied regarding geographical location or patient age. Studies were excluded if they were literature reviews, editorials, case series with fewer than 10 patients, duplicate studies or animal studies. Additionally, studies that lacked relevant data, addressed different endpoints, or did not have a single-arm study design were excluded. The population consisted of UC patients who had previously been exposed to tofacitinib. The intervention was treatment with upadacitinib. The primary outcomes included clinical remission, steroid-free clinical remission (SFCR) and clinical response, while the secondary outcomes were the mean decrease in fecal calprotectin and the incidence of adverse events.

Study selection and data extraction

Two independent reviewers (LA and FF) selected studies and extracted data; any discrepancies were resolved by a third reviewer (HF). Duplicate records were removed using Mendeley Desktop 1.19.8. Data were extracted using a standardized form that captured information on study characteristics (e.g., authors, study design), patient demographics (e.g., age, sex), and primary and secondary outcomes.

Study definitions

Clinical remission and response were defined based on the simple clinical colitis activity index (SCCAI), Patient-Reported Outcome (PRO-2), and the Mayo score.

Statistical analysis and publication bias

We conducted the statistical analysis in R version 4.4.1 using the package "meta." We pooled proportions for single-arm

studies along with their corresponding 95% confidence intervals (CI), risk ratios (RR) with 95%CIs for dichotomous outcomes, and mean differences with 95%CIs for continuous outcomes. Freeman-Tukey double arcsine transformed proportions were used [18]. RRs were calculated using the Mantel-Haenszel method [19], and mean differences using the inverse variance method in a random-effects model. We used the restricted maximum likelihood estimator to calculate the heterogeneity variance τ^2 [20]. The pooled results were represented graphically as forest plots. The chi-square test and the Higgins I^2 statistic were calculated to evaluate the statistical heterogeneity, and an I^2 value of 25-50% was considered mild, 50-75% as moderate, and >75% as severe heterogeneity [21]. Per the Cochrane guidelines, a publication bias assessment could not be conducted, as fewer than 10 studies were included in the meta-analysis (funnel plots are not sufficiently powered to detect publication bias when the number of studies is <10) [22]. A sensitivity analysis was conducted by sequentially omitting each study from the pooled analysis to assess the robustness of the results. A P-value <0.05 was considered statistically significant in all cases.

Risk-of-bias and quality assessment

The risk of bias in the included cohort studies with available full texts was assessed using the Newcastle-Ottawa Scale (Supplementary Table 3). This scale evaluates studies based on 8 criteria across 3 domains: selection of study groups, comparability, and ascertainment of exposure or outcome. The quality assessment of the included case series was conducted using the Joanna Briggs Institute critical appraisal tool, which comprises 10 questions addressing the internal validity and risk of bias associated with case series designs (Supplementary Table 4).

Results

A total of 804 studies were screened for inclusion in the meta-analysis. After a thorough screening process, 10 studies were shortlisted for full-text review. Five studies did not fulfill the eligibility criteria and were excluded [14,23-26], leaving 4 retrospective studies [12,27-29] and 1 prospective study that were ultimately selected [30]. The PRISMA flow diagram details the study selection process (Fig. 1). All of the included studies observed the impact of upadacitinib in patients with UC after prior treatment with tofacitinib. The study and baseline characteristics of the 127 patients and the outcome data are summarized in Table 1.

Clinical remission

The analysis, including 4 studies, indicated that the administration of upadacitinib increased the pooled clinical remission by 57% (95%CI 0.32-0.80; I^2=84%; P<0.01; Fig. 2). In a sensitivity analysis excluding Gilmore 2024, the clinical remission rate was 47% (95%CI 0.34-0.60; I^2=0%; Supplementary Fig. 1).

Steroid-free clinical remission

The analysis, including 3 studies, revealed that the administration of upadacitinib resulted in a pooled steroid-free clinical remission rate of 52% (95%CI 0.26-0.78; I^2=74%; P=0.02; Fig. 3). In a sensitivity analysis excluding Odah 2024, the steroid-free clinical remission rate was 40% (95%CI 0.26-0.54; I^2=0%; Supplementary Fig. 2).

Clinical response

The analysis, including 3 studies, indicated that the administration of upadacitinib resulted in a pooled clinical response rate of 75% (95%CI 0.44-0.96; I^2=86%; P<0.01; Fig. 4). In a sensitivity analysis excluding Odah 2024, the clinical response rate was 60% (95%CI 0.46-0.74; I^2=0%; Supplementary Fig. 3).

Change in the fecal calprotectin

The analysis, including 2 studies, indicated that the administration of upadacitinib decreased the pooled mean fecal calprotectin by 597.59% (95%CI 350.94-844.324; I^2=32%; P=0.23; Supplementary Fig. 4).

Adverse events

The analysis, including 3 studies, indicated that the administration of upadacitinib resulted in a pooled adverse event rate of 34% (95%CI 0.11-0.62; I^2=80%; P<0.01), encompassing headache, acne vulgaris, rash, nasopharyngitis, and infections such as COVID-19 and herpes zoster, etc. (Fig. 5). In a sensitivity analysis excluding Levine 2024, the rate of adverse events decreased by 23% (95%CI 0.10-0.38; I^2=39%; Supplementary Fig. 5).

Discussion

Our systematic review and meta-analysis evaluated the safety and efficacy of upadacitinib in patients with UC who had previously used tofacitinib. The analysis revealed a marked increase in clinical remission and steroid-free clinical remission. The clinical response also demonstrated a notable increase. Additionally, a substantial decline was observed in fecal calprotectin levels.

Our findings reveal a clinical remission rate of 57% and a clinical response rate of 75% with upadacitinib in patients

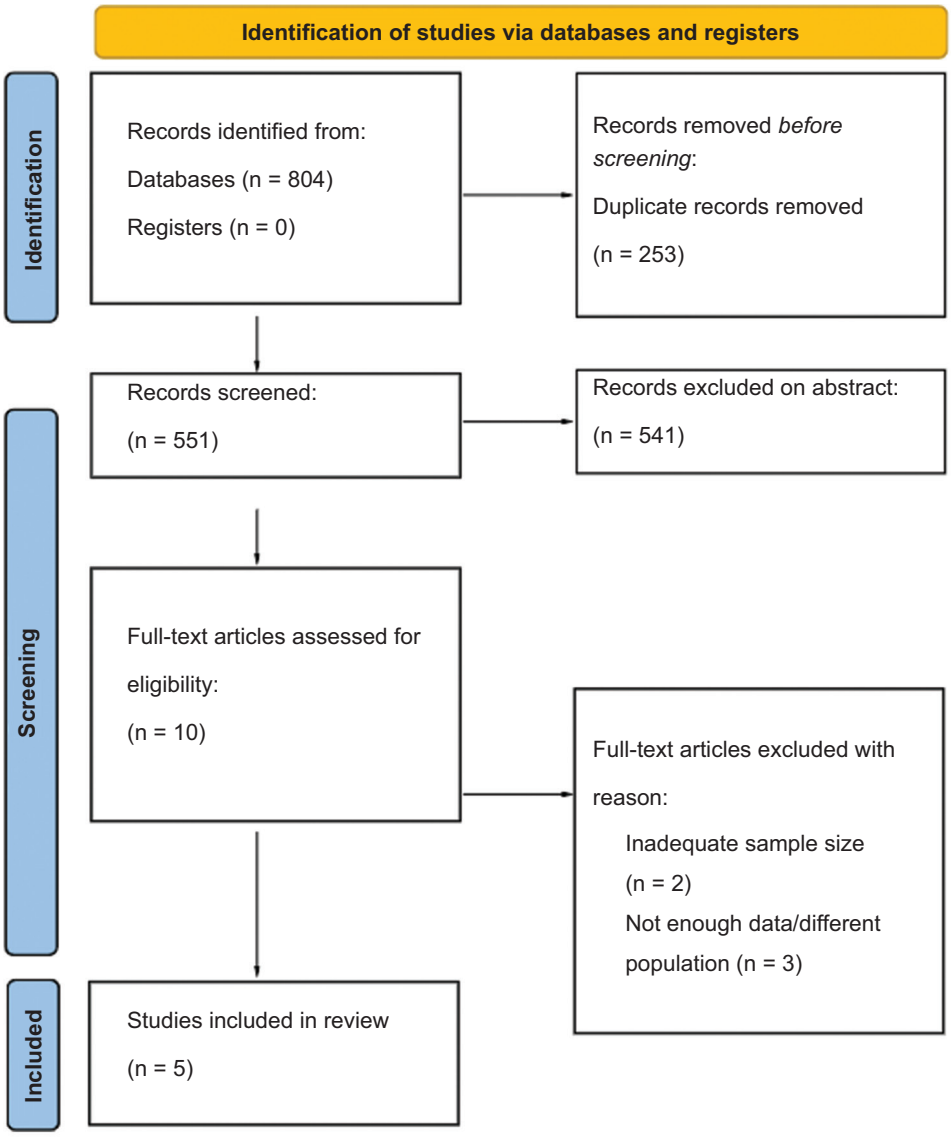


Figure 1 PRISMA flow diagram for included and excluded studies

Table 1 Study and baseline characteristics

Author, year [ref.]	Type of study	Region	Full-text or abstract	Sample size	Intervention	Males (%)	Mean age, years (mean SD)
Gilmore, 2024 [27]	Retrospective	Australia	Abstract	42	UPA	NR	NR
Odah, 2024 [28]	Retrospective	USA	Full-text	31	UPA	51.6	35.6 (12.1)
Levine, 2024 [29]	Retrospective	USA	Full-text	16	UPA	56	37.5 (15.8)
Boneschansker, 2023 [12]	Retrospective	USA	Full-text	12	UPA	NR	NR
Cleveland, 2023 [30]	Prospective	USA	Abstract	26	UPA	65.4	40.2

SD, standard deviation; UPA, upadacitinib; NR, not reported

who had previously received and failed tofacitinib therapy. A proportional analysis by Zheng *et al* reported a clinical remission rate of 38% and a clinical response rate of 61%, regardless of the prior line of therapy [31]. The specific patient population in our study can explain the higher clinical remission and clinical response observed with low heterogeneity. Our findings are consistent with the existing literature. For instance, a network meta-analysis by Zhang *et al* comparing various

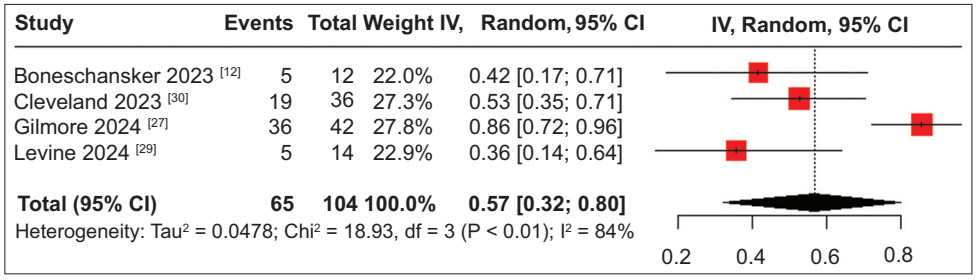


Figure 2 Forest plot showing clinical remission in patients on upadacitinib after tofacitinib exposure
CI, confidence interval

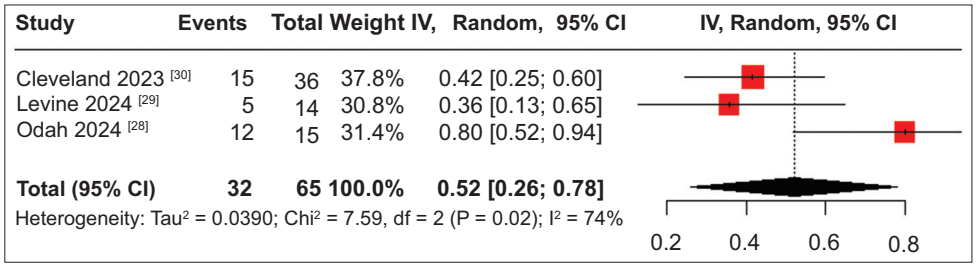


Figure 3 Forest plot showing steroid-free clinical remission in patients on upadacitinib after tofacitinib exposure
CI, confidence interval

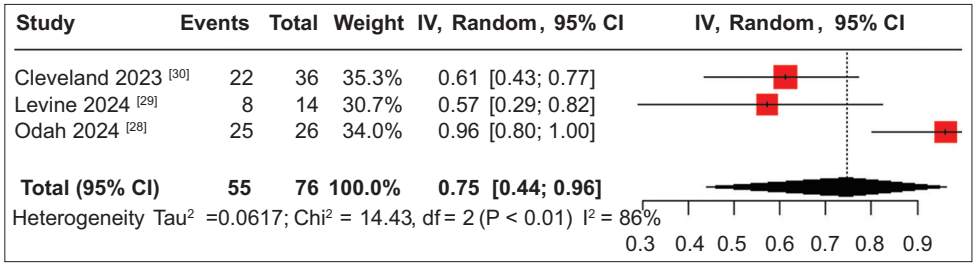


Figure 4 Forest plot showing clinical response in patients on upadacitinib after tofacitinib exposure
CI, confidence interval

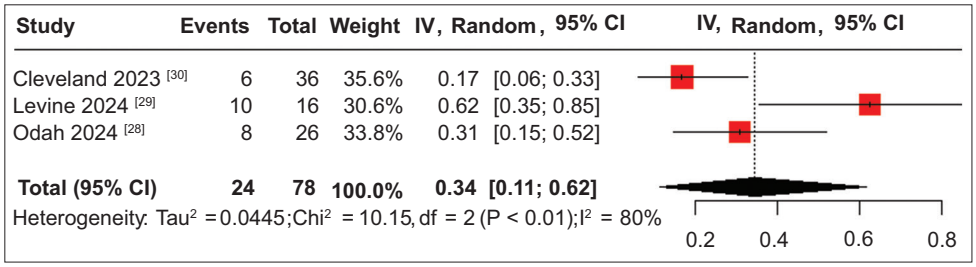


Figure 5 Forest plot showing adverse events in patients on upadacitinib after tofacitinib exposure
CI, confidence interval

drugs used for moderate to severe IBD revealed upadacitinib to be the most effective in achieving the highest clinical remission and clinical response, with cumulative probabilities of 99.3% and 96%, respectively [32]. Another similar study by Shehab *et al* also reported upadacitinib as the highest-ranking drug in achieving PRO-2 clinical remission [33]. These studies and our findings strengthen the evidence supporting upadacitinib as a superior treatment option for IBD, including UC.

Our study included patients who had previously been treated with tofacitinib. A subgroup analysis by Burr *et al* demonstrated that upadacitinib not only showed the highest efficacy among other drugs for IBD, but also showed the highest efficacy in previously treated patients—even higher than in the treatment-naive subgroup that received upadacitinib as first-line treatment [34]. Gilmore *et al* also demonstrated a higher clinical remission rate of 23% with

upadacitinib in patients with prior tofacitinib exposure than in tofacitinib-naive patients [27]. A case series by Radcliffe *et al,* which included patients previously treated with tofacitinib, showed improved clinical remission, steroid-free remission and clinical response [35]. Another case series with patients whose previous JAK inhibitor therapy, specifically filgotinib and tofacitinib, had failed, showed improved outcomes with upadacitinib [25], suggesting a role for a rotation strategy among JAK inhibitors. A study on switching between different JAK inhibitors in rheumatoid arthritis patients showed that it improved outcomes, further strengthening the benefit of JAK inhibitors and suggesting that rotation therapy in inflammatory diseases could be beneficial [36]. Upadacitinib has already shown greater benefits over the other commonly used IBD drugs [32-34]; although the mechanisms of treatment failure may differ between JAK inhibitors and tumor necrosis factor inhibitors (anti-TNF), a study by Wang *et al* found that upadacitinib effectively modulates inflammatory pathways in anti-TNF non-responders, further supporting its role in refractory IBD [37].

Upadacitinib is a selective JAK1 inhibitor, with over 60 times more selectivity than JAK2 and over 100 times more than JAK3 [38]. This greater selectivity allows upadacitinib to precisely and strongly inhibit proinflammatory cytokines, particularly those implicated in the pathogenesis of IBD [39]. The higher selectivity and potency of upadacitinib can explain its greater efficacy in treating inflammatory diseases compared to other JAK inhibitors. Upadacitinib also more potently inhibits IL-2, IL-3, IL-4, IL-15, IL-21, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, interferon-gamma and interferon-alpha, compared to tofacitinib [40]. This greater potency of upadacitinib contributes to its superior efficacy compared to tofacitinib in treating IBD. Tofacitinib, on the other hand, effectively inhibits JAK1 and JAK3, with some activity against JAK2 [41]. This broader inhibition by tofacitinib is implicated as a higher risk of adverse events [40,41]. In comparison, upadacitinib's precise inhibition of JAK1 could be associated with a reduced risk of adverse events [39-41]. These precise and potent effects of upadacitinib make it a valuable second-line treatment option when tofacitinib has failed as the first-line treatment.

The steroid-free clinical remission rate in our analysis was 52%, highlighting the steroid-sparing effect of upadacitinib. A study by Runde *et al*, assessing the efficacy of upadacitinib in children and adolescents with IBD who had previously been treated with tofacitinib, showed an 86% steroid-free remission rate and clinical response [42]. Wu *et al* also found steroid-free remission in 64% of patients receiving upadacitinib for UC after the failure of prior therapies, including tofacitinib, glucocorticoids and biologics [43]. Similar findings were reported by Raine *et al* in a *post hoc* analysis, which demonstrated a higher reinitiation of corticosteroids in the placebo group compared to the upadacitinib group [44]. They also demonstrated that patients receiving corticosteroids sustained a higher rate of treatment-emergent adverse events compared to those who did not. Clinical trials have shown that upadacitinib is more effective than tofacitinib in achieving steroid-free clinical remission [13,14]. The efficacy of upadacitinib can be attributed to its precise and targeted action, which effectively suppresses proinflammatory pathways with sustained efficacy.

Our pooled analysis revealed a substantial reduction in fecal calprotectin by 597.59%. This finding is consistent with the existing literature, which supports the role of upadacitinib in resolving inflammation and significantly reducing inflammatory biomarkers [25,42,43]. This is further evidenced by the analysis of Zheng *et al*, which demonstrated an endoscopic remission rate of 20% in IBD patients with upadacitinib [31]. Zhang *et al* also found a 99% cumulative probability of achieving endoscopic remission with upadacitinib [32]. This is further supported by the endoscopic findings, which demonstrate an improvement and resolution of inflammation in the intestinal mucosa [25,31,32,43]. The reason lies in the targeted and potent inhibition of the JAK1 pathway by upadacitinib [38]. This reduces inflammation and promotes mucosal healing, significantly decreasing inflammatory cytokines and biomarkers, such as fecal calprotectin and C-reactive protein [39,40,43].

The safety profile exhibited an increase in adverse events, with a proportion of 34%. Levine *et al* also reported a 31% incidence of adverse events, all of which were infections [29]. Most adverse events encountered are generally mild and manageable, such as headache, acne, nausea, abdominal pain and arthralgia; however, an increased risk of infections, particularly herpes zoster, has been observed with JAK inhibitor therapy [31]. Some studies have reported liver enzyme elevation, leukopenia, neutropenia and anemia [31,43]. The selective inhibition of JAK1 by upadacitinib reduces adverse effects, particularly hematologic side-effects, compared to other JAK inhibitors, by preventing the inhibition of off-target pathways, such as JAK2 and JAK3 [38,39,41].

We acknowledge several limitations in our meta-analysis. First, the absence of a control group limits direct comparison with other therapeutic options. Second, the relatively small sample size of 127 patients may have limited the statistical power of the analysis for certain outcomes. Third, the short follow-up period may not be sufficient to capture long-term outcomes and rare adverse events. It is also important to note that 2 of the 5 included studies were available only in abstract form, which limited access to full methodological details and may have introduced bias. Additionally, there is heterogeneity in the reasons for tofacitinib discontinuation. While most patients discontinued because of non-response (whether primary, secondary, or partial), information about other reasons, such as adverse events or insurance issues, is limited. For instance, in the study by Odah *et al* adverse events and insurance problems were also cited as reasons for discontinuation.

Despite these limitations, we conducted sensitivity analyses to eliminate heterogeneity and confirm the robustness and reliability of our findings. Therefore, we consider the results of our analysis to be informative within the context of the available data. Moreover, our study focuses on a specific population, i.e., patients who had previously failed treatment with tofacitinib, providing valuable insights for this subgroup.

In conclusion, our systematic review and meta-analysis provide promising evidence that upadacitinib may be

an effective treatment option for UC patients who have previously been treated with tofacitinib. While our findings indicate significant improvements in clinical remission and steroid-free remission rates, and a notable reduction in fecal calprotectin, future research should focus on conducting large-scale randomized controlled trials with longer follow-ups and diverse patient populations, comparing the safety and efficacy of upadacitinib with other therapeutic options to establish its long-term outcomes.

Summary Box

What is already known:

- Tofacitinib, an FDA-approved non-selective oral pan-Janus kinase (JAK) inhibitor for ulcerative colitis (UC), has shown efficacy in inducing and maintaining remission in patients who failed conventional therapies and biologics
- Limitations include primary and secondary non-response, as well as adverse events such as hypercholesterolemia, malignancy, cardiovascular events, venous thromboembolism, and herpes zoster reactivation
- Upadacitinib is a recently approved JAK1 inhibitor for moderate-to-severe UC
- Its efficacy in patients previously treated with tofacitinib remains unclear, as they were excluded from major clinical trials

What the new findings are:

- This is the first meta-analysis evaluating the efficacy of upadacitinib in patients with prior tofacitinib exposure
- Upadacitinib shows promising clinical remission (57%), steroid-free remission (52%) and clinical response (75%) rates
- Treatment with upadacitinib led to a significant reduction in inflammatory markers
- The study provides initial evidence of upadacitinib's efficacy in a real-world setting following tofacitinib failure

References

1. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol* 2019;**114**:384-413.
2. Garud S, Peppercorn MA. Ulcerative colitis: current treatment strategies and future prospects. *Therap Adv Gastroenterol* 2009;**2**:99-108.
3. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. *Aliment Pharmacol Ther* 2018;**47**:162-175.
4. Fernández-Clotet A, Castro-Poceiro J, Panés J. JAK inhibition: the most promising agents in the IBD pipeline? *Curr Pharm Des* 2019;**25**:32-40.
5. Nemeth ZH, Bogdanovski DA, Barratt-Stopper P, Paglinco SR, Antonioli L, Rolandelli RH. Crohn's disease and ulcerative colitis show unique cytokine profiles. *Cureus* 2017;**9**:e1177.
6. Sandborn WJ, Su C, Sands BE, et al; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;**376**:1723-1736.
7. Uzzan M, Bresteau C, Laharie D, et al; GETAID-TALC Study Group. Tofacitinib as salvage therapy for 55 patients hospitalised with refractory severe ulcerative colitis: A GETAID cohort. *Aliment Pharmacol Ther* 2021;**54**:312-319.
8. Berinstein JA, Sheehan JL, Dias M, et al. Tofacitinib for biologic-experienced hospitalized patients with acute severe ulcerative colitis: a retrospective case-control study. *Clin Gastroenterol Hepatol* 2021;**19**:2112-2120.
9. Weisshof R, Aharoni Golan M, Sossenheimer PH, et al. Real-world experience with tofacitinib in IBD at a tertiary center. *Dig Dis Sci* 2019;**64**:1945-1951.
10. Núñez P, Quera R, Yarur AJ. Safety of Janus kinase inhibitors in inflammatory bowel diseases. *Drugs* 2023;**83**:299-314.
11. Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. *Arthritis Res Ther* 2019;**21**:89.
12. Boneschansker L, Ananthakrishnan AN; Massachusetts General Hospital Crohn's And Colitis Center Collaborators. Comparative effectiveness of upadacitinib and tofacitinib in inducing remission in ulcerative colitis: real-world data. *Clin Gastroenterol Hepatol* 2023;**21**:2427-2429.
13. Dalal RS, Kallumkal G, Cabral HJ, Barnes EL, Allegretti JR. One-year comparative effectiveness of upadacitinib vs tofacitinib for ulcerative colitis: a multicenter cohort study. *Am J Gastroenterol* 2024;**119**:1628-1631.
14. Kochhar GS, Khataniar H, Jairath V, Farraye FA, Desai A. Comparative effectiveness of upadacitinib and tofacitinib in ulcerative colitis: a US propensity-matched cohort study. *Am J Gastroenterol* 2024;**119**:2471-2479.
15. Danese S, Vermeire S, Zhou W, et al. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. *Lancet* 2022;**399**:2113-2128.
16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.
17. Cochrane Handbook for Systematic Reviews of Interventions. Available from: https://www.cochrane.org/authors/handbooks-and-manuals/handbook [Accessed 14 July 2025].
18. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;**22**:719-748.
19. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;**67**:974-978.
20. Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat* 2005;**30**:261-293.
21. West SL, Gartlehner G, Mansfield AJ, et al. Comparative effectiveness review methods: clinical heterogeneity. Table 7 Summary of common statistical approaches to test for heterogeneity. NCBI Bookshelf. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53317/table/ch3.t2/[Accessed 14 July 2025].
22. Page MJ, Higgins JP, Sterne JA. Cochrane. Chapter 13: assessing risk of bias due to missing evidence in a meta-analysis. Available

from: https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current/chapter-13 [Accessed 14 July 2025].
23. Troncone E, Marafini I, Del Vecchio Blanco G, Di Grazia A, Monteleone G. Novel therapeutic options for people with ulcerative colitis: an update on recent developments with Janus kinase (JAK) inhibitors. *Clin Exp Gastroenterol* 2020;**13**:131-139.
24. Misselwitz B, Juillerat P, Sulz MC, Siegmund B, Brand S; Swiss IBDnet, an official working group of the Swiss Society of Gastroenterology. Emerging treatment options in inflammatory bowel disease: Janus kinases, stem cells, and more. *Digestion* 2020;**101**(Suppl 1):69-82.
25. Hosomi S, Nishida Y, Fujiwara Y. Efficacy of upadacitinib as a second-line JAK inhibitor in ulcerative colitis: a case series. *Intern Med* 2024;**63**:1882-1885.
26. Berinstein JA, Karl T, Patel A, et al. Effectiveness of upadacitinib for patients with acute severe ulcerative colitis: a multicenter experience. *Am J Gastroenterol* 2024;**119**:1421-1425.
27. Gilmore R, Fernandes R, Hartley I, et al. P1064 Upadacitinib is safe and effective in ulcerative colitis patients with prior exposure to tofacitinib. *J Crohns Colitis* 2024;**18**:i1904.
28. Odah T, Karime C, Desai A, et al. Response to upadacitinib in patients with inflammatory bowel disease previously treated with tofacitinib. *Dig Dis Sci* 2024;**69**:3911-3919.
29. Levine J, McKibbin J, Ham R, et al. Use of upadacitinib in 16 tofacitinib-refractory ulcerative colitis patients: a single-center case series. *Inflamm Bowel Dis* 2024;**30**:2232-2235.
30. Krugliak Cleveland N, Friedberg S, Choi D, et al. P724 Upadacitinib is effective and safe in tofacitinib-experienced patients with ulcerative colitis: a prospective real-world experience. *J Crohns Colitis* 2023;**17**(Suppl_1):i854-i856.
31. Zheng DY, Wang YN, Huang YH, Jiang M, Dai C. Effectiveness and safety of upadacitinib for inflammatory bowel disease: a systematic review and meta-analysis of RCT and real-world observational studies. *Int Immunopharmacol* 2024;**126**:111229.
32. Zhang W, Zhao S, Li J, Sun Y, Wang X. Network meta-analysis of efficacy and safety of drugs for the treatment of moderate to severe ulcerative colitis. *Front Pharmacol* 2024;**15**:1481678.
33. Shehab M, Alrashed F, Alsayegh A, et al. Comparative efficacy of biologics and small molecule in ulcerative colitis: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol* 2025;**23**:250-262.
34. Burr NE, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis. *Gut* 2022;**71**:1976-1987.
35. Radcliffe M, Long M, Barnes E, Herfarth H, Hansen J, Jain A. Efficacy of upadacitinib in pateints previously treated with tofacitinib for the management of ulcerative colitis. *Inflamm Bowel Dis* 2023;**29**:S82.
36. Vassallo C, Sammut L. AB0412 Cycling of JAK-inhibitors in patients with rheumatoid arthritis: a single-centre experience. *Ann Rheum Dis* 2022;**81**:1334-1335
37. Wang J, Macoritto M, Guay H, Davis JW, Levesque MC, Cao X. The clinical response of upadacitinib and risankizumab is associated with reduced inflammatory bowel disease anti-TNF-α inadequate response mechanisms. *Inflamm Bowel Dis* 2023;**29**:771-782.
38. Parmentier JM, Voss J, Graff C, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). *BMC Rheumatol* 2018;**2**:23.
39. Mohamed MF, Bhatnagar S, Parmentier JM, Nakasato P, Wung P. Upadacitinib: mechanism of action, clinical, and translational science. *Clin Transl Sci* 2024;**17**:e13688.
40. Irani M, Fan C, Glassner K, Abraham BP. Clinical evaluation of upadacitinib in the treatment of adults with moderately to severely active ulcerative colitis (UC): patient selection and reported outcomes. *Clin Exp Gastroenterol* 2023;**16**:21-28.
41. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs* 2017;**77**:521-546.
42. Runde J, Ryan K, Hirst J, et al. Upadacitinib is associated with clinical response and steroid-free remission for children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2025;**80**:133-140.
43. Wu H, Xie T, Yu Q, et al. An analysis of the effectiveness and safety of upadacitinib in the treatment of inflammatory bowel disease: a multicenter real-world study. *Biomedicines* 2025;**13**:190.
44. Raine T, Ishiguro Y, Rubin DT, et al. Impact of baseline corticosteroid use on the efficacy and safety of upadacitinib in patients with ulcerative colitis: a post hoc analysis of the phase 3 clinical trial programme. *J Crohns Colitis* 2024;**18**:695-707.

Supplementary material

Supplementary Table 1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review	Pg. 1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Pg. 1
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge	Pg. 1
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses	Pg. 1
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	Pg. 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	Pg. 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used	Pg. 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	Pg. 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	Pg. 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect	Pg. 2
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	Pg. 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	Pg. 2
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results	Pg. 2
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	Pg. 2
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	Pg. 2
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	Pg. 2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	Pg. 2
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression)	Pg. 2

(Contd...)

Supplementary Table 1 *(Continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results	Pg. 2
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	Pg. 2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	Pg. 2
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	Pg. 3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	Pg. 3
Study characteristics	17	Cite each included study and present its characteristics	Pg. 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study	Pg. 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots	Pg. 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	Pg. 3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	Pg. 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results	Pg. 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	Pg. 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	Pg. 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	Pg. 3
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	Pg. 3
	23b	Discuss any limitations of the evidence included in the review	Pg. 4
	23c	Discuss any limitations of the review processes used	Pg. 4
	23d	Discuss implications of the results for practice, policy, and future research	Pg. 4
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	Pg. 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	Pg. 4
Competing interests	26	Declare any competing interests of review authors	Pg. 4

(Contd...)

Supplementary Table 1 *(Continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/

Supplementary Table 2 Search strategy

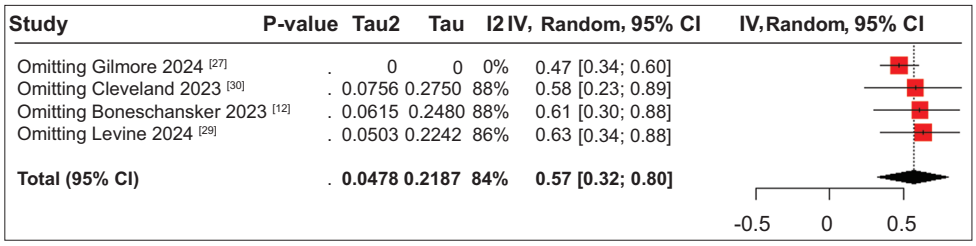
Database	Search strategy/Keywords	Articles Retrieved
PubMed	(upadacitinib OR Rinvoq OR ABT-494 OR UPA) AND (tofacitinib OR Xeljanz OR CP 690550 OR tofacitinib citrate OR TOFA) AND (ulcerative colitis OR UC OR inflammatory bowel disease OR IBD)	105
Embase	(upadacitinib OR Rinvoq OR ABT-494 OR UPA) AND (tofacitinib OR Xeljanz OR CP 690550 OR tofacitinib citrate OR TOFA) AND (ulcerative colitis OR UC OR inflammatory bowel disease OR IBD)	543
Web of Science	(upadacitinib OR Rinvoq OR ABT-494 OR UPA) AND (tofacitinib OR Xeljanz OR CP 690550 OR tofacitinib citrate OR TOFA) AND (ulcerative colitis OR UC OR inflammatory bowel disease OR IBD)	142
Cochrane CENTRAL	(upadacitinib OR Rinvoq OR ABT-494 OR UPA) AND (tofacitinib OR Xeljanz OR CP 690550 OR tofacitinib citrate OR TOFA) AND (ulcerative colitis OR UC OR inflammatory bowel disease OR IBD)	14

Supplementary Table 3 Quality assessment of the included retrospective studies using the Newcastle Ottawa Scale

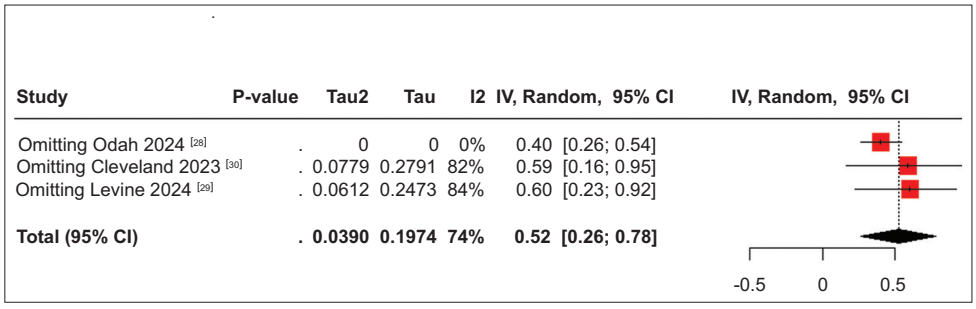
Study ID, year [ref.]	Selection				Comparability	Outcomes			Total Score (9★)
	Representativeness of Exposed Cohort (★)	Selection of Non-exposed Cohort (★)	Ascertainment of Exposure (★)	Outcome of Interest not Present at the Start (★)	(★★)	Assessment of Outcome (★)	Was the Follow-up Long Enough (★)	Adequacy of Follow-up (★)	
Boneschansker, 2023 [12]	★	★	★	★	★	★	★	★	★★★★★★★★ (8/9)
Odah, 2024 [28]	★	-	★	★	-	★	★	★	★★★★★★ (6/9)
Gilmore, 2024 [27]	★	★	★	-	★	★	★	★	★★★★★★★ (7/9)
Cleveland, 2023 [30]	★	-	★	★	-	★	★	★	★★★★★★ (6/9)
Levine, 2024 [29]	★	-	★	★	-	★	★	★	★★★★★★ (6/9)

Supplementary Table 4 Results of Joanna Briggs Institute critical appraisal tool for the quality assessment of the included case series

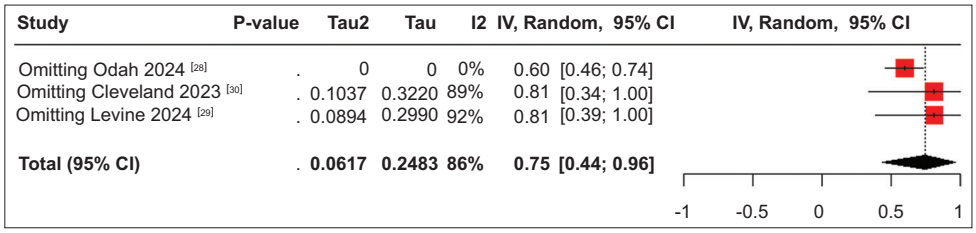
Study, year [ref.]	1	2	3	4	5	6	7	8	9	10	Total Score (9/10)
Levine, 2024 [29]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	9/10



Supplementary Figure 1 Forest plot of clinical remission after sensitivity analysis
CI, confidence interval



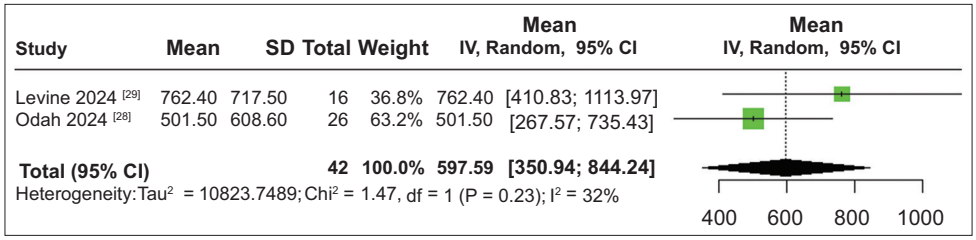
Supplementary Figure 2 Forest plot of steroid-free clinical remission after sensitivity analysis
CI, confidence interval



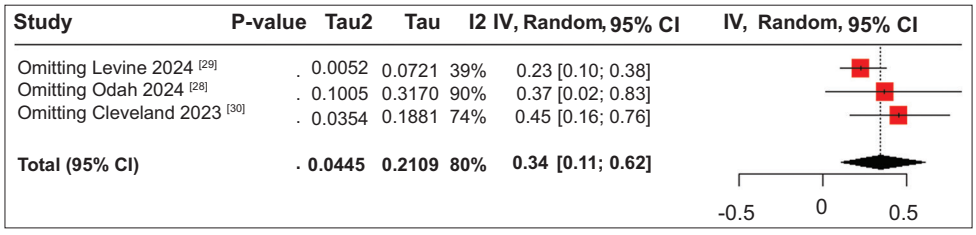
Supplementary Figure 3 Forest plot of clinical response after sensitivity analysis
CI, confidence interval

Questions

1) Were there clear criteria for the inclusion of case series?
2) Was the condition measured in a standard, reliable way for all participants included in the case series?
3) Were valid methods used for the identification of the condition for all participants included in the case series?
4) Did the case series have consecutive inclusion of participants?
5) Did the case series have a complete inclusion of participants?
6) Was there clear reporting of the demographics of the participants in the study?
7) Was there clear reporting of clinical information of the participants?
8) Were the outcomes or follow-up results of cases clearly reported?
9) Was there clear reporting of the presenting sites'/clinics' demographic information?
10) Was statistical analysis appropriate?



Supplementary Figure 4 Forest plot of decrease in fecal calprotectin
CI, confidence interval



Supplementary Figure 5 Forest plot of adverse events after sensitivity analysis
CI, confidence interval