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Safety and efficacy of advanced combination therapies for treating inflammatory bowel disease in adults: a systematic review and meta-analysis

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ABSTRACT

Objectives To systematically synthesise available evidence on the safety of advanced combination therapy (ACT) in adults with inflammatory bowel disease (IBD), with secondary exploratory evaluation of efficacy outcomes.

Design Systematic review and meta-analysis.

Data sources Searches of Embase (via Ovid), MEDLINE and PubMed were initially undertaken on 9 May 2025 and updated on 8 April 2026. Additional studies were identified through hand-searching and reference list screening. Eligible publications were restricted to those published between 1 January 2015 and 31 March 2026.

Eligibility criteria We included randomised controlled trials as well as observational and descriptive studies. Conference abstracts, reviews, editorials and commentaries were excluded. Inclusion was restricted to publications in English.

Data extraction and synthesis Two reviewers independently screened studies, extracted data and assessed risk of bias using Joanna Briggs Institute tools and Cochrane RoB-1. Pooled proportions of total adverse events (TAEs), serious adverse events (SAEs) and treatment discontinuations were calculated using random-effects meta-analysis. Subgroup analyses were conducted by drug class. Where meta-analysis was not appropriate, findings were narratively synthesised.

Results Fifty-two studies (n=2022 participants) were included. The most frequent combinations were anti-TNFa plus integrin inhibitors and interleukin (IL) 23 plus integrin inhibitors. Pooled analyses demonstrated low rates of SAEs (eg, anti-TNFa plus integrin inhibitors: 2.7%, 95% CI 0.22% to 6.86%) and discontinuations (6.38%, 95% CI 2.36% to 11.58%), although heterogeneity was substantial and certainty of evidence was very low, with some analyses based on small sample sizes.

Conclusion ACT may be associated with low rates of SAEs in selected patients with refractory IBD; however, the evidence is limited by small sample sizes, heterogeneity and predominantly observational designs. Robust conclusions regarding safety and efficacy cannot be made due to very low GRADE certainty.

PROSPERO registration number CRD420251025883

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Advanced therapies have improved outcomes in inflammatory bowel disease, but treatment failure remains common.

⇒ Advanced combination therapy (ACT) is increasingly used in refractory disease, although evidence on its safety and efficacy is limited and largely derived from small, observational studies.

WHAT THIS STUDY ADDS

⇒ This systematic review synthesises the available evidence on ACT across a broad range of study designs, highlighting generally low reported rates of serious adverse events, however, with very low certainty of evidence due to small sample sizes, heterogeneity and short follow-up

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support cautious, specialist use of ACT in selected patients while emphasising the need for adequately powered trials and long-term safety data—to better define its role in clinical practice.

INTRODUCTION

There is a growing number of available advanced therapies for the treatment of inflammatory bowel disease (IBD) in adults (biological agents and small molecules), with most developed in the last two decades and many of them now assimilated in worldwide IBD practice for both Crohn's disease (CD) and ulcerative colitis (UC).[1–7] However, there remains the issue of a high level of treatment failures, and an increasingly complex population with advancing disease, comorbidities and increasing lifespan.[8]

Recent evidence syntheses have shown the efficacy of different classes of advanced therapies is relatively similar, which leads to

complexities in clinical decision making about which therapies to use at which time in the patient journey.[4–6] People living with IBD experience negative impacts on their ability to undertake daily activities, with increased levels of disease burden, needing to take time away from work or education due to active disease symptoms, reduced ability to maintain social relationships, and reduced quality of life for both the patient and their families.[9] For these reasons, the development of optimal treatment strategies has been identified as a top research priority for IBD by the UK priority-setting partnership with the James Lind Alliance.[10]

The response and remission rates for advanced therapies used in the induction and maintenance of remission in IBD are usually up to 50% which creates an important clinical problem of a therapeutic ceiling for present medical options.[11] Despite extensive research,[12] there has been a failure by the clinical community to identify and translate clinical biomarkers to predict response to individual advanced therapies.[5 6] There is now a growing interest in the use of advanced combination therapies (ACTs) to treat IBD in adults. Previous evidence syntheses on this topic have been focused on assessments of efficacy of various ACTs and thus have been severely limited by the inclusion of data from only randomised controlled trials (RCTs) and/or comparative studies and have not included non-comparator or observational data,[13–15] which constitute most of the published data. Though the rigour of such methodology aimed to assess efficacy cannot be disputed, there is a severe paucity in the literature on safety analyses of ACTs where the use of observational data sets would be welcome. Historically there have been concerns in relation to the safety of combination advanced therapies for treating IBD.[16]

Several recent systematic reviews and meta-analyses have evaluated the efficacy and safety of advanced combination therapy in IBD, primarily focusing on comparative or controlled study designs.[13–15 17–22] However, these analyses have often been limited by the exclusion of observational and descriptive data, which constitute a substantial proportion of the available safety evidence.

This review presents a comprehensive systematic review focused on safety of ACT, encompassing any kind of available primary research, to inform future research and clinical use of ACT in IBD.

Objectives

The primary objective is to synthesise the evidence available on the safety of dual advanced therapies in IBD. The evidence synthesis on efficacy is a secondary and exploratory objective.

METHODS

This review is reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines,[23] the protocol is available publicly on the PROSPERO registry (CRD420251025883) and a completed PRISMA checklist is presented in online supplemental file 2.

ACT was defined as any combination of biologic, biosimilar or small molecule therapies given for treatment of IBD, IBD and extra intestinal manifestations, or as a treatment for another autoimmune condition in someone who also had a diagnosis of IBD.

Search strategy

Searches of Embase (via Ovid), MEDLINE and PubMed were initially undertaken on 9 May 2025 and updated on 8 April 2026. Additional studies were identified through hand-searching and reference list screening. Eligible publications were restricted to those published between 1 January 2015 and 31 March 2026, due to significant advancement of the field during this time. Inclusion was restricted to publications in English.

Eligible sources included RCTs, clinical trials protocols, observational studies (cohort, case series, case report and case control) and other reports of primary data that reported the use of dual advanced therapies in patients with IBD. There was no minimum or maximum therapy exposure time. Commentary papers and review papers were excluded. The search strategy is provided in online supplemental eAppendix 1.

Protocols were identified during the search to capture ongoing or recently completed studies in this evolving field. As these sources do not report outcome data, they were not included in the quantitative synthesis and were considered for contextualisation of the evidence base only.

Primary and secondary outcomes

Primary outcomes: overall and drug-related total adverse events (TAE), serious adverse events (SAE) and discontinuation of DAT due to adverse events in IBD patients (numbers of patients with at least one event/total number of patients). Definitions of TAEs and SAEs were not standardised across studies and were extracted as reported by the original authors where enough data were available. Where definitions were not explicitly stated, events were classified pragmatically based on reported severity. Broad categorisation of adverse events was undertaken to identify common themes across studies.

Secondary outcomes: clinical remission, endoscopic remission, clinical response and endoscopic response of ACT in CD or UC (numbers of patients achieving remission/response, as defined by the studies/total number of patients). Clinical and endoscopic outcomes (including remission and response) were extracted as defined by the original study authors. Given the heterogeneity in outcome definitions, scoring systems and thresholds across studies, standardisation was not feasible; therefore, these outcomes were synthesised descriptively and interpreted with caution.

Risk of bias and study quality

Sources were screened independently by at least two researchers, with a third, and further if required, being

available to review consensus and resolve any conflicts before moving forward. Joanna Briggs Institute checklist tools were used to assess quality and risk of bias of case control, case report, case series and cohort studies.[24] Risk of bias for included RCT sources was assessed using Cochrane Risk of Bias (RoB) 1 Tool .[25]

Data extraction

Two authors independently extracted data using a standardised extraction form.[25] Disagreements were reviewed by a third or fourth author as required, and consensus was met before moving forward. Where multiple publications from the same study or centre were identified, the most complete or recent data set was used. Studies were assessed for potential overlap based on study setting, recruitment period, author group and participant characteristics, and where overlap was suspected, duplicate data were excluded where possible.

Data were extracted relating to the primary and secondary outcomes of interest. Data extracted were participant demographics, including disease history, previous IBD therapy exposure, indications for dual advanced therapies, dose frequency and duration of treatment with ACT and follow-up periods, where available. Where available, data on TAEs, SAEs and discontinuation of ACT due to safety were recorded. Adjudication as to the adverse event being disease or drug-related was undertaken by two authors independently after reviewing the source documents.

Statistical analysis

For observational studies without a control group, we conducted pooled-effect meta-analyses of proportions using the Freeman–Tukey double arcsine transformation and the DerSimonian and Laird random-effects method. Subgroup analyses were performed by drug class, grouping studies that used therapies with the same mechanism of action, such as the grouping of antibodies to the p40 subunit of IL-12/23 and p19 IL-23 antibodies for this review. Pooling by mechanism of action, rather than individual molecule, allows findings to be more widely applicable across the class of therapies. This was especially important where the contributing sources had small sample sizes and were heterogenous. Pooling by drug class increases the number of participants contributing to each analysis, improving precision of pooled estimates, reducing random error. Analyses based on very small sample sizes were retained to allow comprehensive reporting of available safety data but were interpreted cautiously. Pooled proportions were reported as the number of events per 100 observations. Pooled percentages represent weighted estimates from meta-analysis and may differ from raw proportions. Forest plots were generated in R using the *meta* package. Additionally, we conducted drug-related and disease-related adverse events meta-analyses.

Pairwise meta-analyses were conducted for randomised control trials comparing interventions. Dichotomous outcomes were expressed as risk ratios (RRs) with 95% CIs. Pooled RRs were estimated using a random-effects meta-analysis based on the Mantel–Haenszel method. Forest plots were generated using Review Manager software (V.5.4).

Heterogeneity for both pairwise and pooled effects meta-analyses was estimated using the Higgins I^2 statistics. Publication bias was assessed in outcomes with 10 or more studies and visually inspected using funnel plots, which plot proportions against their SEs, and statistically using Egger's regression test. A value of $p<0.10$ was considered indicative of significant asymmetry.

For those included sources for which statistical analysis was not possible, a narrative synthesis was undertaken.

Certainty of evidence assessment

Certainty of evidence was assessed using the GRADE framework based on risk of bias, inconsistency, imprecision, indirectness and publication bias.[25] We graded the certainty of the evidence for each outcome as high, moderate, low or very low. We justified all decisions to downgrade the certainty of studies using footnotes, and we summarised the results and assessments in summary of findings tables. Absolute risk differences per 100 individuals were estimated by applying the pooled relative risk to the baseline risk in the intervention group and subtracting it from the control group risk.

Predefined thresholds for interpretation of effect magnitude were applied as previously described[26] and are summarised in online supplemental eTable 5.

RESULTS

Our search identified 2317 records of which 70 records were assessed at full text screening. 18 records were excluded (figure 1; online supplemental eTable 4). There were 52 studies (66 associated records) included in this review, including data from n=2022 patients (online supplemental eTables 1–3).

Characteristics of included studies

Out of 52 total studies (66 associated reports) included, 3 were RCTs, 3 RCT protocols, 12 case-series, 16 case-reports, 1 case-control study, 17 cohort studies (online supplemental eTable 1). The full reference list for included studies is provided in online supplemental eAppendix 2.

Across 52 studies, 9 included patients with UC, 21 with CD and 22 mixed IBD populations. Dual therapy class-specific outcomes for safety or efficacy or both were reported in five CD and six UC studies. Adverse events were reported quantitatively in 31 studies.[27–57] 25 studies reported adverse events with unit of analysis as number of patients with at least one event/total number of patients (25 studies[27–35 37 39 40 42 44–52 54 56 57]), followed by number of patients/number of ACT combinations (3 studies[38 41 55]) and number of events/number of patients (4 studies[36 39 43 53]). The number of combinations refers to the total number of treatment combinations tested for

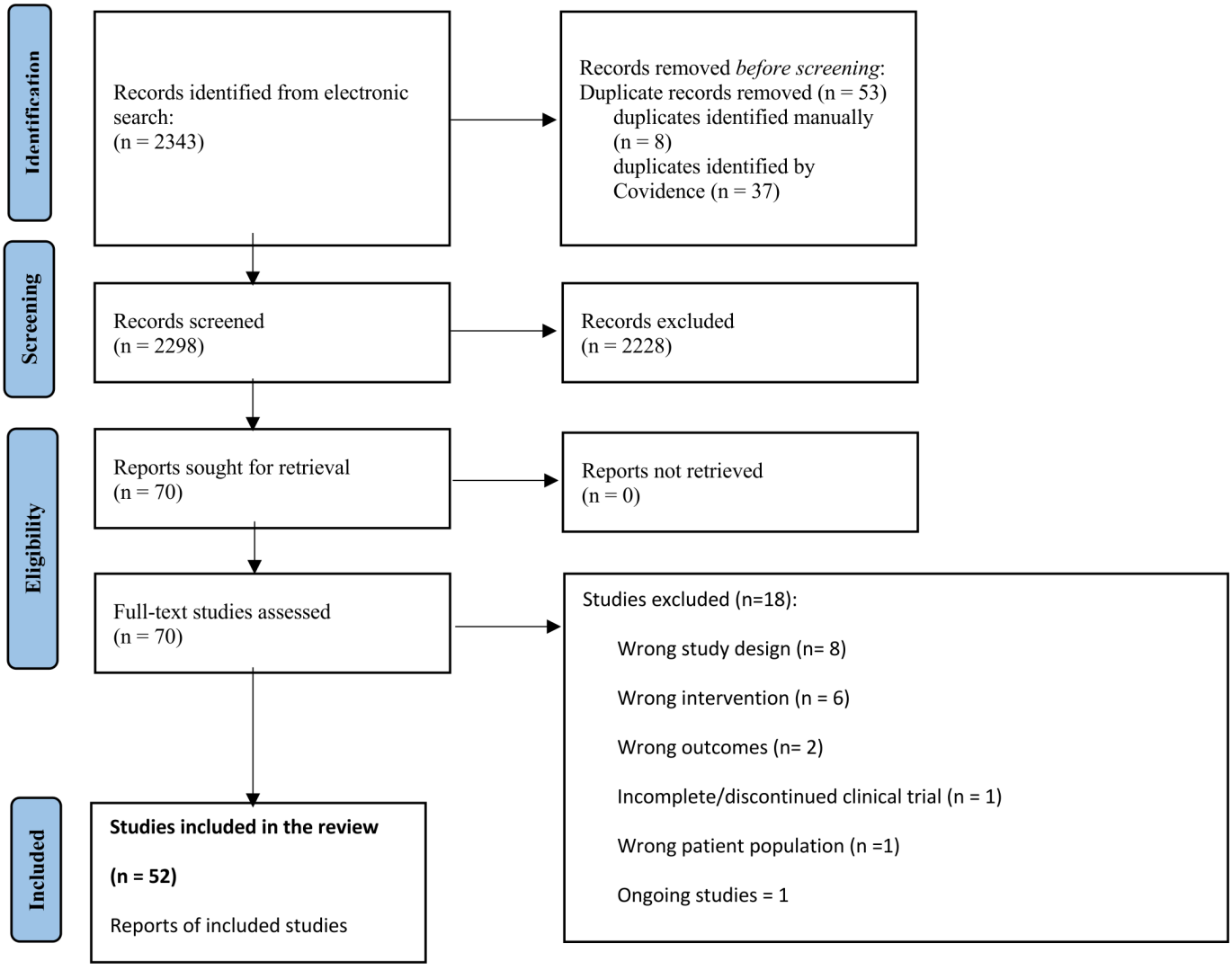

Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart.

each ACT, as a single patient could have received more than one drug combination. The number of patients with events refers to the count of patients who experienced at least one occurrence of a specific adverse event during the study period, regardless of whether a patient experienced multiple events.

Seventeen studies[29 33 34 36 38 39 41–43 45 48 50–53 55 56] reported adverse events both quantitatively and qualitatively, explicitly describing the specific side effects observed. Of these, 16 studies[33 34 36 38 39 41–43 45 48 50 52 53 55 56] reported drug-related adverse events, while 10[36 38 39 41–43 50–53] reported disease-related adverse events. Table 1 presents information on type of adverse event and whether these were drug related or disease related.

TAEs for CD and UC were reported in the following ACT interventions: IL-23 inhibitor + integrin inhibitor 10 out of 52 studies, anti-TNFa + integrin inhibitor 10/52 studies, integrin inhibitor + JAK inhibitor 6/52 studies, IL-23 inhibitor + JAK inhibitor 5/52 studies, anti-TNFa + JAK inhibitor 2/52 studies, anti-TNFa + IL-23 inhibitor 10/52 studies, IL-4 inhibitors + IL-23 inhibitor 1/52 studies, anti-CD20 + integrin inhibitor 1/52 studies, IL-17 inhibitor + integrin inhibitor 1/52 studies.

SAEs for CD and UC were reported in the following ACT interventions: anti-TNFa + integrin inhibitor 10/52 studies, IL-23 inhibitor + integrin inhibitor 11/52 studies, integrin inhibitor + JAK inhibitor 7/52 studies, IL-23 inhibitor + JAK inhibitor 5/52 studies, anti-TNFa + JAK inhibitor 2/52 studies, anti-TNFa + IL-23 inhibitor 10/52 studies, IL-4 inhibitors + IL-23 inhibitor 1/52 studies, anti-CD20 + integrin inhibitor 1/52 studies, IL-17 inhibitor + integrin inhibitor 1/52 studies.

Discontinuation of ACT interventions for CD and UC were reported in the following sources: anti-TNFa + integrin inhibitor 10/52 studies, IL-23 inhibitor + integrin inhibitor 11/52 studies, integrin inhibitor + JAK inhibitor 6/52 studies, anti-TNFa + IL-23 inhibitor 10/52 studies, IL-4 inhibitors + IL-23 inhibitor 1/52 studies, anti-CD20 + integrin inhibitor 1/52 studies, IL-23 inhibitor + JAK inhibitor 4/52 studies, anti-TNFa + JAK inhibitor 1/52 studies, IL-17 inhibitor + integrin inhibitor 1/52 studies.

Table 1 Drug-related and disease-related adverse events by dual therapy combination and unit of analysis

Advanced combination therapy	Unit of analysis	Total adverse events (TAEs)		Serious adverse events (SAEs)		Discontinuation due to adverse events	
		Drug related	Disease related	Drug related	Disease related	Drug related	Disease related
anti-TNFa + IL-23 inhibitor*	N° of patients/N° of patients	Rash on the lower extremities (1), common cold (1), concurrent sepsis and influenza B (1), tuberculosis (1), CMV colitis (1)	Perianal abscess (1)	Concurrent sepsis and influenza B (1), tuberculosis (1), CMV colitis (1)	–	–	–
	N° of events/N° of patients	Upper airway infection (16), headache (6), eczema (5), skin erythema (3), neutropenia (3), fever (2), opportunistic infections (2)	UC flare up (10), arthralgia (3), anaemia (4)	–	–	Eczema (1)	–
anti-TNFa + integrin inhibitor	N° of patients/N° of patients	Upper airway infection (2), headache (1), *Mycobacterium marinum* infection (1), hand-foot-mouth disease and influenza (1), cutaneous reaction (1), *C. difficile* infection (1)	–	Headache (1), *C. difficile* infection (1), *M. marinum* infection (1)	–	Headache (1), cutaneous reaction (1), *M. marinum* infection (1)	–
	N° of patients/N° of combinations	Osteomyelitis after ankle fracture (1), *Campylobacter* colitis (1), herpetic meningoencephalitis (1), erysipelas (1), conjunctivitis (1), adalimumab-induced lupus (1), non-specified infection (1)	Enterocutaneous fistula infection (1)	Osteomyelitis after ankle fracture (1), *Campylobacter* colitis (1), herpetic meningoencephalitis (1), non-specified infection (1), adalimumab-induced lupus (1)	Enterocutaneous fistula infection (1)	Adalimumab-induced lupus (1)	–
	N° of events/N° of patients	Headache (17), upper airway infection (15), nausea (9), (5), DNA antibody positive (4), dyspepsia (4), gastroenteritis (4), urinary infection (3), raised creatinine (3), rash (3), antinuclear antibody positive (3), back pain (3), insomnia (3), fever (4), skin erythema (1), lymphadenopathy (1)	CD flare up (15), arthralgia (12), abdominal pain (11), intestinal obstruction (3), perianal abscess (1), fatigue (7)	Lymphadenopathy (1), fever (1), gastroenteritis (1)	Intestinal obstruction (2), CD relapse (1), perianal abscess (1)	–	–

Continued

Table 1 Continued

Advanced combination therapy	Unit of analysis	Total adverse events (TAEs)		Serious adverse events (SAEs)		Discontinuation due to adverse events	
		Drug related	Disease related	Drug related	Disease related	Drug related	Disease related
anti-TNFa + JAK inhibitor	N° of patients/N° of patients	Influenza (1)	–	–	–	–	–
	N° of events/N° of patients	Oral herpes simplex (1), pneumonia (1)	–	Pneumonia (1)	–	Pneumonia (1)	–
IL-23 inhibitor + integrin inhibitor	N° of patients/N° of patients	Pneumonia (2), headache (1), sinusitis (1), *Clostridioides difficile* infection (1)	CD-related surgery (4), CD relapse (1), postsurgical resection (1)	Pneumonia (1).	CD-related surgery (4), CD relapse (1)	–	CD-related surgery (1)
	N° of patients/N° of combinations	Recurring *C. difficile* infection (1), upper airway infection (1)†, non-specified infection (1)	Perianal abscess (1)	Upper airway infection (1)†, non-specified infection (1)	–	–	–
	N° of events/N° of patients	Headache (1), eyelid twitch (1), lower limbs oedema (1)	–	–	–	–	–
IL-23 inhibitor + JAK inhibitor	N° of patients/N° of patients	Upper airway infection (3), acne (3), nausea and cutaneous fungal infection (1), nausea (1)	Small bowel obstruction (1)	–	–	Nausea (1)	–
Integrin inhibitor + JAK inhibitor	N° of patients/N° of patients	–	Worsening of stool frequency (2)	–	–	–	–

Units of analysis vary across studies and are reported as originally defined by the source publications. These include: number of patients with at least one event / total number of patients; number of events/total number of patients; number of patients/number of treatment combinations.
Where multiple adverse events occurred in a single patient, these may be counted more than once in analyses reporting number of events.
Drug-related and disease-related adverse events were classified based on reporting in the original studies and, where necessary, by reviewer adjudication.
*One patient using the combination of guselkumab + golimumab died of poisoning from an unknown substance.
†Patient required hospitalisation.
CD, Crohn's disease; CMV, Cytomeglovirus; JAK, Janus Kinase; TNFa, tumor necrosing factor alpha; UC, ulcerative colitis.

Clinical and endoscopic remission were reported in 17 and 9 studies for CD and in 10 and 6 for UC, respectively; clinical and endoscopic responses were reported in 10 and 6 for CD and 7 and 2 for UC, respectively.

Risk of bias summary

Of the 47 non-RCT studies assessed, 30 (64%) were rated as low risk of bias, 14 (30%) as moderate and 3 (6%) as high. A single case-control study was rated moderate risk. The most common sources of bias in observational studies were unclear handling of confounding factors, incomplete follow-up and uncertain outcome assessment.

Sands *et al*'s[53] study was rated moderate risk due to uncertainties in randomisation, allocation concealment and blinding. Feagan *et al*'s[39] study was rated low risk, with a minor concern regarding selective outcome reporting. Wu *et al*'s[58] study was incomplete and therefore judged as unclear risk across all domains. Full risk of bias assessments and justifications are available in the materials (online supplemental eTables 6–8).

Primary outcomes (TAEs, SAEs, discontinuation due to adverse events)

For anti-TNFa + IL-23 inhibitors, the most frequently reported safety events were drug-related AEs, with upper airway infection being the most frequent (n=16 events), with only three drug-related SAEs reported.

For anti-TNFa + integrin inhibitors, the most frequently reported safety events were drug-related AEs, with headaches being the most frequent (n=17 events), with 15 drug-related SAEs reported.

For anti-TNFa + JAK inhibitor, there were equal numbers of drug-related, SAE and discontinuations (n=1), with two reported drug-related AEs overall.

For the IL-23 inhibitor + integrin inhibitor association, the most frequently reported safety events were drug-related AEs, with pneumonia being the most frequent (n=2 events), with eight SAEs reported across both drug-related and disease-related groups, with the highest number of SAEs being CD-related surgery (n=4).

For the IL-23 inhibitor + JAK inhibitor, the most frequently reported safety events were drug-related AEs, with upper airway infection and acne being the most frequent (n=3 events each), with no SAEs reported.

For safety information on other ACTs, see table 1.

These analyses for safety outcomes include data from pooled sources containing both UC and CD participants combined (figures 2–4). Disease-related adverse events were indicative of underlying IBD activity, and their profile varied across drug combinations. Further information is available in online supplemental eTable 6.

Anti-TNFa + IL-23 inhibitor

Total adverse events

Across three cohort studies, two case series, four case reports and one RCT there were 59 out of 120 patients who had AEs with a weighted percentage of 23.22% (95% CI 1.01% to 55.68%) with very low certainty due to very high inconsistency.

Serious adverse events

Across three cohort studies, two case series, four case reports and one RCT, there were 4 out of 120 patients with a weighted percentage of 0% with very low certainty.

Discontinuation

Across three cohort studies, two case series, four case reports and one RCT there were eight withdrawals from 120 participants with a weighted percentage of 0% (95% CI 0% to 2.28%) with very low certainty.

IL-23 + integrin inhibitors

Total adverse events

Across 10 studies, 16 out of 52 participants reported AEs with a weighted percentage of 23.84% (95% CI 8.93% to 41.59%) with very low certainty.

Serious adverse events

Across 11 studies, 2 out of 55 participants reported SAEs with a weighted percentage of 0% (95% CI 0% to 3.77%) with very low certainty.

Discontinuation

Across 11 studies, 0 participants out of 55 discontinued from the study with very low certainty and a weighted percentage of 0%.

Anti-TNFa + integrin inhibitor

Total adverse events

Across 10 studies with a weighted percentage of 42.61% (95% CI 17.6% to 69.48%), 135 out of 182 patients reported AEs, as well as very low certainty.

Serious adverse events

Across 10 studies with a weighted percentage of 2.7% (95% CI 0.22% to 6.86%), 12 patients out of 182 reported SAEs, with very low certainty.

Discontinuation

Across 10 studies with a weighted percentage of 6.38% (95% CI 2.36% to 11.58%), 18 out of 182 patients withdrew or discontinued the treatment and very low certainty.

IL-23 inhibitor + JAK inhibitor

Total adverse events

2 out of 40 patients across six studies reported AEs with a weighted percentage of 0% (95% CI 0% to 5.31%) with very low certainty.

Serious adverse events

0 out of 41 patients across seven studies reported any SAE with very low certainty.

Discontinuation

0 out of 37 patients across six studies discontinued from the treatment with very low certainty.

Anti-TNFa + JAK inhibitor

Total adverse events

Across two studies, three out of five participants

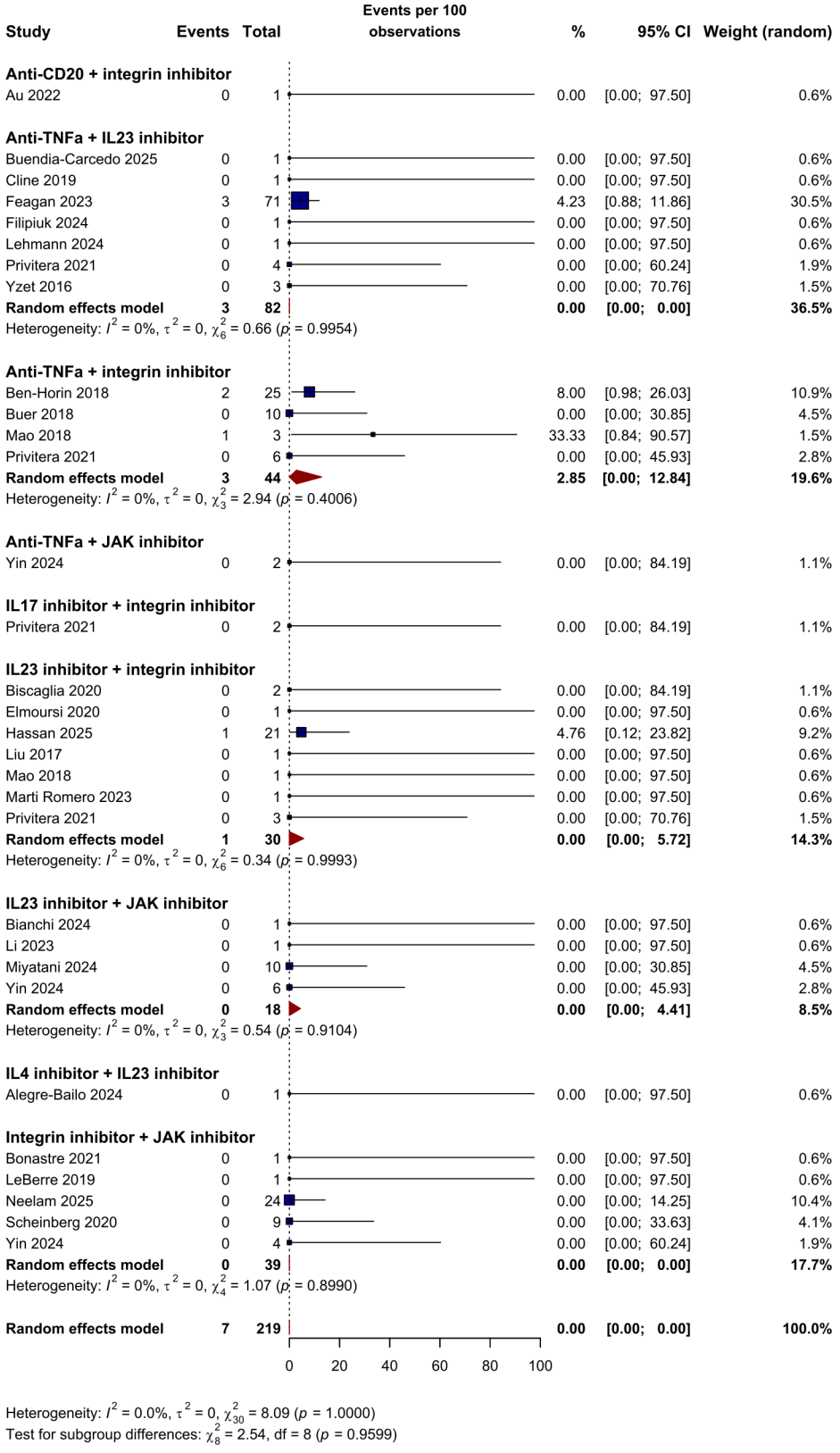

Figure 2 Pooled effects meta-analysis for SAEs (number of patients with at least one event/total numbers of patients). JAK, Janus kinsae inhibitors; TNFa, Tumor necrosing factor Alpha; SAE, serious adverse events.

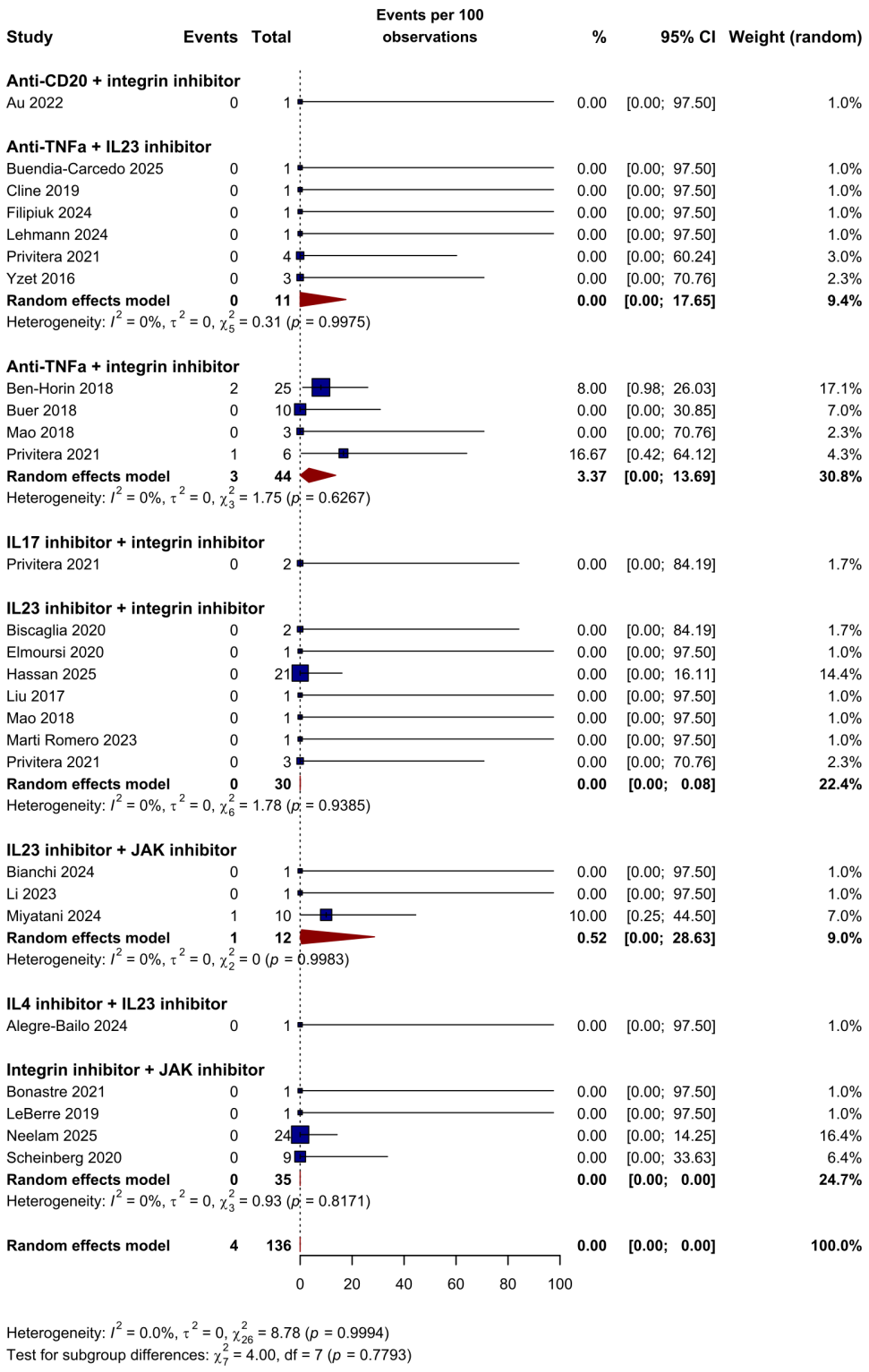

Figure 3 Pooled effects meta-analysis for drug-related events leading to discontinuation (number of patients with at least one events/total numbers of patients). JAK, Janus kinsae inhibitors; TNFa, Tumor necrosing factor Alpha.

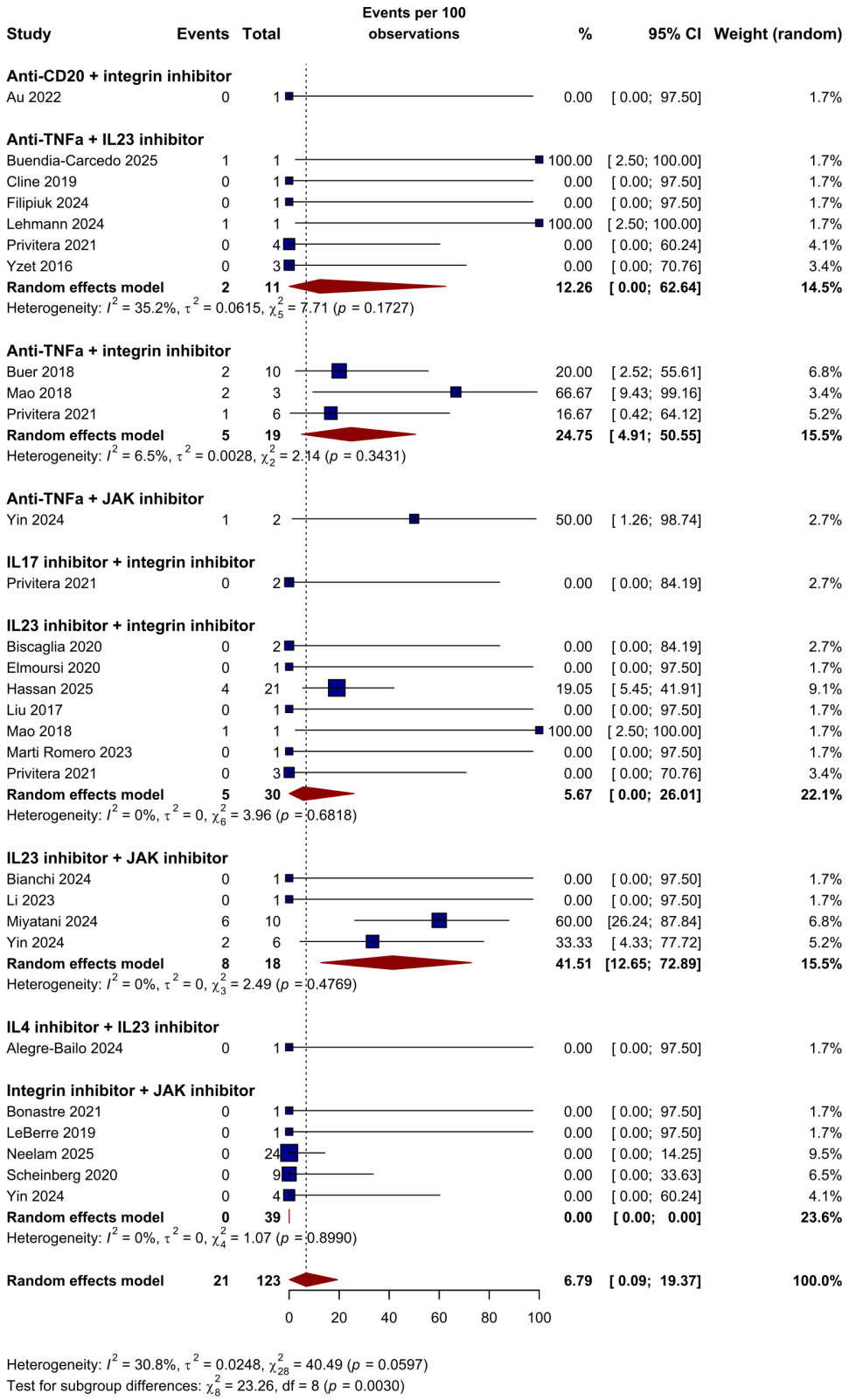

Figure 4 Pooled effects meta-analysis for drug-related TAEs (number of patients with at least one events / total numbers of patients). JAK, Janus kinsae inhibitors;TAE, total adverse event; TNFa, Tumor necrosing factor Alpha.

reported AEs with very low certainty and a weighted percentage of 60.29% (95% CI 10.29% to 99.74%).

Serious adverse events

Across two studies, one out of five participants reported a SAE with very low certainty and weighted percentage of 15.2% (95% CI 0% to 66%)

Discontinuation

Across one study, one participant out of three discontinued the medication with very low certainty and a weighted percentage of 33.33% (95% CI 8.46% to 82.64%).

Integrin inhibitor + JAK inhibitor

Total adverse events

Across six sources, 2 out of 40 participants reported AEs, with trivial magnitude of favour and a weighted percentage of 0% (95% CI 0% to 5.31%).

Serious adverse events

Across seven sources, 0 out of 41 participants reported SAEs; however there is very low certainty.

Discontinuation

Across six sources, 0 out of 37 participants discontinued the medication combination with very low certainty.

IL-4 inhibitor + IL-23 inhibitor

Total adverse events

No AEs were reported in a cohort of one participant.

Serious adverse events

No SAEs were reported in a population of one participant.

Discontinuation

No patient discontinued out of one participant.

Secondary outcomes (clinical, endoscopic remission, endoscopic response)

Anti-TNFa + IL-23 inhibitor

Clinical remission

For CD across one cohort study, one case series and three case reports, seven out of nine patients reported clinical remission with a weighted percentage of 89.12% and very low certainty and moderate magnitude of favour. In UC, across one case report and one RCT, 27 out of 72 patients reported clinical remission and a weighted percentage of 46.39% and very low certainty and small magnitude in favour.

Endoscopic remission

For CD, across one cohort study and one case report, two out of four patients reported endoscopic remission with very low certainty and large magnitude of favour. In UC, across one case report and one RCT, 14/72 patients had endoscopic remission with very low certainty and trivial magnitude of favour.

Clinical response

For CD, three out of five patients across three studies (one cohort and two case reports) reported a clinical response with very low certainty and small magnitude of favour. In UC, 59 out of 71 patients across one RCT reported a clinical response with very low certainty and moderate magnitude of favour.

Endoscopic response

For CD, three out of five patients across one cohort study and two case reports reported an endoscopic response with very low certainty and small magnitude of favour. In UC, 35 out of 71 patients across one RCT reported a clinical response with very low certainty and moderate magnitude of favour.

IL-23 + integrin inhibitors

Clinical remission

In CD, across eight studies 29 out of 37 patients reported clinical remission with very low certainty and large magnitude of favour. In UC, across two case series, both patients in total (2/2) reported clinical remission with very low certainty and very large magnitude of favour.

Endoscopic remission

Across six studies for CD, 14/25 patients reported endoscopic remission with very low certainty and a moderate magnitude of favour. In UC, one case series displayed one patient in total who was in endoscopic remission with very low certainty and very large magnitude of favour.

Clinical response

Across four studies for CD, 23/30 patients reported clinical response with very low certainty and large magnitude of favour compared with the one patient in total with clinical response for UC with very low certainty and very large magnitude of favour.

Endoscopic response

Across three studies, endoscopic response was only reported for CD, 10 out of 20 patients reported endoscopic response with very low certainty and moderate magnitude of favour.

Anti-TNFa + integrin inhibitor

Clinical remission

Across five studies (two cohort studies, two case series and one RCT), in CD 59/126 patients reported clinical remission with very low certainty and moderate magnitude of favour compared with UC, across two case series, in which seven out of seven patients reported clinical remission with very low certainty and a very large magnitude of favour.

Endoscopic remission

Across one cohort study and one case series, for CD, 25/70 patients reported endoscopic remission with very low certainty and small magnitude of favour.

Clinical response

Across two cohort studies, for CD, 29/67 patients reported a clinical response with very low certainty and a moderate magnitude of favour.

Endoscopic response

Across two cohort studies for CD, 35/67 patients reported an endoscopic response with very low certainty and a moderate magnitude of favour.

IL-23 inhibitor + JAK inhibitor

Clinical remission

Across three studies, in CD, 9/15 patients reported clinical remission with very low certainty and moderate magnitude of favour compared with the two out of two patients in UC with very low certainty and very large magnitude of favour.

Endoscopic remission

One case report reported one patient with CD with endoscopic remission with very low certainty and very large magnitude of favour.

Clinical response

Across two studies, 2 out of 11 patients with CD reported a clinical response with very low certainty and small magnitude of favour. In UC, one patient reported clinical response with very low certainty and very large magnitude of favour.

Integrin inhibitor + JAK inhibitor

Clinical remission

Across six studies, 28 out of 61 patients with UC reported clinical remission with very low certainty and moderate magnitude of favour.

Endoscopic remission

Across three studies, 20 out of 51 patients with UC reported endoscopic remission with very low certainty and moderate magnitude of favour.

Clinical response

Across one study, none out of one patient with CD reported a clinical response compared with 39/60 with UC, both with very low certainty. CD had trivial magnitude of favour whereas UC had moderate magnitude of favour.

Endoscopic response

In one RCT, 16 out of 26 patients with UC reported an endoscopic response with very low certainty and moderate magnitude of favour.

Anti-TNFa + JAK inhibitor

Clinical remission

One case series showed both patients (2/2) with UC report clinical remission with very low certainty and a very large magnitude of favour

Clinical response

One case series with four out of five patients with UC reported clinical response with very low certainty and large magnitude of favour.

Efficacy forest plots, GRADE decisions, summary of findings tables and the pairwise meta-analyses can be found in online supplemental eTables 6,7.

DISCUSSION

This review builds on existing evidence syntheses by focusing specifically on safety outcomes across a broad range of study designs, including observational and descriptive data, to provide a more comprehensive overview of adverse events associated with ACT in IBD. All previous reviews have primarily focused on efficacy. Though the quest to understand which is the most efficacious ACT is highly relevant, source data are neither of sufficient quality nor size to be able to make any clinically useful conclusions with only three RCT comparisons available.[39 58] An evidence synthesis focusing on safety events is currently a more pertinent use of published data sets with findings highly relevant as they may inform future trial design. This review allowed for synthesis of disease cohorts to enhance statistical power when investigating drug-specific adverse events. An advantage of our review, which has not been considered before in this context, is that we combined drugs within classes as these target the same immunological pathway, so their safety profiles are mechanistically related. Analysing them together better reflects class level effects and adverse event patterns.

Across 52 included studies, encompassing 2022 participants and any study designs with original data considered, the safety profiles of ACT have been analysed, and this is the most comprehensive approach ever published, including both trial and real world data sources and putting both through rigorous appraisal. The findings suggest that combining advanced therapies with complementary mechanisms of action may represent a feasible therapeutic strategy for selected adults with refractory disease. Pooling by drug class may obscure molecule-specific differences in safety profiles and does not account for variation in exposure duration across studies, which may influence adverse event reporting. No clear signal of new or unexpected adverse events was identified; however, this should be interpreted cautiously given the limitations of the available evidence. Across RCTs and observational data, the most frequently investigated combinations were anti-TNFa plus integrin inhibitors and IL-23 plus integrin inhibitors. The pooled data indicate that the rates of TAEs and SAEs associated with ACT were low, and discontinuations due to safety were uncommon. It should be noted that several pooled analyses were based on small denominators, which limits the stability and interpretability of these estimates and increases the risk of imprecision. These findings align with smaller real world series reporting possible tolerability of such combinations in complex, treatment-refractory IBD

populations. The absence of new or unexpected safety concerns across mechanisms of action provides some preliminary reassurance, though the precision of estimates remains limited.

Evidence regarding efficacy outcomes was heterogeneous, reflecting variation in disease subtype, prior therapy exposure and follow-up duration. Interpretation of efficacy outcomes is further limited by heterogeneity in outcome definitions and reporting across studies. Several studies reported promising rates of clinical and endoscopic remission in CD and UC, particularly for IL-23 plus integrin inhibitor combinations. However, the lack of standardised outcome measures and the predominance of uncontrolled data preclude robust efficacy conclusions. Together, these observations highlight an emerging signal of potential benefit, warranting formal evaluation in controlled studies.

Previous reviews have largely restricted inclusion to randomised or comparative studies (9–11), limiting insight into the growing body of observational and real world evidence. As adverse events generally occur in low numbers, this means that events occurring in case reports, case series and smaller studies can be left unaccounted, something that can be particularly negligent for rare events. By encompassing all forms of primary data, the present review offers a more comprehensive overview of the evolving combination therapies landscape. The findings are consistent with earlier reports indicating the safety concerns related to ACT. Nonetheless, the relative paucity of controlled trials means that the comparative efficacy of specific drug pairings remains uncertain, and mechanistic rationale alone should not yet drive clinical adoption.

Despite the bulk of studies being more real world and observational, the quality of the majority on appraisal was reasonable. In the recent UK IBD guidelines by the British Society of Gastroenterology a systematic search aimed at assessing drug safety identified 15000 potential studies in a 10-year period.[11] From these, only 200 studies met minimal quality criteria and most have significant faults on appraisal. Although the ACT evidence base is real work and observational in nature, many included studies were of reasonable methodological quality; however, the inherent limitations of these designs remain important when interpreting the findings. The use of GRADE has shown very low certainty evidence, and this could appear to be an unclear juxtaposition. This is actually the result of the relative scarcity of adverse events, particularly serious events, which in turn reduces precision and in turn the certainty of the estimates made. This is the strength of the GRADE system, preventing interpretation that can appear overly reassuring, but also presenting a challenge as the growth of ACT is currently limited by the sheer scarcity of adverse event data.

An important emerging area in this field is the development of bispecific antibodies, which are designed to simultaneously target multiple immune pathways within a single therapeutic agent. These therapies may offer a pharmacologically integrated alternative to ACT, potentially reducing the need for concurrent administration of multiple agents while maintaining therapeutic efficacy. In addition, bispecific approaches may allow for more controlled pharmacodynamic interactions and could mitigate some of the safety concerns associated with combining separate therapies.[59] However, clinical data in IBD remain limited, and further studies are required to establish their efficacy, safety profile and role relative to current combination strategies.

While ACT cannot yet be recommended for routine use, the accumulated evidence supports its consideration as a rescue strategy in refractory IBD, where standard monotherapies have failed though the safety observations may suggest that this strategy could potentially be used earlier in the disease course. The absence of a strong safety signal provides preliminary reassurance for carefully selected use under specialist supervision. This strategy may be limited by drug cost reimbursement in various healthcare jurisdictions.

Strengths and limitations

This study has various strengths. First, this is the largest meta-analysis published to date on dual advanced therapy in IBD. Second, here we have tried to analyse the combinations per class and combined CD and UC cohorts for safety readouts. Well-designed RCTs comparing combination therapy with monotherapy, and large safety cohorts with long-term follow-ups that could capture rare events, are ideal. Interventional trials should prioritise safety outcomes and have explicitly defined efficacy outcomes, including clinical and endoscopic response and remission, and thresholds of minimum clinically important difference and effect size.[3 26] A recent international consensus on the design of these trials in IBD has put forward recommendations to conduct these clinical trials efficiently which would enable us to confirm the role of dual advanced therapy in IBD.[59] We adhered to PRISMA guidelines and prospectively registered the review protocol to ensure transparency and minimise selective reporting. The methods we employed follow Cochrane and GRADE standards and promote accuracy, reproducibility and transparency. We critically identified potential conflicts of interest, particularly in industry-funded studies. Given the off-label use and theoretical safety risks associated with dual advanced therapy, we interpreted efficacy and safety findings cautiously, explicitly acknowledging uncertainty, heterogeneity and limitations of the available evidence, and avoided overstating clinical implications or advocating premature adoption into routine practice.

A limitation of this study is that most of the included studies are observational and so the results are prone to the inherent risk of bias of these study designs. This has been mitigated using an appropriate methodological approach to appraise them, but readers need to consider this when interpreting the findings. Additionally, few of the studies reported all clinically important outcomes and most did not classify according to each combination. The small sample sizes of the included studies did not allow for a subanalysis relating to the impact of study design on outcomes.[60] The use of various definitions to determine adverse events and efficacy outcomes such as clinical and endoscopic response or remission led to significant heterogeneity among the studies. The

different units of analysis used was another issue we encountered which limited synthesis. Most studies, which we were able to synthesise, reported numbers of patients with at least one event over the total number of patients, but others reported numbers of patients with at least one event over the number of ACT they received and others total numbers of events (where the same patient can experience multiple) over total numbers of participants. Due to this reason the data from the studies using the latter two could not be meaningfully synthesised. Due to incomplete reporting in some studies, it was not always possible to definitively exclude overlapping patient populations, which may have introduced bias into pooled estimates. Finally, the included studies did not have a minimum exposure time or follow-up period, which could have affected the adverse event rates. A further limitation is that no minimum exposure or follow-up duration was required for study inclusion. While this pragmatic approach allowed inclusion of a broader evidence base and increased the number of eligible studies and participants, it introduces potential bias in the estimation of adverse event rates. Shorter exposure periods may underestimate the occurrence of adverse events, especially those that are time-dependent or cumulative. This heterogeneity in treatment duration and follow-up contributes to imprecision and limits the comparability of findings across studies.

Future research should prioritise well-designed, adequately powered RCTs directly comparing dual versus sequential monotherapy approaches, with harmonised definitions of clinical, endoscopic and patient-reported outcomes. Real world registry data and pharmacovigilance studies will also be essential to characterise long-term safety. Mechanistic and pharmacodynamic studies exploring synergistic or antagonistic immune effects between therapy classes will further refine rational drug pairing. In addition, synthesis of safety data from future studies should be used to update well-designed systematic reviews so that we may see improvements in the problems of imprecision and inconsistency we have detected and described in this review.

CONCLUSIONS

In summary, this systematic review showed that most adverse events reported were drug-related with no new or unexpected safety events in adult patients with IBD exposed to ACT. The certainty of the evidence is very low, so it is not possible to make any further conclusions on frequency or severity of adverse events in DAT-exposed patients. As therapeutic options expand, ACT may emerge as a valuable approach to address treatment failure and improve long-term disease control. However, confirmation through prospective, adequately powered, controlled studies and large cohorts with long-term follow-ups is essential before widespread implementation in clinical practice.

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REFERENCES

1 Gordon H, Minozzi S, Kopylov U, *et al*. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2024;18:1531–55.
2 Raine T, Bonovas S, Burisch J, *et al*. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohns Colitis* 2022;16:2–17.
3 Darie A-M, Sinopoulou V, Ajay V, *et al*. BSG 2024 IBD guidelines protocol (standard operating procedures). *BMJ Open Gastroenterol* 2023;10:e001067:1:.
4 Sinopoulou V, Gordon M, Vuyyuru S, *et al*. P756 Efficacy and safety of medical therapies for maintenance of surgically induced remission in Crohn's disease: a systematic review and network meta-analysis. *J Crohns Colitis* 2024;18:i1400.

5 Sinopoulou V, Gordon M, Vuyyuru S, *et al*. P1043 Immunomodulator and advanced therapies for prevention of clinical relapse and loss of response during maintenance phase in Crohn's disease: a systematic review and network meta-analysis. *J Crohns Colitis* 2024;18:i1872.
6 Sinopoulou V, Gordon M, Vuyyuru S, *et al*. P556 Immunomodulator and advanced therapies for Induction of clinical remission and response in Crohn's disease: a systematic review and network meta-analysis. *J Crohns Colitis* 2024;18:i1085.
7 Sinopoulou V, Gordon M, Vuyyuru S, *et al*. P1043 Immunomodulator and advanced therapies for prevention of clinical relapse and loss of response during maintenance phase in Crohn's disease: a systematic review and network meta-analysis. *Journal of Crohn's and Colitis* 2024;18:i1872.
8 Moss AC. Approach to treatment failure in inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2022;18:360–3.
9 Devlen J, Beusterien K, Yen L, *et al*. The burden of inflammatory bowel disease: a patient-reported qualitative analysis and development of a conceptual model. *Inflamm Bowel Dis* 2014;20:545–52.
10 Hart AL, Lomer M, Verjee A, *et al*. What are the top 10 research questions in the treatment of inflammatory bowel disease? A priority setting partnership with the James Lind Alliance. *J Crohns Colitis* 2017;11:204–11.
11 Moran GW, Gordon M, Sinopolou V, *et al*. British Society of Gastroenterology guidelines on inflammatory bowel disease in adults: 2025. *Gut* 2025;74:s1–101.
12 Serna-Valverde AL, Rodriguez-Suarez E, Marks DJB, *et al*. Identification of novel molecular drivers, prognostic and diagnostic biomarkers for Inflammatory Bowel Disease (IBD): protocol for the Nottingham/AstraZeneca prospective IBD observational cohort study. *BMJ Open* 2025;15:e105790.
13 Ahmed W, Galati J, Kumar A, *et al*. Dual biologic or small molecule therapy for treatment of inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2022;20:e361–79.
14 Altieri G, Zilli A, Parigi TL, *et al*. Dual therapy in inflammatory bowel disease. *Biomolecules* 2025;15:222.
15 Berinstein EM, Sheehan JL, Jacob J, *et al*. Efficacy and safety of dual targeted therapy for partially or non-responsive inflammatory bowel disease: a systematic review of the literature. *Dig Dis Sci* 2023;68:2604–23.
16 Solitano V, Facciorusso A, Jess T, *et al*. Comparative risk of serious infections with biologic agents and oral small molecules in inflammatory bowel diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2023;21:907–21.
17 Gros B, Varkas G, Speeckaert R, *et al*. Combining advanced therapies in patients with inflammatory bowel disease and extraintestinal manifestations or associated immune-mediated diseases: who, what, when and at what cost? *Frontline Gastroenterol* 2025.
18 Alayo QA, Fenster M, Altayar O, *et al*. Systematic review with meta-analysis: safety and effectiveness of combining biologics and small molecules in inflammatory bowel disease. *Crohns Colitis 360* 2022;4:tac002.
19 Ribaldone DG, Pellicano R, Vernero M, *et al*. Dual biological therapy with anti-TNF, vedolizumab or ustekinumab in inflammatory bowel disease: a systematic review with pool analysis. *Scand J Gastroenterol* 2019;54:407–13.
20 Fabisiak A, Caban M, Dudek P, *et al*. Advancements in dual biologic therapy for inflammatory bowel diseases: efficacy, safety, and future directions. *Therap Adv Gastroenterol* 2025;18.
21 Gold SL, Steinlauf AF. Efficacy and safety of dual biologic therapy in patients with inflammatory bowel disease: a review of the literature. *Gastroenterol Hepatol (Que)* 2021;17:406–14.
22 Anderson SR, Osman A, Zamani M, *et al*. Systematic review with meta-analysis: safety and effectiveness of combining biologics and small molecules in inflammatory bowel diseases. *Inflamm Bowel Dis* 2026;32:39–52.
23 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
24 M. Z. Moola S, Tufanaru C, Aromataris E, *et al*. *JBI manual for evidence synthesis*. JBI, 2020.
25 T. J. Higgins JPT, Chandler J, Cumpston M, *et al*. *Cochrane handbook for systematic reviews of interventions*.2024. Available: www.cochrane.org/handbook
26 Gordon M, Shaban N, Sinopoulou V, *et al*. Developing IBD outcome effect size thresholds to inform research, guidelines, and clinical decisions. *Inflamm Bowel Dis* 2025;31:2798–804.
27 Alegre-Bailo A, Sánchez-Gilo A, Gonzalo González I, *et al*. Combination treatment with monoclonal antibodies: dupilumab and ustekinumab for the treatment of severe atopic dermatitis and Crohn disease. *Australas J Dermatol* 2024;65:63–6.
28 Au M, Mitrev N, Leong RW, *et al*. Dual biologic therapy with ocrelizumab for multiple sclerosis and vedolizumab for Crohn's disease: a case report and review of literature. *World J Clin Cases* 2022;10:2569–76.
29 Ben-Horin S, Ungar B, Kopylov U, *et al*. Safety, efficacy and pharmacokinetics of vedolizumab in patients with simultaneous exposure to an anti-tumour necrosis factor. *Aliment Pharmacol Ther* 2018;47:1117–25.
30 Bianchi E, Pata AP, Cantarini L, *et al*. Upadacitinib and ustekinumab combination treatment for a refractory case of spondyloarthritis and Crohn's disease. *Clin Exp Rheumatol* 2023;0766.
31 Biscaglia G, Piazzolla M, Cocomazzi F, *et al*. Landmarks for dual biological therapy in inflammatory bowel disease: lesson from two case reports of vedolizumab in combination with ustekinumab. *Eur J Gastroenterol Hepatol* 2020;32:1579–82.
32 Taberner Bonastre P, Torres Vicente G, Cano-Marron M, *et al*. A patient with ulcerative colitis treated with a combination of vedolizumab and tofacitinib. *Eur J Hosp Pharm* 2021;28:353–5.
33 Buendía Carcedo L, Arreba González P, Higuera Álvarez R, *et al*. Combination treatment risankizumab and subcutaneous infliximab for refractory Crohn's disease: a case report. *Rev Esp Enferm Dig* 2024;187–8.
34 Buer LCT, Høivik ML, Warren DJ, *et al*. Combining anti-TNF-α and vedolizumab in the treatment of inflammatory bowel disease: a case series. *Inflamm Bowel Dis* 2018;24:997–1004.
35 Cline A, Pichardo RO. Successful treatment of hidradenitis suppurativa in the setting of Crohn disease with combination adalimumab and ustekinumab. *Dermatol Online J* 2019;25:9.
36 Colombel J-F, Ungaro RC, Sands BE, *et al*. Vedolizumab, adalimumab, and methotrexate combination therapy in Crohn's disease (EXPLORER). *Clin Gastroenterol Hepatol* 2024;22:1487–96.
37 Elmoursi A, Barrett TA, Perry C. Double biologic therapy for refractory stricturing Crohn's disease: a successful case of deep remission with ustekinumab and vedolizumab. *Inflamm Bowel Dis* 2020;26:e62–3.
38 Eronen H, Kolehmainen S, Koffert J, *et al*. Combining biological therapies in patients with inflammatory bowel disease: a Finnish multi-centre study. *Scand J Gastroenterol* 2022;57:936–41.
39 Feagan BG, Sands BE, Sandborn WJ, *et al*. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. *Lancet Gastroenterol Hepatol* 2023;8:307–20.
40 Filipiuk A, Gonciarz M. Rare extraintestinal manifestations of ulcerative colitis treated with dual biologic therapy: a case report. *World J Clin Cases* 2024;12:5441–7.
41 Goessens L, Colombel J-F, Outtier A, *et al*. Safety and efficacy of combining biologics or small molecules for inflammatory bowel disease or immune-mediated inflammatory diseases: a European retrospective observational study. *United European Gastroenterol J* 2021;9:1136–47.
42 Hassan SA, Perry C, Carey P, *et al*. Dual biologic therapy induces remission in refractory Crohn's disease with vedolizumab and ustekinumab. *Crohn's & Colitis 360* 2024;7:tae080.
43 Jin X, Sun K, Wang L, *et al*. Efficacy and safety of dual-targeted therapy for inflammatory bowel disease: a retrospective multicenter study in China. *Therap Adv Gastroenterol* 2025;18:17562848241307598.
44 Le Berre C, Loeuille D, Peyrin-Biroulet L. Combination therapy with vedolizumab and tofacitinib in a patient with ulcerative colitis and spondyloarthropathy. *Clin Gastroenterol Hepatol* 2019;17:794–6.
45 Lehmann A, Vosbeck J, Kyburz D, *et al*. Risankizumab and certolizumab pegol dual-targeted therapy for Crohn's disease and axial spondyloarthritis: a case report. *Case Rep Gastroenterol* 2024;19:22–30.
46 Li N, Leong R, Youssef P. Combination non tumour necrosis factor biologic and small-molecule therapy in a patient with ankylosing spondylitis and Crohn disease. *Intern Med J* 2023;53:1083–4.
47 Liu EY, Loomes DE. Ustekinumab and vedolizumab dual biologic therapy in the treatment of Crohn's disease. *Case Rep Med* 2017;2017:5264216.
48 Mao EJ, Lewin S, Terdiman JP, *et al*. Safety of dual biological therapy in Crohn's disease: a case series of vedolizumab in combination with other biologics. *BMJ Open Gastroenterol* 2018;5:e000243.
49 Martí Romero L, Peño Muñoz L, Martínez Escapa V, *et al*. Use of teduglutide for short bowel syndrome and Crohn's disease in a

patient treated with ustekinumab and vedolizumab dual biologic therapy. *Rev Esp Enferm Dig* 2022;331–2.
50 Miyatani Y, Choi D, Choi NK, *et al*. Dual-targeted therapy with upadacitinib and ustekinumab in medically complex Crohn's disease. *Dig Dis Sci* 2024;69:355–9.
51 Neelam PB, Mekala D, Patel R, *et al*. Efficacy and safety of vedolizumab and tofacitinib (VETO) combination therapy in refractory ulcerative colitis unresponsive to anti-TNF and a second-line advanced therapy: a prospective cohort nested within a randomised trial. *Aliment Pharmacol Ther* 2026;63:81–92.
52 Privitera G, Onali S, Pugliese D, *et al*. Dual targeted therapy: a possible option for the management of refractory inflammatory bowel disease. *Journal of Crohn's and Colitis* 2021;15:335–9.
53 Sands BE, Kozarek R, Spainhour J, *et al*. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. *Inflamm Bowel Dis* 2007;13:2–11.
54 Scheinberg AR, Dauer RM, Damas OM, *et al*. S0895 Is two better than one? Combination therapy with vedolizumab and tofacitinib for the treatment of patients with inflammatory bowel disease. *Am J Gastroenterol* 2020;115:S460–1.
55 Yang E, Panaccione N, Whitmire N, *et al*. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. *Aliment Pharmacol Ther* 2020;51:1031–8.
56 Yin J, El-Najjar Y, Cordova N, *et al*. Short-term use of upadacitinib in combination with biologic therapy for inducing clinical remission in patients with active inflammatory bowel disease. *Inflamm Bowel Dis* 2024;30:1914–6.
57 Yzet C, Dupas J-L, Fumery M. Ustekinumab and anti-TNF combination therapy in patients with inflammatory bowel disease. *American Journal of Gastroenterology* 2016;111:748–9.
58 Wu H, Su T, Wu L, *et al*. DOP058 efficacy and safety of vedolizumab combined with upadacitinib in moderate-to-severe ulcerative colitis: a multicenter, prospective, randomized controlled trial. *Journal of Crohn's and Colitis* 2025;19:i197–9.
59 Solitano V, Hanžel J, Ma C, *et al*. An international consensus on the design of clinical trials for advanced combination treatment (ACT) in inflammatory bowel disease. *EClinicalMedicine* 2025;89:103582.
60 Gordon M, Lakunina S, Sinopoulou V, *et al*. Minimum sample size estimates for trials in inflammatory bowel disease: a systematic review of a support resource. *World J Gastroenterol* 2021;27:7572–81.