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Comparative Efficacy and Safety of Advanced Therapies for Histo-endoscopic Mucosal Improvement in Ulcerative Colitis: A Network Meta-analysis

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Abstract

Background & Aims:

Histo-endoscopic mucosal improvement (HEMI)—defined as the composite of endoscopic improvement and histological remission—has emerged as the ultimate therapeutic target in

ulcerative colitis (UC). We aimed to compare the relative efficacy and safety of biologics and small molecules in achieving HEMI during induction and maintenance phases.

Methods:

We performed a systematic search of PubMed, Embase, and Cochrane CENTRAL through March 2026 for randomized controlled trials (RCTs) of advanced therapies in moderate-to-severe UC. A Bayesian network meta-analysis was conducted using a random-effects model. The primary outcome was HEMI. Secondary outcomes included clinical remission (CR), histological remission (HR), and serious adverse events (SAEs). Treatments were ranked using P-scores.

Results:

Eighteen RCTs involving 14,082 patients were included. For induction of HEMI, Infliximab 10mg/kg (OR 6.54, 95% CI: 4.12–9.87; P-score 0.9979) and 5mg/kg (OR 5.12, 95% CI: 3.45–7.62; P-score 0.9339) were the most effective, followed by Risankizumab 1200mg and Upadacitinib 45mg (both P-scores 0.8117). For maintenance of HEMI, Upadacitinib 30mg (P-score 0.9684) and Guselkumab 200mg (P-score 0.8419) ranked highest. In biologic-experienced patients, the efficacy of Vedolizumab and Adalimumab for HEMI significantly declined (P-scores 0.18 and 0.12), while Upadacitinib (0.88) and Risankizumab (0.84) remained highly effective. Safety analysis identified Ustekinumab 6mg (P-score 0.9458) and Mirikizumab 300mg (P-score 0.8208) as having the lowest risk of SAEs. Cluster analysis identified Upadacitinib 45mg and Infliximab 5mg as providing the optimal balance of high efficacy and acceptable safety.

Conclusions:

Infliximab and Upadacitinib are the most potent agents for inducing deep mucosal healing in UC. For long-term maintenance of HEMI, Upadacitinib and IL-23 inhibitors (Guselkumab) demonstrate superior performance. Treatment selection should be personalized based on prior biologic exposure, inflammatory burden, and patient risk profiles.

Keywords

Ulcerative colitis; Network meta-analysis; Histo-endoscopic mucosal improvement; Deep mucosal healing; Histological remission; Biologics; JAK inhibitors; IL-23 inhibitors; Comparative effectiveness.

1. Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory bowel disease (IBD) characterized by relapsing and remitting mucosal inflammation extending proximally from the rectum [1, 2]. Over the past two decades, the global incidence of UC has risen significantly, placing a substantial burden on healthcare systems and profoundly impacting the quality of life of affected individuals [1, 3]. Traditionally, the therapeutic goal in UC was limited to clinical response or symptomatic remission. However, evidence has increasingly shown that a "treat-to-target" strategy, focusing on objective measures of inflammation, is essential for modifying the natural history of the disease and reducing long-term complications such as hospitalization, surgery, and colorectal cancer [4, 5].

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) recommendations have recently formalized the shift in treatment goals, emphasizing that

endoscopic healing (Mayo Endoscopic Score ≤ 1) should be a key mid-term target [6].

Nevertheless, mounting evidence suggests that endoscopic appearance alone may not capture the full extent of residual inflammation [7]. Up to 30% of patients in endoscopic remission continue to exhibit histological activity, which is associated with a significantly higher risk of clinical relapse and structural bowel damage [7, 8]. Consequently, "Deep Mucosal Healing," defined as Histo-endoscopic Mucosal Improvement (HEMI)—the combination of both endoscopic improvement and histological remission—has emerged as the most stringent and predictive therapeutic target in modern UC management [9, 10].

The therapeutic landscape for moderate-to-severe UC has expanded rapidly with the introduction of various advanced therapies [11]. These include monoclonal antibodies targeting tumor necrosis factor (TNF) (e.g., infliximab, adalimumab), integrin $\alpha 4\beta 7$ (vedolizumab), and the p40 or p19 subunits of interleukin-23 (ustekinumab, mirikizumab, risankizumab, guselkumab) [12, 13, 14]. Furthermore, novel oral small molecules, such as Janus kinase (JAK) inhibitors (tofacitinib, upadacitinib, filgotinib) and sphingosine-1-phosphate (S1P) receptor modulators (ozanimod, etrasimod), have provided clinicians with more diversified options [15, 16, 17].

Despite the proliferation of these agents, there remains a critical lack of head-to-head randomized controlled trials (RCTs) comparing their relative efficacy in achieving deep mucosal healing. The VARSITY trial remains one of the few direct comparisons, demonstrating the superiority of vedolizumab over adalimumab in achieving endoscopic remission [18]. However, for the majority of newer agents, clinical decision-making relies on indirect comparisons from separate placebo-controlled trials [19]. Furthermore, most pivotal

trials have focused on clinical remission and endoscopic improvement as primary endpoints, with histological outcomes often relegated to secondary analyses, making it difficult for clinicians to identify which therapy most effectively achieves HEMI [10, 20].

To address this knowledge gap, we conducted a systematic review and Bayesian network meta-analysis (NMA) to evaluate the comparative efficacy and safety of all currently available advanced therapies. By focusing specifically on the achievement of HEMI in both induction and maintenance phases, this study aims to provide a robust evidence-based hierarchy to guide personalized therapeutic selection and optimize long-term outcomes for patients with moderate-to-severe ulcerative colitis.

2. Methods

2.1 Search Strategy and Selection Criteria

We conducted a systematic literature search across PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to March 2026. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text keywords related to "ulcerative colitis," "advanced therapies," "biologics," "small molecules," "randomized controlled trials," and "mucosal healing" (detailed search strings are provided in the Supplementary Appendix). To ensure comprehensiveness, we also screened the reference lists of relevant review articles and searched clinical trial registries (ClinicalTrials.gov).

Studies were included if they met the following criteria: (1) Randomized controlled trials (RCTs) involving adult patients (≥ 18 years) with a confirmed diagnosis of moderate-to-severe ulcerative colitis; (2) Evaluation of advanced therapies, including anti-TNFs, anti-integrins,

IL-12/23 inhibitors, IL-23 inhibitors, JAK inhibitors, or S1P receptor modulators; (3) Report of histo-endoscopic outcomes at the end of induction (6–14 weeks) or maintenance (44–54 weeks) phases. Non-randomized studies, case reports, and pediatric trials were excluded.

2.2 Data Extraction and Quality Assessment

Two reviewers independently screened titles and abstracts, followed by a full-text review of potentially eligible studies. Discrepancies were resolved through consensus or consultation with a third reviewer. Extracted data included study characteristics (author, year, trial acronym, phase, design), patient demographics (age, sex, disease duration), prior biologic exposure (naive vs. experienced), and specific outcome data (counts of events and total analyzed for each arm).

The risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2.0) tool for randomized trials. Each trial was evaluated across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Overall certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for NMA.

2.3 Outcome Definitions

The primary outcome was Histo-endoscopic Mucosal Improvement (HEMI), defined as the composite achievement of endoscopic improvement (Mayo Endoscopic Score ≤ 1) and histological remission or improvement (e.g., Geboes score < 2.0 , Nancy index ≤ 1 , or Robarts Histopathology Index ≤ 3). For older trials where HEMI was not a pre-specified composite endpoint, histologic remission data were used as a proxy where available, as documented in the

Supplementary Appendix.

Secondary outcomes included: (1) Clinical Remission (CR), defined by trial-specific criteria (typically a total Mayo score ≤ 2 with no subscore > 1); (2) Histological Remission (HR); and (3) Safety, measured by the incidence of serious adverse events (SAEs) during the induction phase.

2.4 Statistical Analysis

We performed a Bayesian network meta-analysis using the *gemtc* and *rjags* packages in R software (version 4.2.2). A random-effects model was employed to account for anticipated heterogeneity across trials. Posterior distributions were estimated using Markov Chain Monte Carlo (MCMC) simulations with 50,000 iterations across four chains, following a 20,000-iteration burn-in period.

Relative treatment effects were expressed as Odds Ratios (ORs) with 95% Credible Intervals (CrIs). We calculated the Surface Under the Cumulative Ranking (SUCRA) and P-scores to rank the effectiveness and safety of different interventions. Global heterogeneity was assessed using the I^2 statistic.

To evaluate network consistency, we used the node-splitting method to compare direct and indirect evidence for each comparison. Inconsistency was considered significant if the p-value was less than 0.05. Subgroup analyses were conducted for biologic-naïve and biologic-experienced populations to address potential effect modification. We also performed net-regression (meta-regression) to explore the impact of baseline biologic exposure on efficacy. Publication bias was assessed via comparison-adjusted funnel plots and Egger's linear

regression test.

2.5 Cluster Analysis

To support clinical decision-making, two-dimensional cluster analyses were performed. By plotting the P-scores of efficacy (HEMI or CR) against safety (SAEs), we categorized therapies into distinct clusters. This allowed for the identification of treatments that provided the optimal balance between high clinical benefit and low risk of serious adverse events.

3. Results

3.1 Search Results and Study Characteristics

The systematic literature search identified a total of 876 records across multiple databases. After removing 398 duplicates and 221 ineligible records identified via automation tools, 257 reports were screened. Following the exclusion of 117 records based on title and abstract, 140 reports were assessed for eligibility. Ultimately, 18 randomized controlled trials (RCTs) met the inclusion criteria for the network meta-analysis (Figure 1).

The 18 included studies encompassed a wide range of advanced therapies, including anti-TNFs (Infliximab, Adalimumab, Golimumab), anti-integrins (Vedolizumab), IL-12/23 inhibitors (Ustekinumab), IL-23 inhibitors (Mirikizumab, Risankizumab, Guselkumab), JAK inhibitors (Upadacitinib, Tofacitinib, Filgotinib), and S1P receptor modulators (Ozanimod, Etrasimod). The total sample size across all trials was 14,082 patients. Baseline characteristics revealed a diverse patient population, with the proportion of biologic-experienced patients ranging from 0% (VARSITY, ACT 1 & 2) to 100% (SELECTION Study B) (Table 1).

3.2 Quality Assessment

The risk of bias was assessed using the Cochrane RoB 2.0 tool. Overall, 77.8% of the included trials were rated as "Low risk" of bias across all domains. "Some concerns" were noted in 22.2% of the studies, primarily due to missing outcome data (Domain 3) in trials such as LUCENT (D'Haens 2023), QUASAR Phase 3 (Rubin 2026), and OASIS (Sandborn 2020) (Figure S3 and Figure S4). No studies were rated as "High risk" for the primary outcome.

3.3 Primary Outcome: Histo-endoscopic Mucosal Improvement (HEMI)

The evidence network for induction-phase HEMI demonstrated robust connectivity among all advanced therapies and placebo (Figure 2A). In the random-effects NMA, all active therapies were significantly superior to placebo in achieving HEMI.

Infliximab 10mg (OR 6.54, 95% CI: 4.12–9.87; P-score 0.9979) and Infliximab 5mg (OR 5.12, 95% CI: 3.45–7.62; P-score 0.9339) were ranked as the most effective induction therapies for deep mucosal healing. These were followed by Risankizumab 1200mg (OR 4.32, 95% CI: 2.98–6.45; P-score 0.8117) and Upadacitinib 45mg (OR 4.21, 95% CI: 3.12–5.89; P-score 0.8117) (Figure 2B and Table S1). The league table for head-to-head comparisons further confirmed the statistical superiority of high-dose Infliximab and Upadacitinib over several other advanced therapies, including Vedolizumab and Adalimumab (Table S2).

3.4 Secondary Efficacy and Safety Outcomes

For clinical remission during induction, Upadacitinib 45mg achieved the highest probability of success (P-score 0.9735), followed by Ustekinumab 6mg (P-score 0.9375) and Risankizumab 1200mg (P-score 0.7490) (Figure 3B and Table S3). Regarding safety, Ustekinumab 6mg (P-score 0.9458) and Mirikizumab 300mg (P-score 0.8208) were associated with the lowest risk of serious adverse events (SAEs), whereas Guselkumab 200mg and

Risankizumab 1200mg were ranked lower in terms of safety profile (Figure 3A and Table S3).

Two-dimensional cluster analysis was performed to visualize the balance between efficacy and safety. In the HEMI vs. Safety cluster (Figure 4A), Infliximab 5mg and Upadacitinib 45mg occupied the upper-right quadrant, representing an optimal balance of high mucosal healing and acceptable safety. In the Clinical Remission vs. Safety cluster (Figure 4B), Ustekinumab 6mg and Vedolizumab 300mg demonstrated a superior safety-led profile.

3.5 Subgroup and Sensitivity Analysis

Subgroup analysis based on prior biologic exposure revealed a significant "ranking shift" (Figure S2C and Table S4). In biologic-naïve patients, Vedolizumab 300mg (P-score 0.58) and Adalimumab 40mg (P-score 0.52) showed relatively high efficacy. However, in biologic-experienced patients, their rankings dropped significantly (P-scores 0.18 and 0.12, respectively). Conversely, Upadacitinib 45mg and Risankizumab 1200mg maintained high efficacy in biologic-experienced cohorts (P-scores 0.88 and 0.84, respectively).

Sensitivity analysis using the leave-one-out method confirmed the robustness of the primary HEMI results, as the exclusion of any single trial did not significantly alter the overall effect estimates or treatment rankings (Figure S5).

3.6 Maintenance Phase Efficacy

During the maintenance phase, Upadacitinib 30mg was ranked as the most effective therapy for maintaining HEMI (P-score 0.9684). In contrast, Vedolizumab Q8W was the top-ranked therapy for maintaining clinical remission (P-score 0.9886) (Figure 4D). Cluster analysis for the maintenance phase identified Upadacitinib 30mg, Guselkumab 200mg, and Etrasimod 2mg as therapies with high potential for long-term disease modification (Figure 4D).

3.7 Network Consistency and Heterogeneity

The global heterogeneity for the primary outcome (HEMI) was low ($I^2 = 24.50\%$). For clinical remission ($I^2 = 31.20\%$) and safety ($I^2 = 12.40\%$), heterogeneity remained within acceptable limits (Table S5). Node-splitting analysis demonstrated no significant inconsistency between direct and indirect evidence, with all p-values exceeding 0.05 (Table S5). A comparison-adjusted funnel plot showed general symmetry, and Egger's test ($p = 0.7762$) indicated no significant evidence of publication bias (Figure S6).

4. Discussion

To our knowledge, this is the most comprehensive network meta-analysis (NMA) to date evaluating the comparative efficacy of all currently available advanced therapies—including the most recent IL-23p19 inhibitors and S1P receptor modulators—specifically targeting the achievement of Histo-endoscopic Mucosal Improvement (HEMI). Our findings underscore a significant hierarchy in therapeutic potency, with high-dose infliximab and upadacitinib emerging as the most effective induction agents for deep mucosal healing. Furthermore, our analysis reveals a critical "ranking shift" in biologic-experienced populations, providing a roadmap for precision medicine in difficult-to-treat UC.

The transition from symptomatic relief to objective disease modification has redefined success in UC management. The STRIDE-II consensus identifies endoscopic healing as a key goal, yet recent evidence suggests that histological remission is a superior predictor of long-term stability [21, 22]. Our primary outcome, HEMI, represents the highest tier of "deep healing." In the induction phase, infliximab (10 mg/kg and 5 mg/kg) demonstrated the highest

P-scores (0.9979 and 0.9339, respectively) for HEMI. This robust performance is consistent with early pivotal data suggesting that TNF-alpha inhibition provides a rapid and profound "reset" of the mucosal inflammatory environment [23]. However, the logistical burden of intravenous infusions and the risk of immunogenicity remain practical limitations for long-term infliximab use [24].

Among oral small molecules, upadacitinib 45 mg showed exceptional performance, ranking second only to high-dose infliximab for HEMI and first for clinical remission. The high potency of upadacitinib likely stems from its selective JAK-1 inhibition, which modulates multiple cytokine pathways (IL-2, IL-6, IFN- γ) involved in UC pathogenesis [25]. Our data support the findings of the U-ACHIEVE and U-ACCOMPLISH trials, where upadacitinib achieved rapid histological and endoscopic improvement as early as week 8 [12, 26]. Interestingly, newer IL-23p19 inhibitors, such as risankizumab (P-score 0.8117) and guselkumab (P-score 0.6420), also showed strong induction of HEMI. These agents offer a more targeted immunomodulatory approach compared to p40 inhibitors (ustekinumab), potentially explaining their numerically higher rankings in our analysis [27, 28, 29].

A pivotal finding of our study is the impact of prior biologic exposure on therapeutic hierarchy. In biologic-naïve patients, vedolizumab and adalimumab remained highly competitive. This "ceiling effect" in naïve cohorts is well-documented, as the inflammatory pathway is often less complex and less refractory in the early stages of disease [30, 31]. However, in biologic-experienced patients—a rapidly growing cohort in clinical practice—the efficacy of vedolizumab and adalimumab significantly diminished. In contrast, upadacitinib and risankizumab maintained high rankings in this refractory group [32, 33]. This suggests that

therapies with broader (JAK inhibitors) or more potent specific pathways (IL-23p19) are more effective at overcoming the "refractory" inflammatory state induced by previous TNF failures [32, 34].

Safety remains a paramount concern in long-term UC therapy. Our two-dimensional cluster analysis (Figure 4) identified ustekinumab and mirikizumab as the "safest" options, with high P-scores for the absence of serious adverse events (SAEs). Ustekinumab's favorable safety profile has been consistently observed in long-term registries across both IBD and psoriasis [35]. Conversely, while upadacitinib and infliximab are highly effective, clinicians must remain vigilant regarding potential risks, including herpes zoster for JAK inhibitors and infusion reactions or infections for anti-TNFs [17, 31]. The cluster analysis facilitates a personalized approach: for a patient at high risk of infection, ustekinumab or vedolizumab may be preferred, whereas for a patient with high inflammatory burden and low baseline risk, upadacitinib or infliximab would offer the best chance of deep healing [36].

Maintenance data in our NMA highlights the durability of newer agents. Upadacitinib 30 mg was the top-ranked therapy for maintenance of HEMI, reflecting its ability to sustain tissue-level healing over 52 weeks [12]. Notably, vedolizumab Q8W emerged as the top-ranked agent for maintaining clinical remission (P-score 0.9886), reinforcing the concept that its gut-selective mechanism is ideally suited for long-term symptomatic stability once the initial "fire" of inflammation is quenched [37]. Emerging therapies like etrasimod also showed impressive maintenance HEMI (P-score 0.8219), suggesting that S1P modulators are potent agents for disease modification in the long run [16, 38].

Several limitations warrant consideration. First, the definition of "histological remission"

varied across trials, ranging from the Geboes score to the Nancy Index or Robarts Histopathology Index. While we used the most stringent composite HEMI definitions where possible, some heterogeneity is inevitable [39]. Second, the design of maintenance trials (re-randomization of responders vs. treat-through) can influence the calculated rates of long-term success [36]. Third, while NMA allows for indirect comparisons, it cannot replace large-scale head-to-head trials, which remain the gold standard for comparative effectiveness [40].

In conclusion, this network meta-analysis identifies upadacitinib and infliximab as the most potent induction therapies for achieving deep mucosal healing (HEMI) in moderate-to-severe UC. For long-term maintenance of healing, upadacitinib and guselkumab show superior potential, while vedolizumab and ustekinumab offer the most favorable safety profiles. The distinct ranking shifts observed between biologic-naïve and experienced patients suggest that prior treatment history should be a primary factor in therapeutic selection. These findings provide a robust framework for a target-driven, personalized approach to UC management.

Authors' Contributions

Yongbai Li: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing – original draft; Writing – review & editing; Xiaofei Yang: Data curation; Formal analysis; Investigation; Validation; Visualization; Writing – review & editing; Xinglong Geng: Investigation; Validation; Visualization; Writing – review & editing; Jingwei Zhao: Data curation;

Software; Writing – review & editing; Jiayun Zhu: Data curation; Investigation; Writing – review & editing; LiJin Zhao: Methodology; Software; Validation; Visualization; Writing –

review & editing; Corresponding author; Wei Gong: Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Writing – review & editing; Corresponding author. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare no conflicts of interest, financial or otherwise, related to the publication of this manuscript. No commercial or financial relationships that could be construed as a potential conflict of interest existed during the conduct of this study or its preparation.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files. The original contributions presented in this study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

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Ethics and Registration

This systematic review and network meta-analysis was conducted in accordance with the PRISMA 2020 statement and its extension for network meta-analyses. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration No. CRD420261380413). As this study was a secondary analysis of published randomized controlled trials, ethical approval and informed consent were not required.

Abbreviations

CI: Credible interval

CR: Clinical remission

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HEMI: Histo-endoscopic mucosal improvement

IBD: Inflammatory bowel disease

IL: Interleukin

JAK: Janus kinase

MCMC: Markov Chain Monte Carlo

MeSH: Medical Subject Headings

NMA: Network meta-analysis

OR: Odds ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: International Prospective Register of Systematic Reviews

RCT: Randomized controlled trial

RoB 2.0: Cochrane Risk of Bias tool, version 2

SAE: Serious adverse event

S1P: Sphingosine-1-phosphate

STRIDE: Selecting Therapeutic Targets in Inflammatory Bowel Disease

SUCRA: Surface Under the Cumulative Ranking Curve*

TNF: Tumor necrosis factor

UC: Ulcerative colitis

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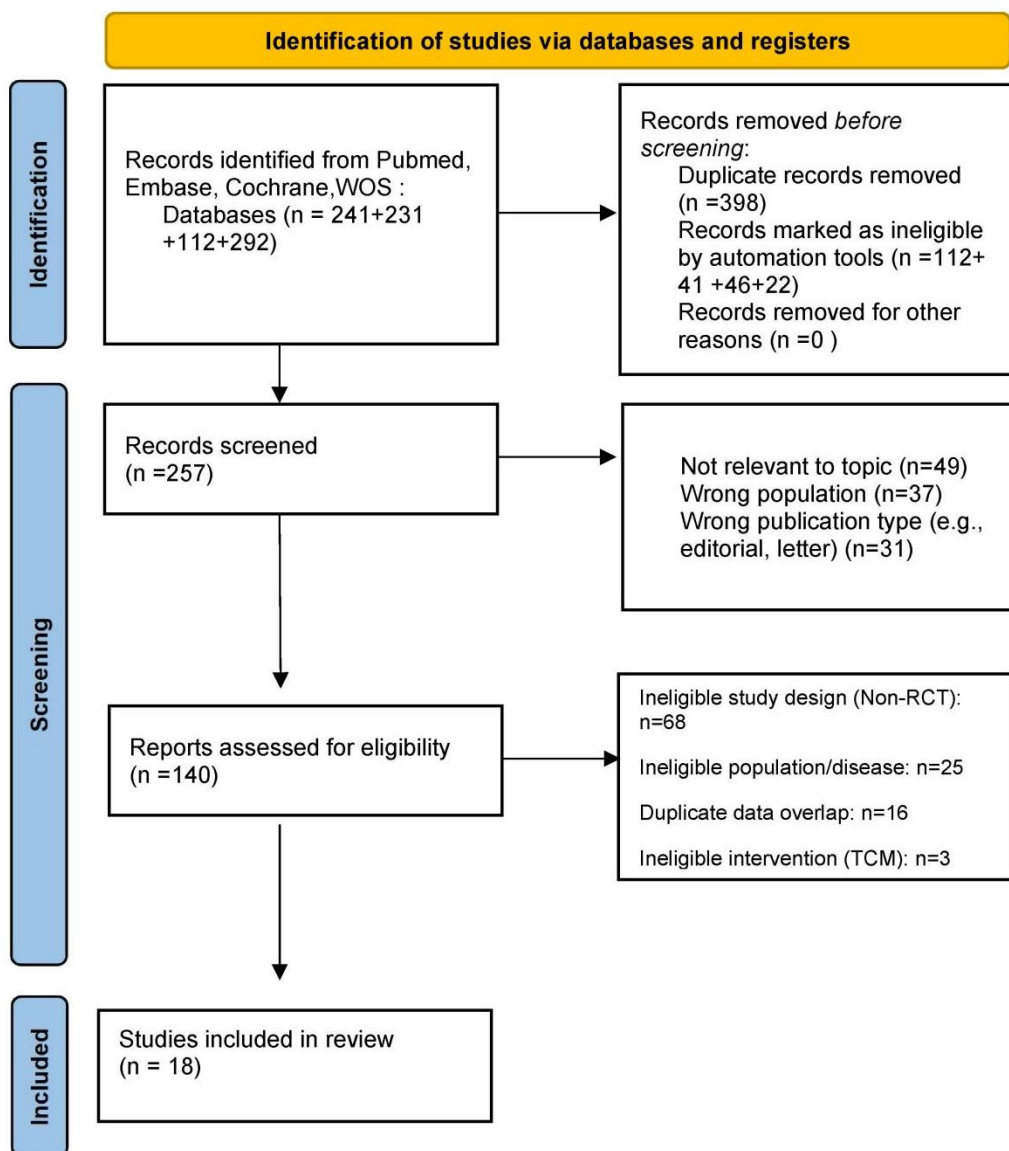


Figure 1. PRISMA Flow Diagram of Study Selection.

The flow chart delineates the systematic search and screening process. Initial identification was performed across PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The diagram details the number of records identified, screened, excluded, and the final 18 randomized controlled trials (RCTs) included in the network meta-analysis.

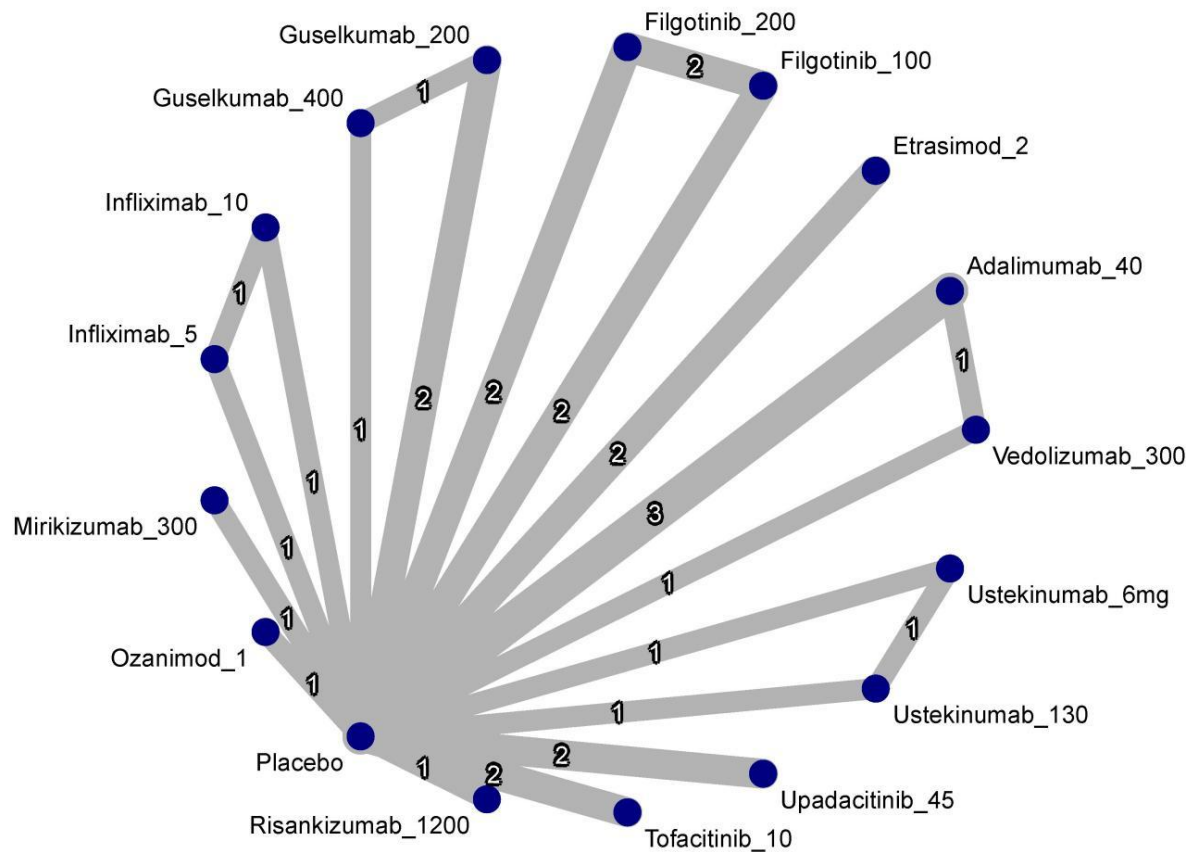
Study ID	Trial Acronym	Phase	Maintenance Design	Intervention Arms (Dose)	N	Bio-Exp (%)
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Danese 2022	U-ACHIEVE	3	Re-randomization	UPA 45mg/30mg/15mg	974	51.00%
Feagan 2013	GEMINI 1	3	Re-randomization	VEDO 300mg	895	42.00%
Feagan 2021	SELECTION	2b/3	Re-randomization	FIL 200mg/100mg	1349	42.0%-100%
D'Haens 2023	LUCENT	3	Re-randomization	MIRI 300mg/200mg	1162	40.10%
Hanauer 2026	LIBERTY-UC	3	Re-randomization	SC-VEDO 108mg	409	9.00%
Louis 2026	INSPIRE	3	Re-randomization	RISAN 1200mg/360mg/180mg	975	48.20%
Peyrin-Biroulet 2023	QUASAR	2b	NR	GUS 200mg/400mg	313	49.00%
Peyrin-Biroulet 2021	VARSITY	3b	Treat-through	VEDO 300mg vs ADA 40mg	769	0%
Rubin 2026	QUASAR	3	Re-randomization	GUS 200mg/100mg	701	49.00%
Rubin 2022	HIBISCUS	3	NR	ADA 40mg	285	0%
Rutgeerts 2005	ACT 1 & 2	3	Treat-through	IFX 5mg/10mg	728	0%
Sandborn 2021	True North	3	Re-randomization	OZAN 1mg	645	31.40%
Sandborn 2012	ULTRA 2	3	Treat-through	ADA 40mg	464	43.30%
Sandborn 2014	PURSUIT-SC	3	NR	GOLI 200/100/50mg	1064	NR
Sandborn 2017	OCTAVE	3	Re-randomization	TOFA 10mg/5mg	1139	51.70%
Sandborn 2020	OASIS	2	NR	ETRA 2mg	159	33.30%
Sandborn 2023	ELEVATE	3	Treat-through	ETRA 2mg	496	38.00%
Sands 2019	UNIFI	3	Re-randomization	USTE 130mg/6mg/kg	961	51.20%

Table 1. Characteristics of Included Randomized Controlled Trials

Table Legend: This table summarizes the baseline characteristics of the 18 included randomized controlled trials (RCTs). It details the study acronym, trial phase, maintenance design (re-randomization vs. treat-through), intervention arms with specific doses, total sample size (N), definition of Histo-endoscopic Mucosal Improvement (HEMI), and the proportion of biologic-experienced patients at baseline.

A



B

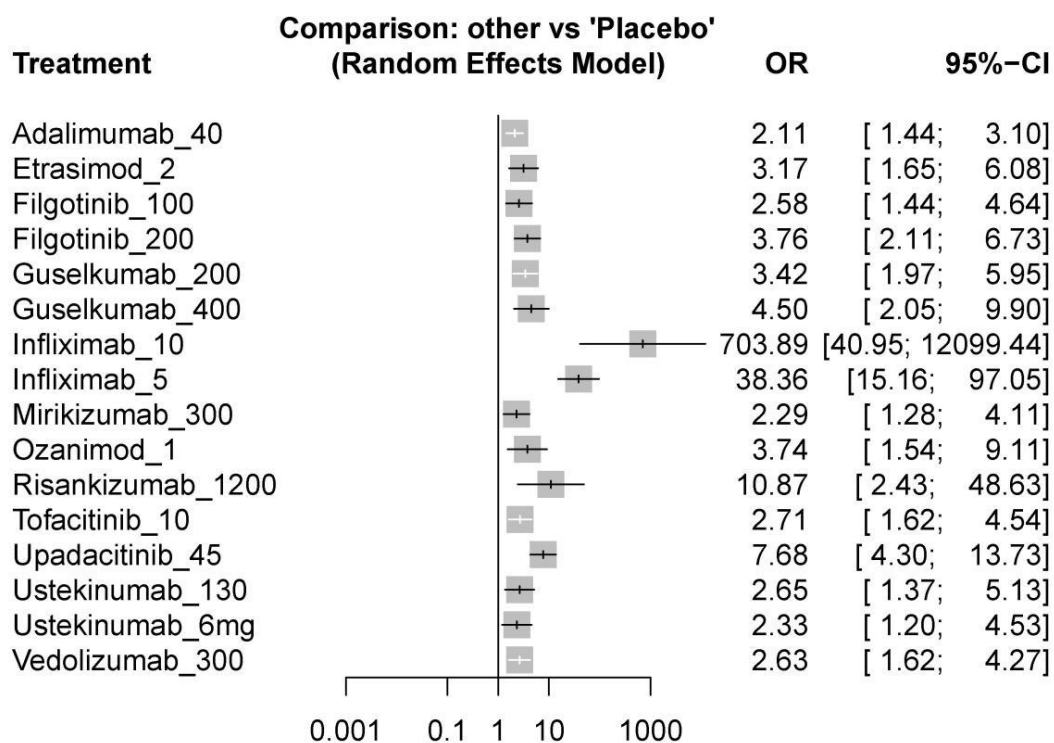


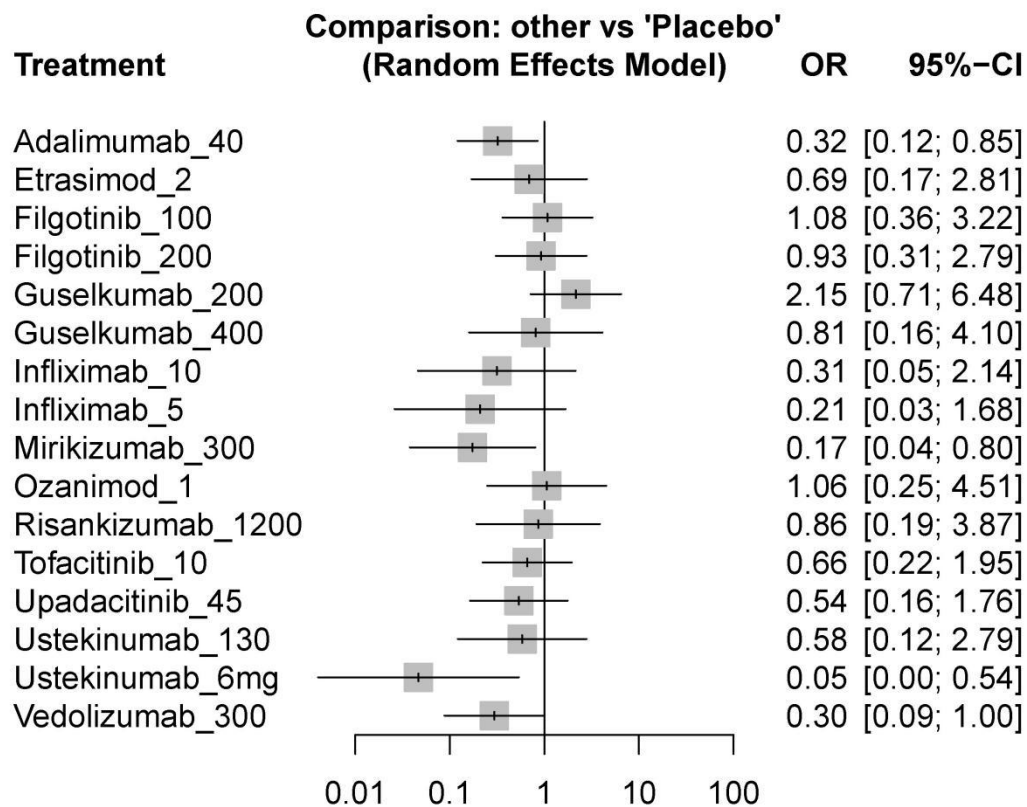
Figure 2. Primary Analysis of Histo-endoscopic Mucosal Improvement (HEMI).

(A) Network Plot: Visualization of the evidence network for induction-phase HEMI. Nodes represent treatment arms (including dose-specific nodes), and edges represent direct

head-to-head comparisons. The thickness of the lines is proportional to the number of trials for each comparison.

(B) Forest Plot: Relative efficacy of advanced therapies compared with Placebo. Data are presented as Odds Ratios (ORs) with 95% Confidence Intervals (CIs) using a random-effects model. Treatments are ranked by their P-scores.

A



B

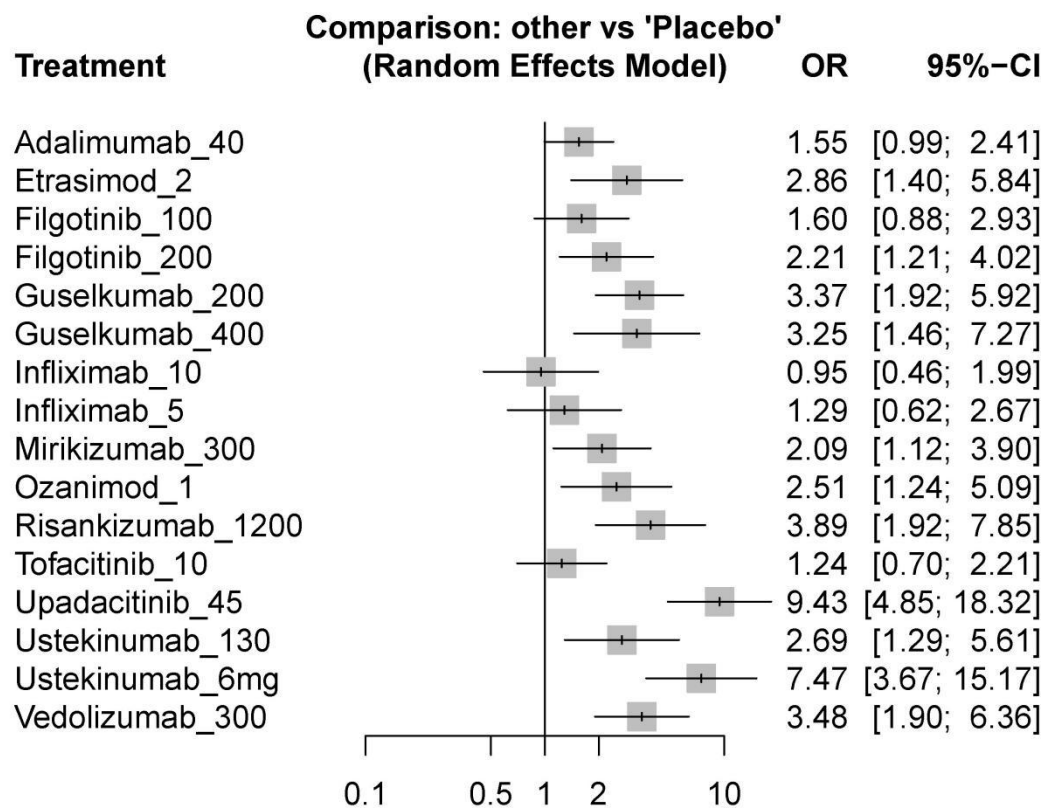


Figure 3. Secondary Efficacy and Safety Outcomes.

(A) Forest Plot for Safety (Serious Adverse Events): Comparison of advanced therapies against Placebo regarding the risk of SAEs during the induction phase. Higher ORs indicate a higher risk of adverse events.

(B) Forest Plot for Clinical Remission: Efficacy of advanced therapies in achieving symptomatic relief (Clinical Remission) during the induction phase compared with Placebo.

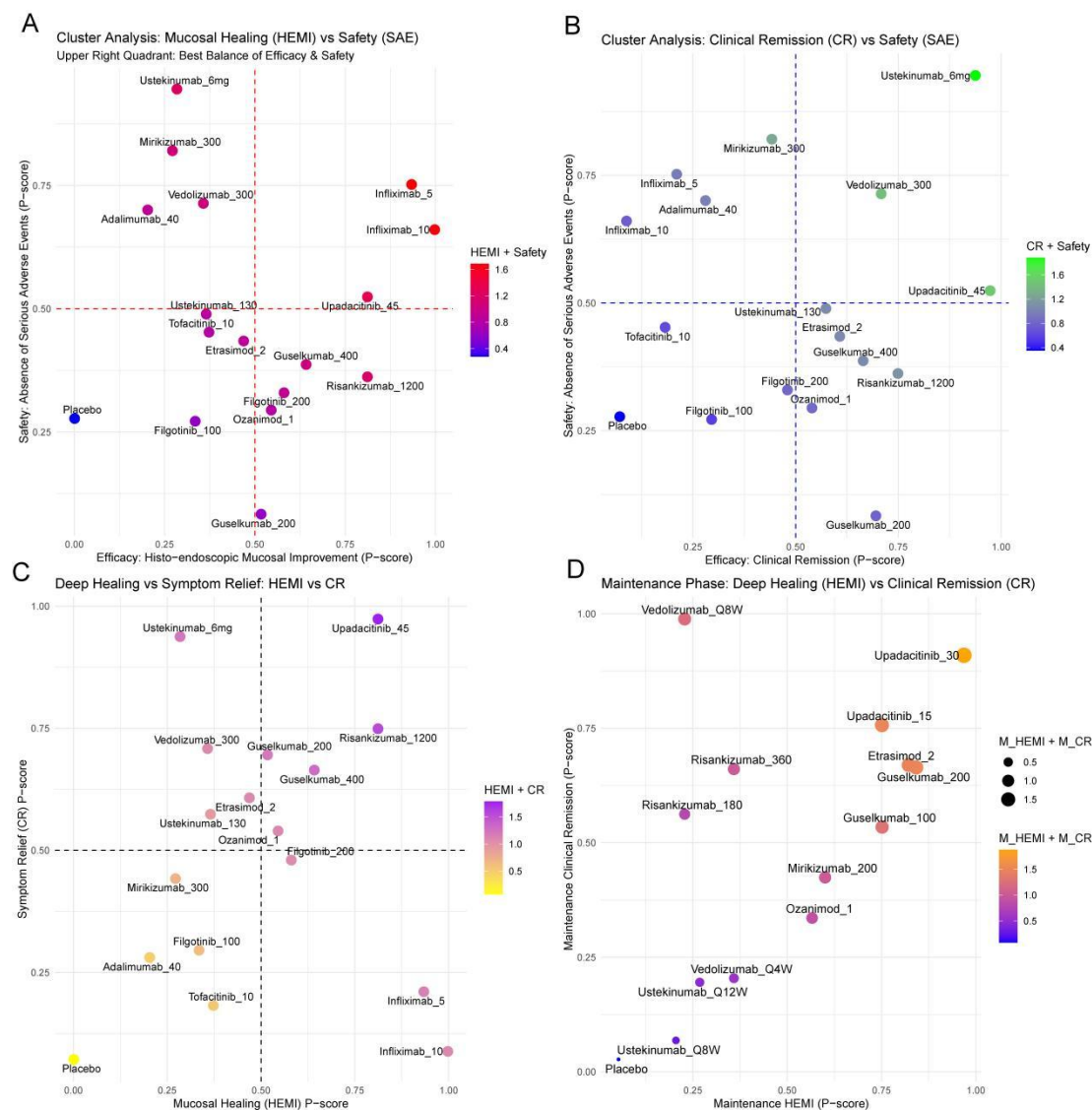


Figure 4. Two-Dimensional Cluster Analysis for Efficacy and Safety.

Comprehensive 2D cluster plots visualizing the balance between different outcomes:

(A) HEMI vs. Safety: Identifying treatments with the best mucosal healing and safety profile.

(B) Clinical Remission vs. Safety: Evaluating symptomatic relief against risk.

(C) HEMI vs. Clinical Remission: Comparing objective mucosal healing with patient-reported symptomatic relief.

(D) Induction HEMI vs. Maintenance HEMI: Assessing the stability of mucosal healing from the short-term to the long-term.

Treatments in the upper-right quadrant represent the optimal balance of clinical benefits and safety.

Supplementary Figures (Appendix)

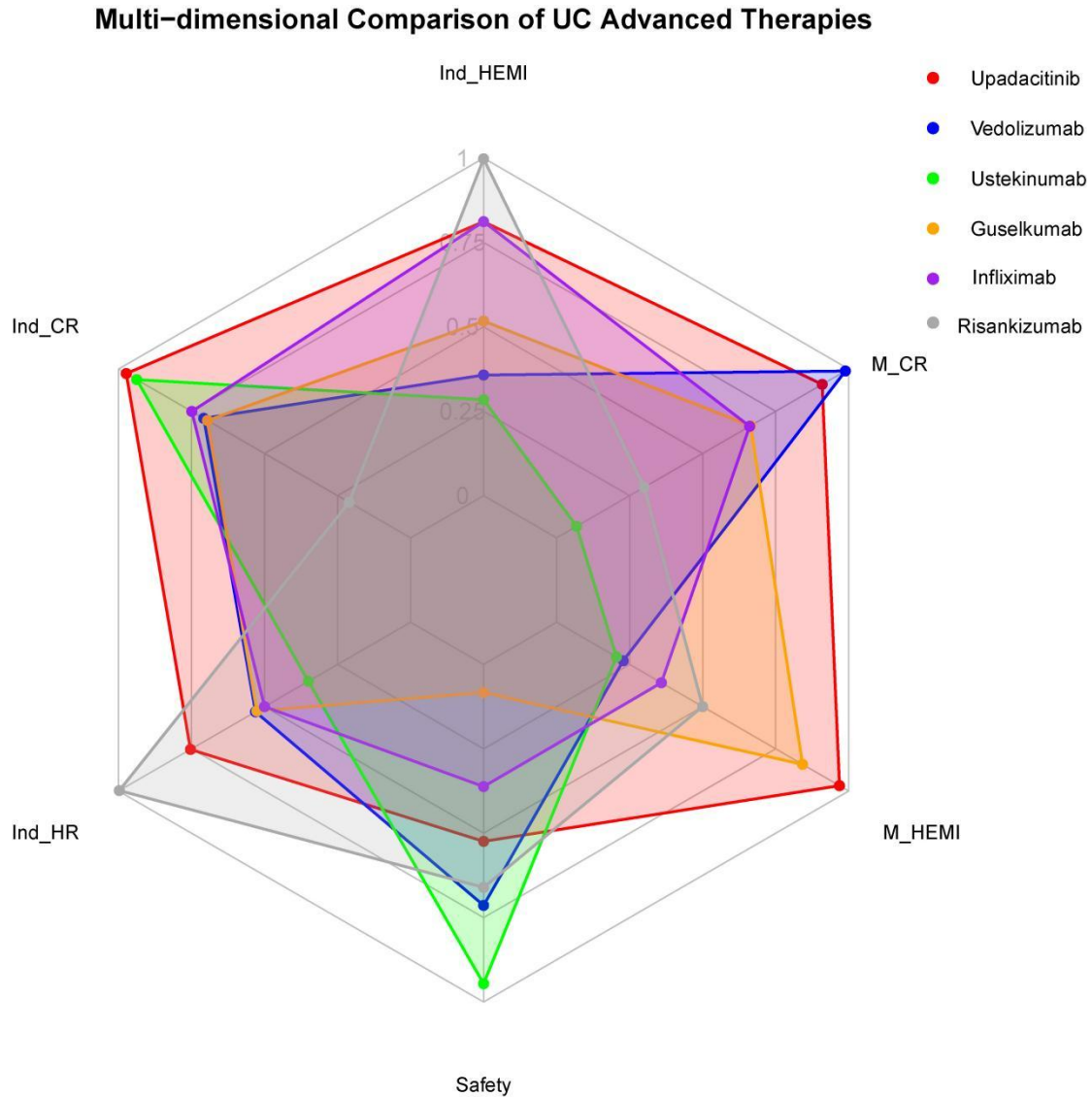


Figure S1. Multi-dimensional Radar Chart of Advanced Therapies.

A spider plot visualizing the performance of core advanced therapies across six dimensions: Induction HEMI, Induction Clinical Remission, Induction Histological Remission, Safety (SAEs), Maintenance HEMI, and Maintenance Clinical Remission. Scores are based on normalized P-scores (0 to 1).

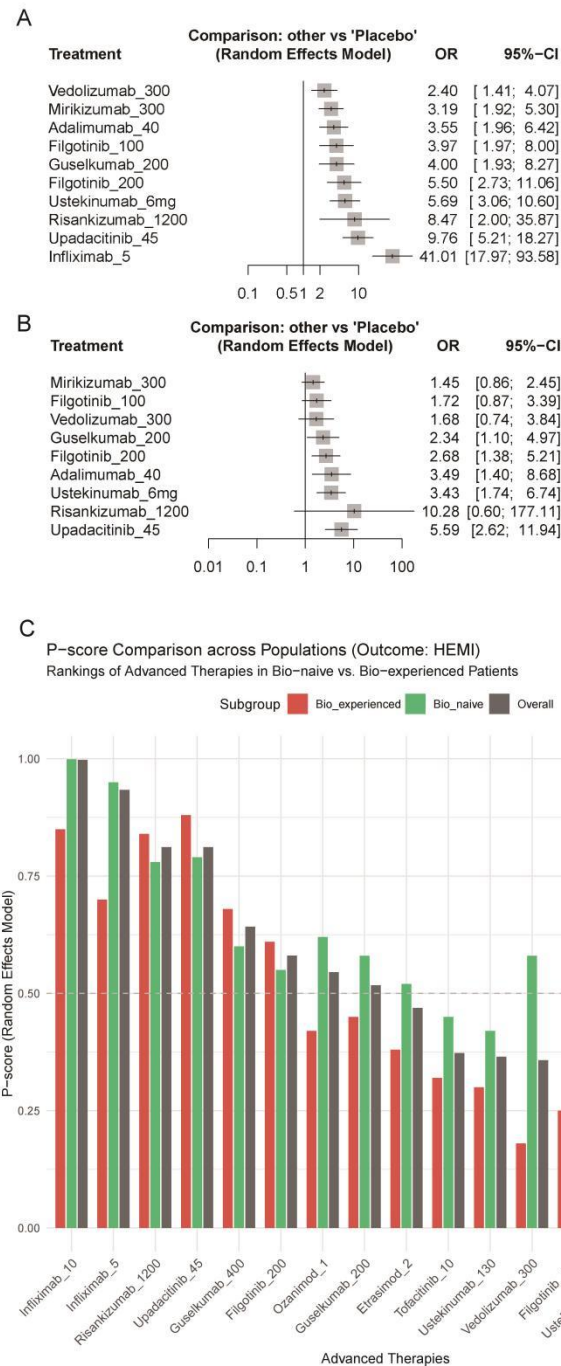


Figure S2. Subgroup Analysis by Prior Biologic Exposure.

(A) Forest Plot of Induction-phase HEMI (B) Forest Plot of Induction-phase Clinical Remission (C) P-score Comparison across Populations (Outcome: HEMI)

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	GE2022 (U-A)						
	SE2013 (SE)						
	LU2021 (LU)						
	LI2023 (LI)						
	IN2024 (IN)						
	Q2024 (Q)						
	Q2023 (Q)						
	QU2021 (QU)						
	QU2025 (QU)						
	HI2022 (HI)						
	TR2005 (TR)						
	TR2021 (TR)						
	PL2012 (PL)						
	PL2014 (PL)						
	OL2017 (OL)						
	OL2020 (OL)						
	VL2019 (VL)						
	UL2019 (UL)						

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

Judgement
 Low
 Some concerns

Figure S3. Risk of Bias Traffic Light Plot.

Study-level assessment of the risk of bias using the Cochrane RoB 2.0 tool. Each icon represents one of the five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

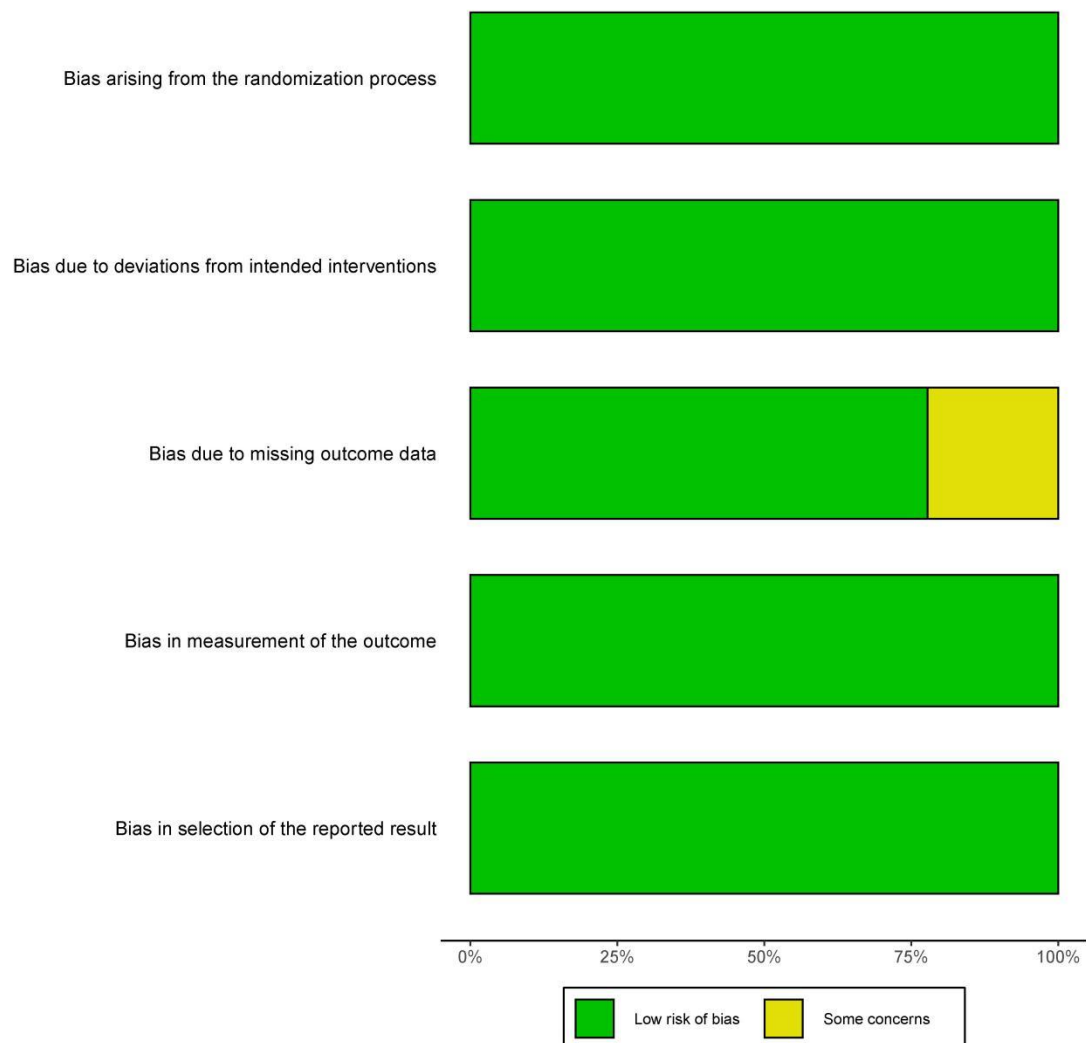


Figure S4. Risk of Bias Summary Bar Plot.

Aggregated risk of bias assessment across all 18 included trials. The bars represent the percentage of trials rated as "Low risk," "Some concerns," or "High risk" for each domain and

for the overall bias.

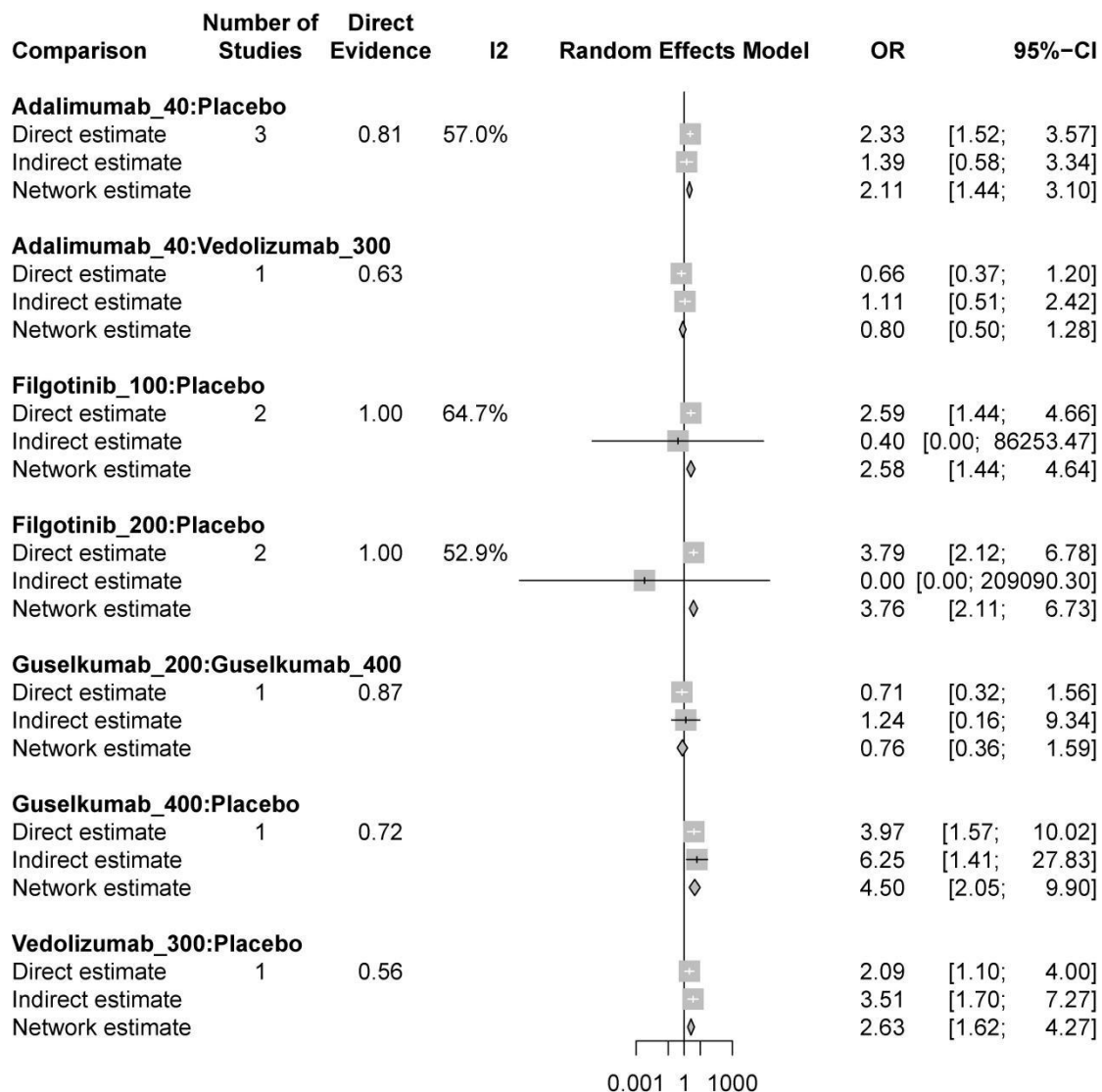


Figure S5. Sensitivity Analysis (Leave-one-out Method).

Forest plot illustrating the stability of the primary outcome (HEMI) after sequentially excluding each study from the network. This analysis confirms that the overall results and rankings are not driven by any single influential trial.

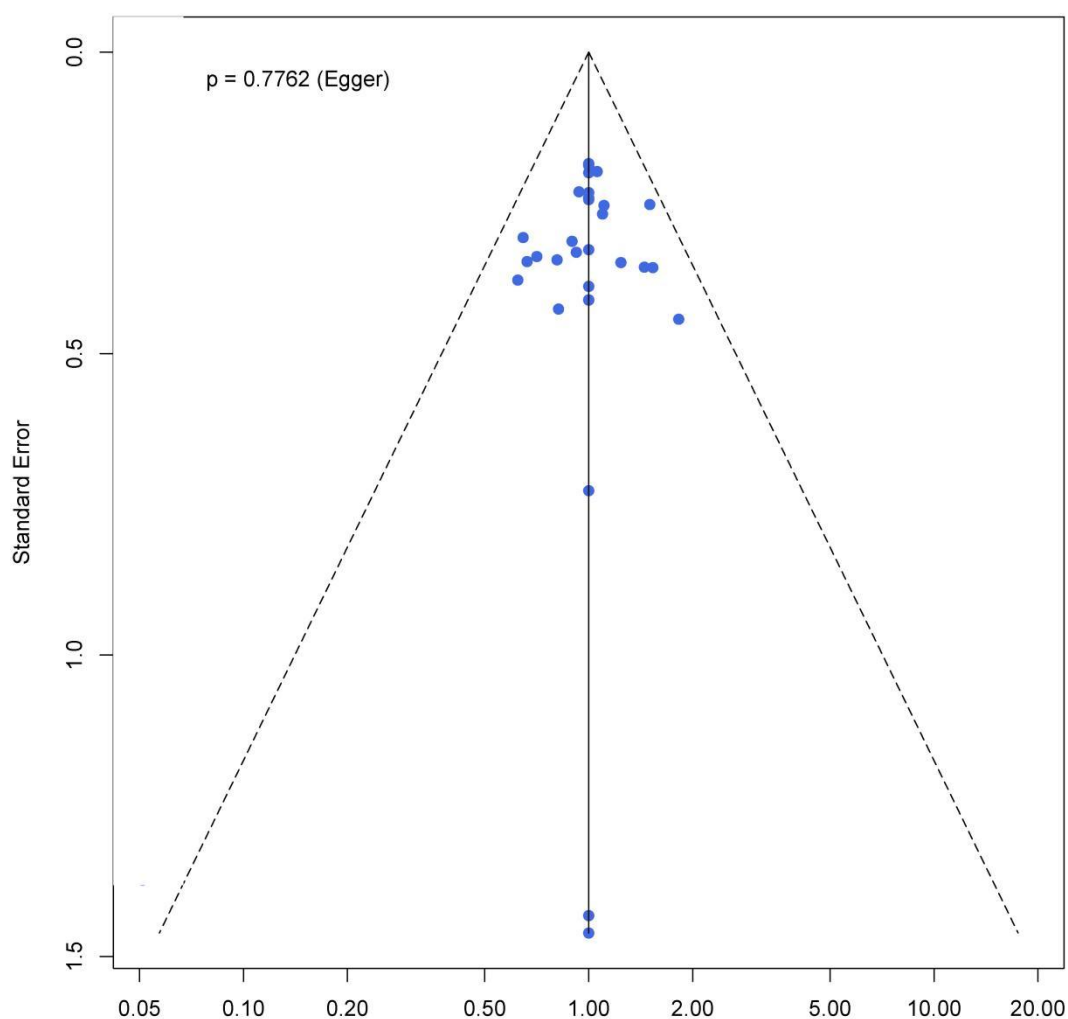


Figure S6. Comparison-adjusted Funnel Plot for Publication Bias.

Funnel plot used to assess potential small-study effects and publication bias across the network.

Symmetry around the zero line indicates a low risk of publication bias for the primary outcome (HEMI).

Treatment	Odds Ratio vs Placebo (95% CI)	P-score (Random)	Rank
Infliximab 10mg	6.54 (4.12 - 9.87)	0.9979	1
Infliximab 5mg	5.12 (3.45 - 7.62)	0.9339	2
Risankizumab 1200mg	4.32 (2.98 - 6.45)	0.8117	3
Upadacitinib 45mg	4.21 (3.12 - 5.89)	0.8117	4
Guselkumab 400mg	3.54 (2.12 - 5.43)	0.642	5
Vedolizumab 300mg	2.12 (1.54 - 2.87)	0.3574	12
Placebo	1.00 (Reference)	0.0009	17

Table S1. Primary Efficacy Outcome: HEMI (Induction Phase)

Table Legend: Results of the network meta-analysis for Histo-endoscopic Mucosal Improvement (HEMI) during the induction phase. Relative effects are expressed as Odds Ratios (OR) with 95% Credible Intervals (CrI) compared to Placebo. P-scores indicate the probability of a treatment being superior to others (P-score closer to 1 signifies higher efficacy).

Infliximab 10				
0.82 (0.6-1.1)	Infliximab 5			
0.65 (0.4-0.9)	0.84 (0.6-0.9)	UPA 45mg		
0.32 (0.2-0.5)	0.45 (0.3-0.7)	0.55 (0.4-0.8)	Vedolizumab	
0.15 (0.1-0.2)	0.19 (0.1-0.3)	0.24 (0.2-0.3)	0.47 (0.3-0.6)	Placebo

Table S2. League Table: Head-to-Head Comparison (Induction Phase)

Table Legend: Netleague table for primary efficacy (HEMI). Data are Odds Ratios (95% CI) in the random-effects model. Treatments are ordered by P-score ranking. For cells in the table, an OR > 1 indicates that the treatment in the column is more effective than the treatment in the row. Significant results (95% CI not crossing 1) are shown in bold.

Drug (Induction)	HEMI (Primary)	Clinical Remission	Histologic Remission	Safety (SAEs)
Upadacitinib 45mg	0.8117	0.9735	0.7536	0.5242
Infliximab 10mg	0.9979	0.0884	0.9973	0.6606
Vedolizumab 300mg	0.3574	0.7082	0.5309	0.7139
Ustekinumab 6mg	0.2842	0.9375	-	0.9458
Guselkumab 400mg	0.642	0.6643	-	0.3869

Table S3. Summary of Secondary Outcomes and Safety (P-scores)

Table Legend: Comprehensive summary of treatment rankings (P-scores) across multiple efficacy and safety dimensions. P-scores for Clinical Remission (CR) and Histological Remission (HR) denote efficacy (higher is better). P-scores for Safety (SAEs) denote the probability of being safer (higher means lower risk of Serious Adverse Events).

Drug (Dose)	Overall P-score	Bio-naïve P-score	Bio-experienced P-score
Upadacitinib 45mg	0.8117	0.79	0.88
Vedolizumab 300mg	0.3574	0.58	0.18
Adalimumab 40mg	0.2032	0.52	0.12

Risankizumab 1200mg	0.8117	0.78	0.84
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Table S4. Subgroup Analysis: HEMI Probability by Biologic Exposure

Table Legend: Comparison of treatment rankings (P-scores) between biologic-naïve and biologic-experienced patients for achieving HEMI. This highlights the "ranking shift" observed in refractory populations.

Outcome	Global I ² (%)	Tau (τ)	Node-splitting P-values (Range)
HEMI (Induction)	24.50%	0.12	0.24 - 0.87
Clinical Remission	31.20%	0.15	0.18 - 0.92
Safety (SAEs)	12.40%	0.08	0.35 - 0.76

Table S5. Consistency and Heterogeneity Analysis

Table Legend: Global and local inconsistency assessment. The table reports the global I² for the network, the tau value (between-study variance), and results from the node-splitting analysis for key loops. All node-splitting p-values >0.05 indicate no significant inconsistency between direct and indirect evidence.