Efficacy of Advanced Therapies in Achieving Remission by Disease Location in Crohn's Disease: A Systematic Review and Meta-analysis

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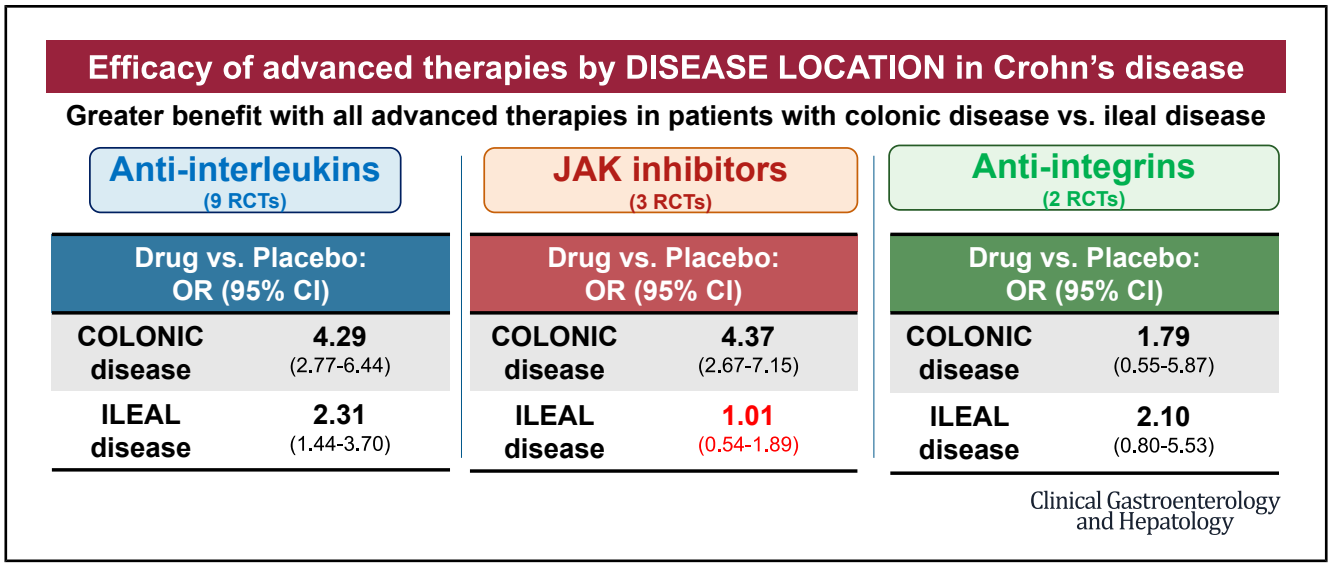

BACKGROUND & AIMS: We compared the efficacy of different advanced therapies by disease location in patients with Crohn's disease (CD) through a systematic review and meta-analysis.

METHODS: Through a systematic review, we identified 14 randomized controlled trials in 3139 patients with moderate-to-severe CD who were treated with different advanced therapies vs placebo, and reported efficacy in inducing clinical remission, stratified by disease location (isolated colonic vs ileal disease, excluding ileocolonic disease). We grouped advanced therapies based on the primary mechanism of action: anti-interleukins, Janus kinase inhibitors (JAK inhibitors), anti-integrins, and tumor necrosis factor (TNF) antagonists. We calculated treatment efficacy (drug vs placebo), overall and by drug class, for colonic vs ileal disease.

RESULTS: Overall treatment efficacy of advanced therapies vs placebo was higher in patients with colonic (odds ratio [OR], 4.09; 95% confidence interval [CI], 3.02–5.54) vs ileal CD (OR, 1.80; 95% CI, 1.23–2.63; $P < .001$). By drug class, anti-interleukins demonstrated a higher efficacy in colonic disease (OR, 4.29; 95% CI, 2.77–6.64) vs ileal disease (OR, 2.31; 95% CI, 1.44–3.70; $P = .059$),

Abbreviations used in this paper: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; GALT, gut-associated lymphoid tissue; GI, gastrointestinal; IL, interleukin; JAK, Janus kinase; OR, odds ratio; RCT, randomized controlled trial; SES-CD, Simple Endoscopic Score-Crohn's Disease; TNF, tumor necrosis factor.

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whereas no difference in efficacy was observed with anti-integrins (colonic vs ileal: OR, 1.79; 95% CI, 0.55–5.87 vs 2.10; 95% CI, 0.80–5.53; $P = .84$). For JAK inhibitors, efficacy was observed only in patients with isolated colonic disease (OR, 4.37; 95% CI, 2.67–7.15), but not in ileal disease (OR, 1.01; 95% CI, 0.54–1.89; $P < .001$). All analyses had minimal to moderate heterogeneity.

CONCLUSIONS: **The magnitude of efficacy of advanced therapies for ileal CD is generally lower compared with isolated colonic CD, with JAK inhibitors showing particularly limited efficacy for ileal disease. These results may help inform treatment selection.**

Keywords: Biologics; Crohn's Disease; Inflammatory Bowel Diseases; Interleukin Inhibitors; Janus Kinase Inhibitors.

Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by transmural inflammation of the gastrointestinal (GI) tract.[1] Unlike ulcerative colitis, CD can involve any part of the GI tract from the mouth to the anus. The Montreal classification system based on disease location—terminal ileum (L1), colon (L2), ileocolonic (L3), and upper gastrointestinal location (L4)—continues to be widely used.[2] Approximately 80% of CD cases involve the small intestine, of which about 30% are limited to the small intestine.[1] There are several differences in epidemiology, clinical presentation, and disease course of ileum-dominant vs isolated colonic disease, suggesting that they may represent distinct pathophysiological entities.[3,4] Ileal CD is strongly associated with smoking and is more likely to be associated with perianal disease and a higher risk of progression to disease complications, such as strictures and penetrating disease.[5–8] In contrast, colonic CD shows a higher prevalence in females, more frequent extraintestinal manifestations, and may have a more benign disease course.[6,9,10] These clinical distinctions extend to therapeutic responses, with ileal CD generally considered more difficult to manage.

With the approval of several novel advanced therapies for CD, there is increasing focus on comparative efficacy and drug positioning in treatment paradigms. Although the majority of clinical trials evaluating these therapies in CD report their primary efficacy outcomes regardless of disease location, this generalized approach overlooks the diverse phenotypes of CD, which may lead to variability in treatment responses in real-world clinical settings. Disease location may be a critical factor that influences treatment response overall and based on the mechanism of action of classes of advanced therapies. It is particularly important to identify which therapies are most effective for the challenging subset of patients with ileal-dominant CD.

Therefore, we aimed to address this gap by examining treatment efficacy of different classes of therapies by disease location, through a systematic review and meta-analysis of randomized controlled trials (RCTs) of advanced therapies for moderate-to-severe CD.

Methods

This systematic review was performed using an a priori established protocol and is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[11]

Study Selection

We identified phase II or III RCTs that met the following inclusion criteria: (1) Patients: adults (age >18 years) with moderately-to-severely active CD; (2) Intervention: advanced therapies (biologics and small molecules) with a minimum duration of therapy of 14 days; (3) Comparator: placebo; (4) Outcome: achieving clinical remission. From these RCTs, we specifically included studies which reported efficacy of active intervention vs placebo in subgroup analyses, focusing on isolated colonic disease (L2, based on Montreal classification) vs ileal disease (L1), excluding patients with ileocolonic disease (L3); this approach was taken because it is not feasible from post-hoc analyses to determine the dominant disease location when categorized as ileo-colonic. We grouped advanced therapies based on primary mechanism of action: anti-interleukins (interleukin [IL]-12/23 antagonist and IL-23p19 antagonists), Janus kinase inhibitors (JAK inhibitors), anti-integrins, and tumor necrosis factor (TNF) antagonists; in post hoc analyses, we separately analyzed efficacy of IL-12/23 antagonist and IL-23p19 antagonists by disease location.

We excluded the following studies: (1) trials where results were not stratified by disease location; (2) trials of novel agents or novel approaches (combination therapy of advanced therapies) in development but without phase III RCT data yet; (3) head-to-head trials without a placebo arm because efficacy of drug vs placebo could not be estimated; or (4) pediatric studies.

Study Population

We conducted a comprehensive search of multiple electronic databases through November 30, 2024, with no language restrictions, and which was subsequently updated on May 19, 2025. The databases included Ovid MEDLINE, Ovid EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews, as well as clinical trial registries. The search strategy was designed and implemented by an experienced medical librarian, using controlled

vocabulary supplemented with keywords, for RCTs of biologic therapy and small molecules in patients with CD. We searched the bibliographies of these selected articles, systematic reviews, and clinical trial registries (www.clinicaltrials.gov) to identify any additional studies. Finally, we contacted experts in the field to identify other unpublished studies. Two sets of investigators independently reviewed the title and abstract of studies identified in the search to exclude studies that did not address the research question of interest based on prespecified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information. Conflicts in study selection at this stage were resolved by consensus.

Data on study-, participant-, disease-, and treatment-related characteristics were abstracted onto a standardized form, by 2 sets of investigators independently, and discrepancies were resolved by consensus. Two sets of study investigators independently rated the quality of included trials using the Cochrane Risk of Bias Tool version 2.0.[12]

What You Need to Know

Background

Disease location impacts treatment response to advanced therapies differentially in patients with Crohn's disease (CD).

Findings

In patients with moderate-to-severe CD, the magnitude of efficacy of advanced therapies for isolated ileal CD is lower compared with isolated colonic CD, with Janus kinase (JAK) inhibitors showing particularly limited efficacy for ileal disease.

Implications for patient care

Anti-interleukins may be preferred over JAK inhibitors in patients with CD with isolated ileal disease, whereas JAK inhibitors may be preferred in patients with isolated colonic disease.

Outcomes

The primary efficacy outcome was achieving clinical remission (defined as Crohn's Disease Activity Index [CDAI] score <150), primarily assessed at end of induction therapy. The timing of outcome assessment with induction trials was up to 24 weeks; when outcomes at multiple time points were reported, we used outcomes at the primary time point used in the index trial. For treat-straight-through trials, clinical remission outcome was reported at week 48. When data for multiple doses of the same medication was available, for agents that have received regulatory approval, only data for the approved dose and administration was considered. The denominator used in all trials was based on intention-to-treat analysis, and all dropouts were assumed to be treatment failures for the primary outcome of clinical remission.

Data Synthesis and Statistical Analysis

We first calculated odds ratios (ORs) and 95% confidence intervals (CIs) for active drug vs placebo for each trial, within a stratum of patients with isolated colonic disease and ileal disease. We pooled ORs and 95% CIs, overall and by advanced therapy class, using the DerSimonian and Laird approach. We estimated treatment efficacy by examining comparing treatment efficacy (OR of drug vs placebo) by disease location, within each class of advanced therapies. In this analysis, a P value for differences between subgroups (colonic vs ileal) of $< .10$ was considered statistically significant. Subsequently, we calculated the ratio of odds ratio, by dividing the OR of (drug vs placebo) in patients with isolated colonic CD by the OR of drug vs placebo in patients with ileal CD and pooled these results using the DerSimonian and Laird approach. We assessed heterogeneity between study-specific estimates using the inconsistency index (I^2), and used thresholds of 0 to 40%, 30% to 60%, 50% to 90%, and 75% to 100% to suggest minimal, moderate, substantial and considerable heterogeneity, respectively.[13] Due to the small number of included studies, we did not perform statistical assessment for publication bias.[14] All analyses were performed using Comprehensive Meta-Analysis version 2 (Biostat).

Results

Our search strategy yielded 5353 unique studies, from which we included data from 14 RCTs of advanced therapies vs placebo, that reported induction of clinical remission, stratified by disease location in CD. These included 9 RCTs of anti-ILs (3 RCTs of IL12/23 antagonists; 6 RCTs of IL23p19 antagonists, including one RCT in which IL12/23 antagonists were an active comparator), 3 RCTs of JAK inhibitors (2 RCTs of upadacitinib; 1 RCT of filgotinib), and 2 RCTs of anti-integrins (1 RCT of vedolizumab; 1 RCT of etrolizumab); we did not identify any RCT of TNF antagonists that reported induction of remission based on disease location. In these trials, 1976 patients (62.9%) had isolated colonic disease and 1163 patients (37.1%) had isolated ileal CD; patients with ileocolonic disease were excluded from this analysis (Supplementary Table 1). All trials were deemed to be at low risk of bias.

Overall Treatment Efficacy for Isolated Colonic vs Ileal CD

Across all agents combined, the magnitude of treatment efficacy (active intervention vs placebo) for induction of clinical remission was higher for isolated

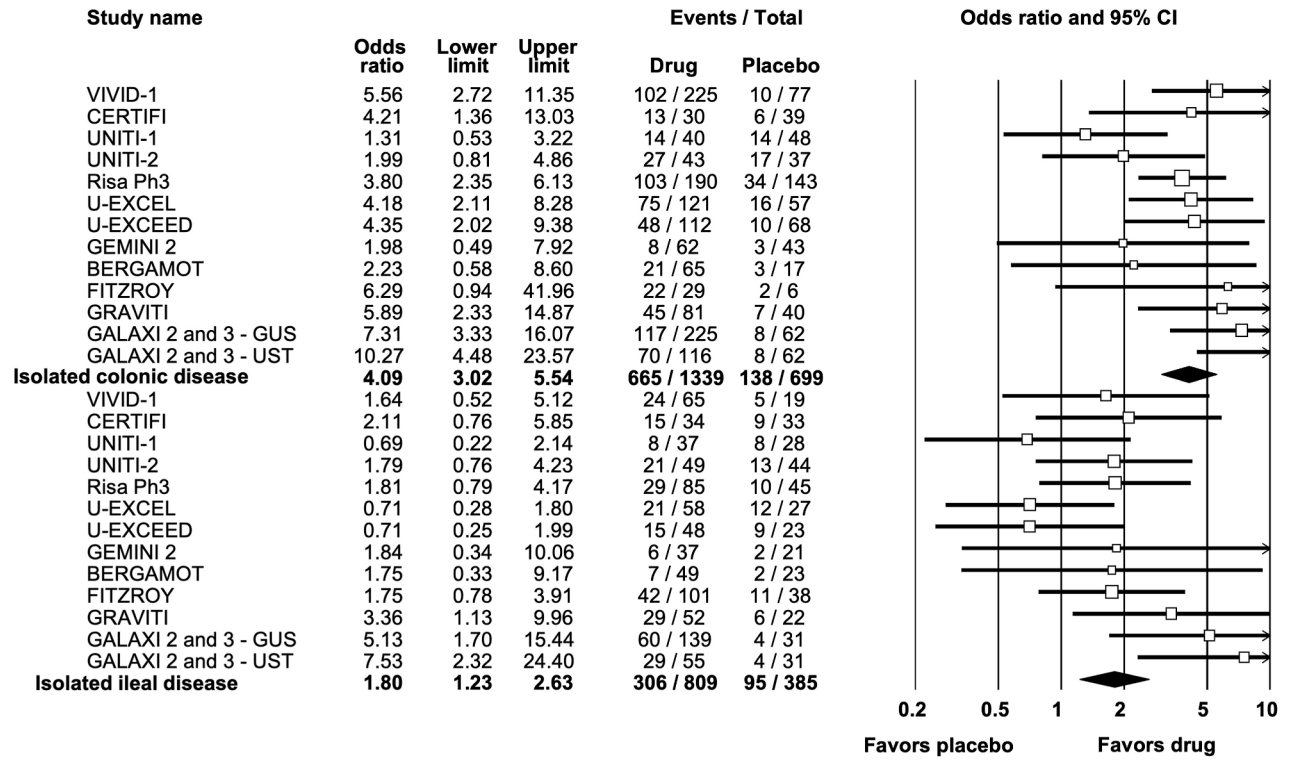

Figure 1. Efficacy of advanced therapies (vs placebo) for induction of clinical remission in patients with moderate-to-severe CD, by disease location.

colonic disease (665/1339 vs 138/699; OR, 4.09; 95% CI, 3.02–5.54; $I^2 = 37\%$), compared with ileal CD (306/809 vs 95/385; OR, 1.80; 95% CI, 1.23–2.63; $I^2 = 41\%$; $P < .001$) (Figure 1).

Efficacy for Isolated Colonic vs Ileal CD by Drug Class

Anti-ILs. In 9 RCTs (Risa Phase III combines ADVANCE and MOTIVATE trials, GALAXI 2 and 3 pooled analyses) of anti-ILs (1296 [63.7%] with isolated colonic CD; 738 [36.3%] with ileal CD),[15–20] benefit of drug vs placebo was observed for both patients with isolated colonic and ileal CD. However, the magnitude of benefit with drug vs placebo was significantly higher in patients with isolated colonic CD (OR, 4.29; 95% CI, 2.77–6.64; $I^2 = 58\%$) compared with patients with ileal CD (OR, 2.31; 95% CI, 1.44–3.70; $I^2 = 40\%$; P value for difference between subgroups = .059) (Figure 2). The corresponding ratio of OR for treatment efficacy in patients with isolated colonic vs ileal CD was 1.75 (95% CI, 1.33–2.30) (Figure 3). We subsequently analyzed IL-12/23 antagonists and IL23p19 antagonists separately. In 4 studies of IL-12/23 antagonists, the magnitude of benefit with ustekinumab over placebo was numerically higher in patients with isolated colonic disease (ustekinumab vs placebo: 124/229 [54.1%] vs 45/186 [24.2%]; OR, 3.26; 95% CI, 1.25–8.48) vs isolated ileal disease (ustekinumab vs placebo: 73/175 [41.7%] vs 34/136 [25%]; OR, 2.07; 95% CI, 0.87–4.92; P value for difference between subgroups = .49). In 4 studies of IL23p19 antagonists, the magnitude of benefit with IL23p19 antagonists over placebo was numerically higher in patients with isolated colonic disease (IL23p19 antagonists vs placebo: 367/721 [50.9%] vs 59/322 [18.3%]; OR, 4.90; 95% CI, 3.52–6.82) vs isolated ileal disease (IL23p19 antagonists vs placebo: 142/341 [41.6%] vs 25/117 [21.4%]; OR, 2.54; 95% CI, 1.52–4.22; P value for difference between subgroups = .034).

JAK inhibitors. In 3 RCTs of JAK inhibitors (393 [57.1%] with isolated colonic CD; 295 [42.9%] with ileal CD),[21,22] benefit of drug vs placebo was observed only in patients with isolated colonic disease (145/262 vs 28/131; OR, 4.37; 95% CI, 2.67–7.15; $I^2 = 0\%$), but not in patients with ileal CD (78/207 vs 32/88; OR, 1.01; 95% CI, 0.54–1.89; $I^2 = 28\%$; P value for difference between subgroups < .001) (Figure 4). The corresponding ratio of OR for treatment efficacy in patients with isolated colonic vs ileal CD was 5.92 (95% CI, 4.84–7.08), with minimal heterogeneity ($I^2 = 0\%$) (Figure 3).

Anti-integrins. In 2 RCTs of anti-integrins (187 [59.0%] with isolated colonic CD; 130 [41.0%] with ileal CD),[23,24] the magnitude of benefit with drug vs placebo was similar in patients with isolated colonic CD (OR, 1.79; 95% CI, 0.55–5.87; $I^2 = 0\%$) and patients with ileal

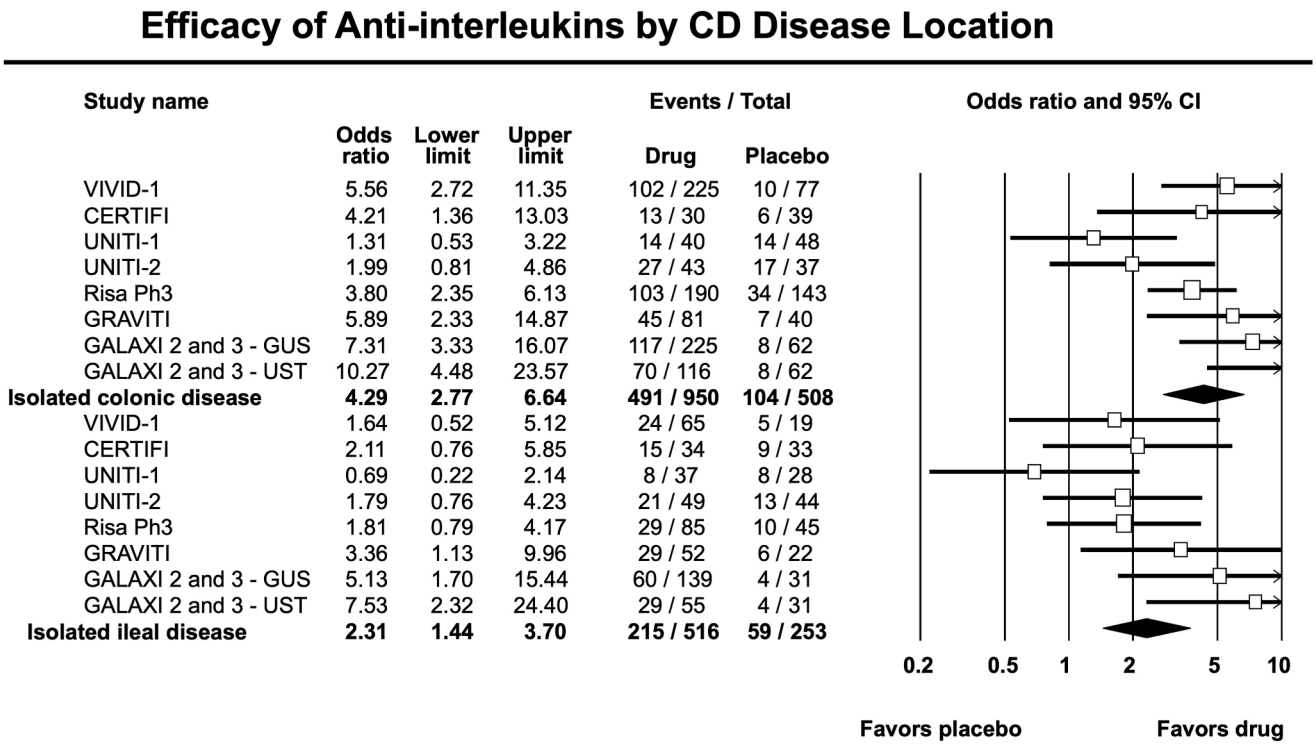

Figure 2. Efficacy of anti-ILs (vs placebo) for induction of clinical remission in patients with moderate-to-severe CD, by disease location.

CD (OR, 2.10; 95% CI, 0.80–5.53; $I^2 = 0\%$) (*P* value for difference between subgroups = .84) (Figure 5). The corresponding ratio of OR for treatment efficacy in patients with isolated colonic vs ileal CD was 1.17 (95% CI, 0.94–1.45), with minimal heterogeneity ($I^2 = 0\%$) (Figure 3).

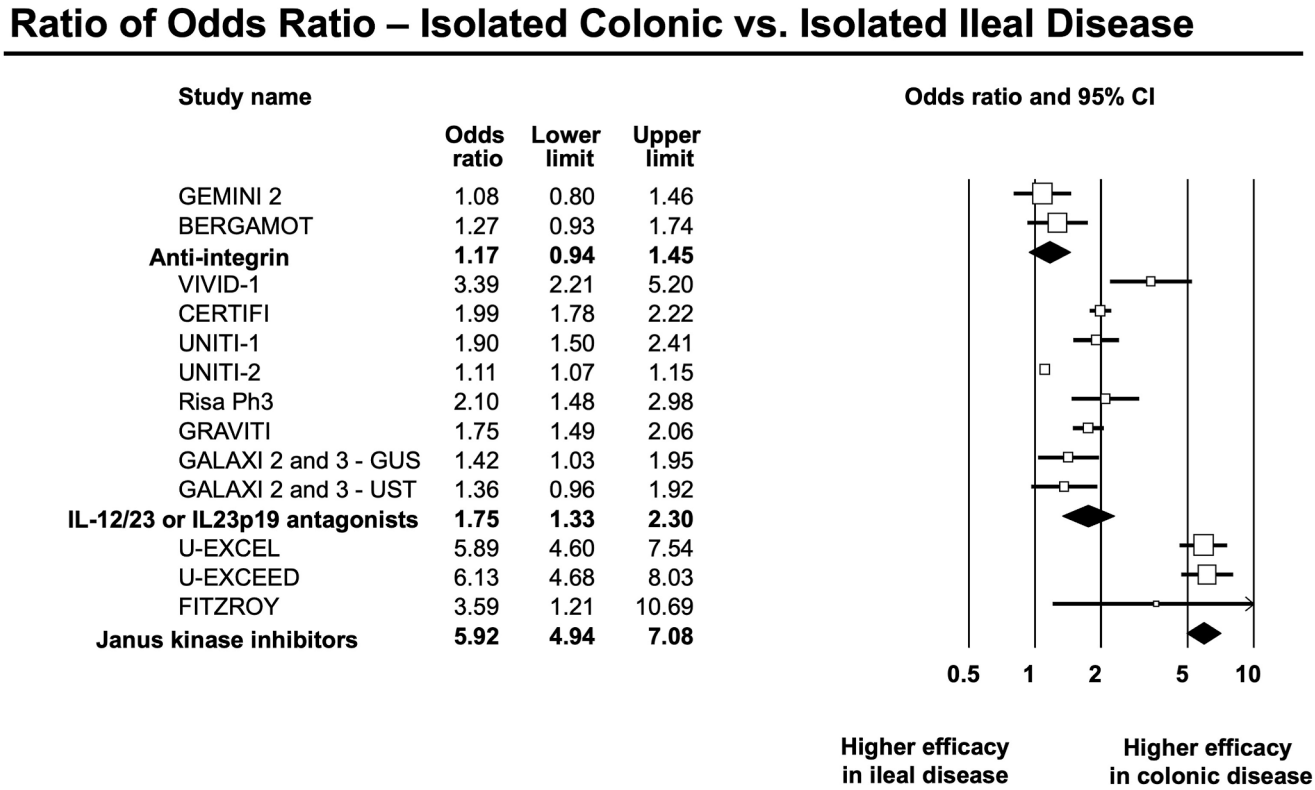

Figure 3. Heterogeneity of treatment efficacy – ratio of OR of efficacy of drug vs placebo for induction of clinical remission in patients with moderate-to-severe CD, by disease location.

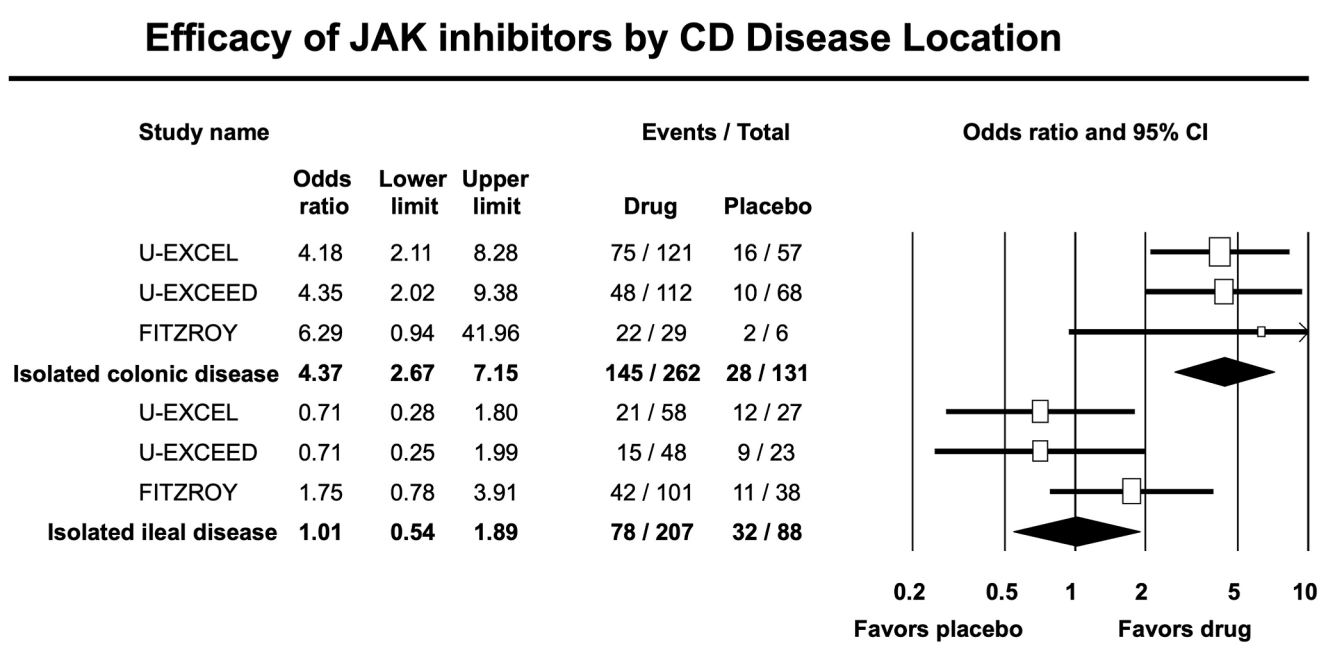

Figure 4. Efficacy of JAK inhibitors (vs placebo) for induction of clinical remission in patients with moderate-to-severe CD, by disease location.

Discussion

Disease location may be an important treatment effect modifier in patients with CD. Through a systematic review of 14 RCTs of advanced therapies for moderate-to-severe CD, we made several key observations. First, we confirmed prior observations that the magnitude of treatment efficacy (drug vs placebo) for achieving clinical remission is significantly lower for patients with ileal CD compared with isolated colonic CD. Second, disease location differentially modifies treatment efficacy of different classes of advanced therapies. Although anti-ILs are efficacious for both patients with isolated colonic and ileal CD, the magnitude of benefit is significantly higher for isolated colonic CD. In contrast, JAK inhibitors may be highly effective only in a subset of patients with isolated colonic CD, but without any significant efficacy for ileal CD. Anti-integrins may not have differential efficacy for isolated colonic vs ileal CD, although the overall magnitude of benefit with these agents is low. These findings provide clues into the potentially distinct pathophysiology of ileum-dominant vs isolated colonic CD. Our insights may also have potentially important clinical implications, namely that selection of therapeutic agents may be tailored based on the dominant location of the disease, favoring anti-ILs over JAK inhibitors for patients with isolated ileal disease, whereas the latter may be preferred in patients with isolated colonic disease.

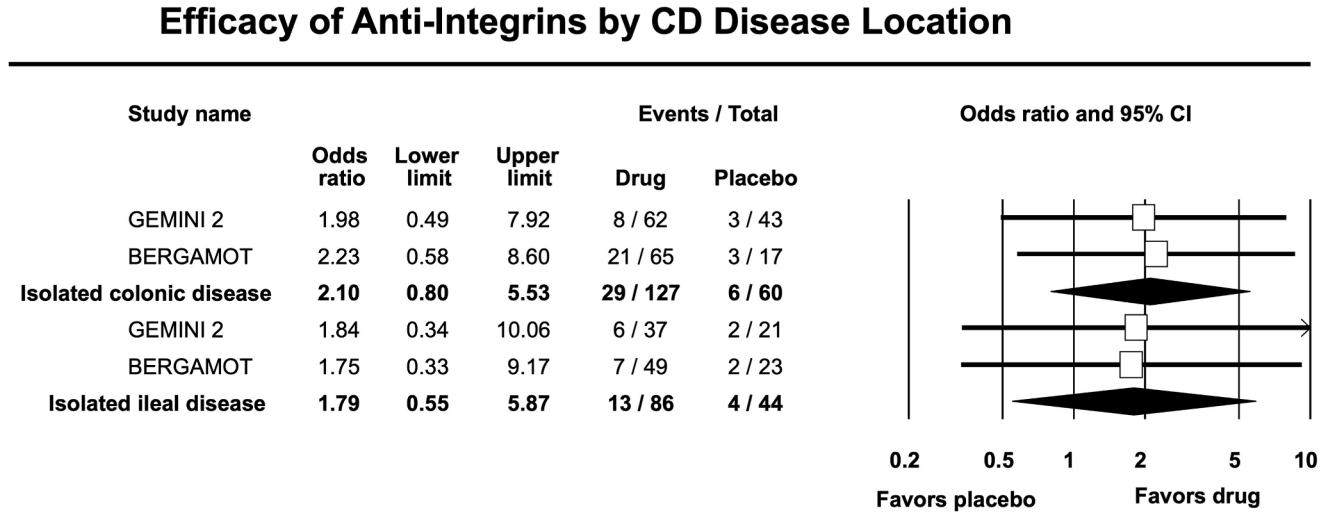

Figure 5. Efficacy of anti-integrins (vs placebo) for induction of clinical remission in patients with moderate-to-severe CD, by disease location.

Further, our findings that treatment responses differ between isolated ileal and colonic CD are in line with prior observations suggesting that CD in the small bowel vs colon may represent distinct disease entities with unique characteristics. Genetically, polymorphisms in the NOD2 gene are strongly associated with ileal CD,[25–27] whereas HLA alleles and IL23R polymorphisms have been reported to have a stronger association with colonic CD.[9,28,29] The NOD2 gene is involved in bacterial sensing and innate immune responses, and mutations in this gene alter the recognition of bacterial components, leading to disruptions in immune homeostasis.[30] In contrast, HLA plays a critical role in the selection of the T cell receptor repertoire and induction of adaptive immune responses. Specific HLA alleles, such as HLA-DRB1, have been reported to be associated with colonic CD, suggesting that antigen-specific T cells may play an important role in the pathogenesis of colonic CD.[31] Moreover, the enhanced benefit of IL-12/23 antagonist therapies for colonic CD observed here may suggest a more central role for Type 1 and 17 immunity in colonic compared with small bowel CD.

Unique anatomical features of the small intestine may also contribute to differences in efficacy observed for therapies with distinct mechanisms of action. Peyer's patches and Paneth cells, which are specific to the small intestine, play pivotal roles in maintaining intestinal homeostasis by facilitating antigen uptake, inducing tolerance, and defending against microbial challenges.[32] Dysfunction of these structures has been implicated in the pathogenesis of ileal CD, highlighting distinct mechanisms that may not apply to colonic CD. By contrast, we observed that anti-integrin therapies did not exhibit differential efficacy for small intestine vs colonic CD. These results raise the possibility that the inflammatory response in CD may be less dependent on lymphocyte trafficking than ulcerative colitis and perhaps more dependent on gut-resident immune cells.[33] Alternatively, because it has been demonstrated in a humanized mouse model that T cells can utilize a4b1 to traffic to the ileum when a4b7 is blocked by vedolizumab,[34] an analogous escape mechanism may occur in CD. Lastly, in light of the observation that vedolizumab may act through regulating the function of gut-associated lymphoid tissue (GALT),[35] the observation that the overall efficacy of anti-integrin agents was low in CD overall may suggest that the GALT is less critically involved in CD pathophysiology.

Differences in treatment efficacy between ileal and colonic CD have also been observed in conventional therapies prior to the introduction of advanced therapies. For instance, exclusive enteral nutrition has been reported to achieve higher remission rates in ileal CD compared with colonic CD.[36,37] In contrast, antibiotic therapy based on metronidazole has demonstrated greater efficacy in colonic CD.[38,39] Although 5-ASA agents are not recommended as a treatment for CD,[40,41] earlier studies have demonstrated efficacy of sulfasalazine in colonic CD.[42,43]

One of the key findings of this study is the striking difference in the efficacy of JAK inhibitors depending on whether disease affected the ileum or colon. Notably, JAK inhibitors showed no efficacy compared with placebo in ileal CD, whereas they were highly effective for isolated colonic disease. In addition to the pivotal Phase III trials of upadacitinib in patients with moderate-severe CD, which clearly showed no differences in treatment efficacy in a subset of patients with ileal CD, the DIVERGENCE-1 trial comparing the efficacy of filgotinib vs placebo for isolated small bowel CD failed to show benefit of filgotinib using objective endpoints like radiologic remission. These findings suggest that one or more of the known cytokines targeted by JAK inhibitors, which include IL-2, IL-4, IL-6, IL-7, IL-9, IL-15, and interferons, may be more relevant in the pathogenesis of colonic CD compared with ileal CD. Indeed, the same immune cell subset may exhibit distinct molecular and functional characteristics depending on its localization in the colon vs small intestine,[44] leading to differential dependence on cytokines for its function and survival. Moreover, in contrast to colonic CD, fibrosis and stenosis may be integral components of the pathogenesis of small bowel CD. Although JAK inhibitors can effectively block pro-inflammatory cytokine signaling, their ability to reverse fibrosis may be limited. This may be one mechanistic explanation that contributes to the observation presented here that JAK inhibitors may exhibit reduced therapeutic efficacy in small bowel CD.

Although we made several compelling findings examining the interaction between disease location and treatment efficacy in patients with CD through a systematic review of clinical trials, with mild to low heterogeneity, there are several important limitations. First, our primary outcome was achieving clinical remission, implying a short-term evaluation and a reliance on symptoms. Published clinical trials did not specifically report endoscopic findings stratified by disease location. Second, we were limited in our ability to examine impact of disease location on treatment efficacy of TNF antagonists due to paucity of clinical trial level data. However, observational studies have confirmed that TNF antagonists may have advantages in small bowel CD. In a study evaluating the endoscopic healing rate in patients with ileal Simple Endoscopic Score-Crohn's Disease (SES-CD) scores $\geq$3 after 1 year of treatment found no significant differences between infliximab, adalimumab, ustekinumab, and vedolizumab. Nonetheless, infliximab demonstrated the highest rate of improvement in large ileal ulcers (>0.5 cm).[45] Additionally, infliximab has been reported to reduce fibrostenosis-associated inflammation,[46] making it currently the most suitable therapeutic option for small bowel CD. Third, the observed superior efficacy in colonic CD may not solely reflect the intrinsic properties of the therapies but could also be influenced by external factors. Disease location was not a stratification factor in the included trials, which limits the benefits of randomization for this meta-analysis. We

were unable to adjust for potential confounders. Fourth, the classification of isolated ileal vs isolated colonic CD was based on historical factors based on the Montreal classification and did not necessarily represent active areas of inflammation. We excluded patients with ileocolonic disease. Future prospective cohort studies using patient-level data investigating the efficacy of therapies according to active disease location, as assessed by colonoscopy or cross-sectional imaging for small bowel CD are required. We are also unable to comment on the efficacy of different advanced therapies in patients with upper gut CD.

Conclusion

In conclusion, through a systematic review and meta-analysis of advanced therapies for moderate-to-severe CD, we confirmed that the magnitude of treatment efficacy of advanced therapies is probably higher in patients with isolated colonic vs ileal disease. Anti-ILs are efficacious in patients with both colonic and ileal CD, with a higher magnitude of efficacy in patients with isolated colonic disease. In contrast, JAK inhibitors may demonstrate efficacy exclusively in patients with isolated colonic disease but not in patients with ileal CD. Future studies examining the impact of disease location on endoscopic (or radiologic) remission target are warranted, along with studies examining potential biological drivers of differences in treatment efficacy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.07.009.

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