Best Practice & Research Clinical Gastroenterology 77 (2025) 101981

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: www.elsevier.com/locate/bpg

Reaching the therapeutic ceiling in IBD: Can Advanced Combination Treatment (ACT) offer a solution?

Virginia Solitano [a,b,c], Jurij Hanžel [d], Maria Manuela Estevinho [e,f], Rocio Sedano [b], Luca Massimino [a], Federica Ungaro [a], Vipul Jairath [b,c,*]

[a] Division of Gastroenterology and Gastrointestinal Endoscopy, IRCCS Ospedale San Raffaele, Università Vita-Salute San Raffaele, Milan, Italy
[b] Division of Gastroenterology, Department of Medicine, Western University Schulich School of Medicine, London, Ontario, Canada
[c] Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada
[d] Medical Faculty, University of Ljubljana, Department of Gastroenterology, UMC Ljubljana, Ljubljana, Slovenia
[e] Department of Gastroenterology, Unidade Local de Saúde Gaia Espinho (ULSGE), Vila Nova de Gaia, Portugal
[f] Department of Biomedicine, Unit of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Porto, Portugal

ARTICLE INFO

Handling Editor: Dr. Manon Spaander

Keywords:
Dual
Immune-mediated inflammatory diseases
Therapeutic ceiling
Crohn's disease
Ulcerative colitis

ABSTRACT

The term Advanced Combination Treatment (ACT) involves the combination of at least two biologics or the use of a biologic with a small molecule drug, each with different mechanisms of action. This narrative review evaluates the current evidence supporting ACT in inflammatory bowel disease (IBD), focusing on preclinical studies, real-world evidence, and randomized controlled trials. A systematic review of randomized controlled trials has concluded that ACT significantly improves clinical outcomes, without significant safety concerns in patient with IBD. However, variability in trial designs and the lack of standardized outcome measures have led to initiatives aimed at mitigating these issues through a clear expert consensus. While the evidence for ACT in IBD is compelling, substantial challenges remain in standardizing treatment protocols and ensuring long-term safety. In the meantime, the use of ACT in clinical practice remains off-label and requires careful consideration of patient-specific factors. Future clinical trials should consider robust biomarkers for patient selection and leverage mechanistic insights to select combination components.

1. Introduction

Over the past three decades, the treatment landscape of inflammatory bowel disease (IBD) has changed markedly. Several biological therapies and small molecules have been approved, leading to improved outcomes, such as reduced steroid use and lower rates of surgery [1]. Despite these significant advancements, the therapeutic efficacy of biologics has plateaued indicating a therapeutic ceiling—a limit on the maximum achievable effectiveness of these treatments [2]. Clinical remission rates remain modest, with most biologics achieving only 30 %–40 % clinical and endoscopic remission at 52 weeks [2,3]. In line with this, a systematic review and meta-analysis of 25 randomized controlled trials (RCTs) focusing on moderate-to-severe Crohn's disease (CD) found no substantial improvement in clinical remission and response rates over placebo over time, corroborating the existence of a therapeutic ceiling [4]. While selecting patients with a shorter disease duration and limited therapeutic exposure (bio-naïve) would likely result in better efficacy for newer drugs in RCTs, this strategy would inevitably result in recruitment challenges, in real-world settings, still leave a significant gap between suboptimal current remission rates and the ideal goal of a universally effective treatment. Addressing this gap is critical. One proposed strategy is to mimic precision therapy approaches used in cancer treatment, which rely on biomarkers to guide treatment decisions [5,6]. However, despite numerous small-scale biomarker studies, no biomarker has been validated as a reliable predictor of therapeutic response in IBD. In the absence of validated biomarkers, the most effective way to increase response and remission rates of CD is early diagnosis and treatment initiation [3]. This was further demonstrated in the PROFILE trial, where ultra early introduction of infliximab combined with immunomodulators achieved significantly higher - and among the best in the field - rates of sustained steroid-free remission in CD (79 %) compared to conventional step-up therapy (29 %) [7]. Notably, in this trial the median time from diagnosis to trial enrolment was 12 days (range 0–191), challenging prior definitions of early disease

* Corresponding author. Division of Gastroenterology, Department of Medicine, Western University Schulich School of Medicine, London, Ontario, Canada.
E-mail address: vjairath@uwo.ca (V. Jairath).

https://doi.org/10.1016/j.bpg.2025.101981
Received 27 November 2024; Accepted 18 December 2024
Available online 8 January 2025

[7]. Additional strategies, such as therapeutic drug monitoring, adjusting treatment based on inflammatory markers and optimizing drug sequencing have also been suggested to overcome the current treatment ceiling for both CD and UC [2]. Furthermore, accumulating evidence suggests that advanced combination treatment (ACT), which targets multiple disease pathways simultaneously, holds promise for improving outcomes in patients with IBD [8,9]. The complex, multi-pathway nature of immune-mediated inflammation often limits the effectiveness of single biologic agents, as sequential use of these agents frequently leads to reduced efficacy, likely due to immune adaptation [10]. Additionally, while some biologics can effectively manage luminal disease, they often provide limited benefit for extraintestinal manifestations (EIMs) or other coexisting immune-mediated conditions, underscoring the need for a more comprehensive approach. ACT involves combining at least two biologics or pairing a biologic with a small molecule drug, each targeting distinct mechanisms of action. The term "ACT" is used interchangeably for "advanced combination treatment" or "therapy," chosen for its simplicity and alignment with our prior publications to ensure consistency. ACT effectively captures the approach of using multiple advanced therapies to optimize outcomes in managing complex disease. This narrative review examines the current evidence supporting ACT in IBD, focusing on preclinical research, real-world evidence, and RCTs.

2. Translating preclinical studies from Rheumatology to Gastroenterology

Preclinical studies for the use of ACT for immune-mediated inflammatory diseases (IMIDs) for rheumatological indications, particularly rheumatoid arthritis (RA), remount to the late 1990s. The first studies analyzed the combination of PEGylated soluble tumour necrosis factor receptor type I (PEG sTNF-RI) with interleukin-1 receptor antagonist (IL-1Ra) [11] or with methotrexate [12] in rat models of adjuvant arthritis. The combinations demonstrated greater-than-additive efficacy compared to either agent alone, laying the groundwork for subsequent studies. Another pivotal study demonstrated that the combination of two anti-cytokine treatments (anti-IL-1 and anti-TNF) exhibited a synergistic capacity to inhibit joint inflammation, loss of bone mineral density and weight loss, even when combining doses that did not affect lesion severity when used alone [13]. Similarly, the combined use of etanercept, an anti-TNF agent, and the calcineurin inhibitor tacrolimus suppressed the radiographic progression and the clinical signs of arthritis in mice, while single-drug treatments did not [14]. This was achieved by suppressing matrix metalloproteinase-3 production and decreasing the mobilization of osteoclast precursors, key factors in joint damage [14]. Furthermore, dual kinase inhibition targeting JAK and spleen tyrosine kinase demonstrated efficacy by simultaneously modulating multiple inflammatory pathways, thus altering cytokine cascades, reducing bone and cartilage destruction [15]. Based on the accumulating evidence on ACT, research gradually moved to the development of bispecific antibodies, designed specifically to recognize and bind simultaneously to two different antigens or epitopes, maximizing the "therapeutic coverage" for IMIDs involving multiple inflammatory pathways. Among these studies, one has explored the effects of a bispecific antibody targeting TNF-α and CXCL10 in a murine arthritis model [16]. The use of this antibody reduced synovial inflammation, osteoclast activation, cartilage and bone damage.

Concerning IBD, studies have demonstrated that in patients who do not respond to anti-TNF therapy, intestinal TNFR2+IL23R + $CD4^+$ T cells remain activated by IL-23 secreted from $CD14^+$ macrophages, despite the inhibition of TNF-α signalling. As those cells can still promote anti-apoptotic and proinflammatory effects via the IL-23-IL23R/STAT3 pathway, successful treatment requires the concurrent blockade of both the TNF-α and IL-23 pathways [17]. This has prompted scientists to investigate the role of ACT in IBD. In an in silico and in vivo study [18], researchers used patient-derived molecular networks from CD to bridge preclinical models with human disease, focusing on combined therapy with anti-TNF and anti-IL-23. Simultaneous inhibition of these two pathways was shown to target both shared and unique molecular pathways in IBD pathogenesis, emerging as a promising therapeutic strategy. To test this hypothesis, mice were treated with varying doses of anti-IL-23, anti-TNF, or their combination. A synergistic response to combination therapy was observed, with reductions in systemic weight loss and local colonic inflammation confirmed by histopathology.

In line with this, Roberts et al. developed V56B2, the first oral dual-specificity domain antibody targeting both anti-TNFα and anti-IL-23 for the treatment of IBD [19]. To evaluate the hypothesis that dual inhibition of TNFα and IL-23 could enhance efficacy in IBD, ex vivo UC biopsies were treated with V565, V900, a combination of the two, or a control. Treatment with V565 and V900, both individually and in combination, resulted in significant reductions in the phosphorylation of various signalling proteins, indicating effective neutralization of TNFα and IL-23 in the biopsies. This first-in-human, Phase 1 study (SOR102-101; NCT06080048) aimed to evaluate the safety, tolerability, and pharmacokinetics of single ascending (SAD) and multiple ascending doses of SOR102 in 42 healthy subjects. SOR102 is engineered to release active monomers upon enzymatic cleavage within the gastrointestinal (GI) tract, ensuring localized therapeutic action while minimizing systemic absorption and potential off-target effects. SOR102 was well tolerated across all doses, with no systemic exposure of the drug or its monomers, supporting its gut-targeted action. Low levels of intact SOR102 and high monomer levels in faeces confirm effective cleavage after oral administration. Monomer concentrations increased with higher doses, and monomer concentrations remained consistently high during the dosing period, confirming the drug's localized GI activity.

Supporting the dual therapeutic strategy, the ACT produced the most pronounced decrease in the phosphorylation of signalling proteins associated with colonic inflammation. More recently, Wang et al. [20] designed bispecific nanobodies targeting simultaneously TNF-α and IL-23, which effectively inhibited the release of cytokines in CD4+T cells during co-culture experiments. In addition, the nanobodies effectively alleviated colitis severity in mouse model with acute colitis induced by DSS or TNBS, outperforming the infliximab and ustekinumab combination. Other studies aimed to explore the dual blockade of the JAK/-STAT signalling cascade. In this context, Cui et al. [21] developed an oral small molecule which is a JAK1/TYK2 dual inhibitor. The authors demonstrated superior therapeutic effects compared to tofacitinib in mouse models of UC.

3. Real-world evidence

Data on the use of ACT in real-world studies are accumulating, although several limitations should be borne in mind [22–24]. ACT can be used in different clinical settings and its effectiveness is expected to differ accordingly: it may be reasonable to expect that remission rates will be lower in patients with refractory intestinal disease, compared to patients receiving ACT for concomitant EIMs or IMIDs. Real-world studies in ACT are without exception retrospective and have non-standardized definitions of treatment outcomes [25] with emphasis on symptom-based outcomes and only a minority reporting on endoscopic and biomarker- or imaging-based outcomes. Retrospective studies may also record adverse events less consistently and smaller studies are more prone to bias.

Three largely overlapping systematic reviews [22–24] have been published, including around 280 patients. Studies including at least 40 patients are presented in Table 1. Most patients had CD (211/79, 76 %) and initiated ACT for medically refractory intestinal disease (225/279, 81 %). The median number of biologics prescribed previously was 2 (interquartile range 2–4) [22]. Partly owing to the RCT, the commonest combination was a TNF antagonist and anti-integrin (48 %), followed by vedolizumab and ustekinumab (19 %), and vedolizumab and tofacitinib (11 %). The choice of individual components of ACT regimens

Table 1
Real-world studies on advanced combination treatment including at least 40 patients with inflammatory bowel disease.

Author (year)	Study design	Population	Combination	Effectiveness	Safety
Glassner et al. (2020)	Retrospective single centre cohort study	50 (18 UC, 32 CD) Median number of prior biologics 2 10 with concomitant IMIDs	53 ACT trials Vedolizumab plus ustekinumab (25) Tofacitinib plus anti-TNF (9) Tofacitinib plus vedolizumab (8) Vedolizumab plus anti-TNF (7) Tofacitinib plus ustekinumab (3) Anti-TNF plus apremilast (1)	Clinical (50 % vs 14 %) and endoscopic remission (34 % vs 6 %) *at follow-up compared to baseline*	Adverse events in 26 % Serious adverse events in 12 % (mostly infections)
Goessens et al. (2021)	Retrospective multicentric cohort study	98 (40 UC, 58 CD) Median number of prior biologics 3 41 with concomitant IMIDs	104 ACT trials Vedolizumab plus anti-TNF (41) Anti-IL-23 plus vedolizumab (21) Tofacitinib plus vedolizumab (13) Anti-TNF plus anti-IL-23 (11) Tofacitinib plus anti-TNF (1) Others (17)	Improvement of IBD disease activity in 70 % Improvement of IMID/EIM activity in 81 %	Adverse events in 42 % (10 serious infections, 1 skin cancer)
McShane et al. (2024)	Retrospective multicentric cohort study	109 (27 UC, 82 CD), Median number of prior biologics 3 13 with concomitant IMIDs	122 ACT trials Vedolizumab plus ustekinumab (42) Vedolizumab plus anti-TNF (32) Anti-IL-23 plus JAK inhibitor (4) Ustekinumab plus anti-TNF (16) Vedolizumab plus JAK inhibitor (12) Anti-TNF plus JAK inhibitor (2) Other (14)	39 % corticosteroid-free clinical response at week 12 29 % corticosteroid-free clinical and biochemical response at week 12	Adverse events in 26 % (mostly related to active IBD) 10 infections (2 serious) 2 venous thromboembolisms (none related to JAK inhibitor use) 3 cases of non-melanoma skin cancer (2 with prior history)

Abbreviations: CD – Crohn's disease; EIM – extraintestinal manifestation; IBD ¬¬– inflammatory bowel disease; IL – interleukin; IMID – immune-mediated inflammatory disease; JAK – Janus kinase; TNF – tumor necrosis factor; UC – ulcerative colitis.

undoubtedly reflects the safety profile of ustekinumab and vedolizumab, rather than perceived mechanistic advantages of these combinations [26]. Overall, the pooled clinical remission rate at a median follow-up of 32 weeks was 59 % (95 % confidence interval [CI]: 42–74 %) and the endoscopic remission rate 34.3 % (95 % CI: 23–46 %) [22]. Roughly only a third of all included patients had available data on endoscopic outcomes. Lower rates of clinical (40 vs. 86 %) and endoscopic (23 vs. 50 %) remission were observed in patients initiating ACT solely for uncontrolled luminal disease compared to patients receiving ACT for concomitant extraintestinal manifestations. The pooled rate of patients undergoing surgery was 12.2 % (95 % CI 4.2–23.7 %).

Acknowledging the substantial limitations of comparing individual therapeutic combinations given unmeasured residual confounding impacting the selection of specific combinations, pooled rates of clinical remission were 55.1 % (95 % CI: 19.6–88.5 %) for TNF antagonists and vedolizumab, 59.9 % (95 % CI: 37.2–80.8 %) for vedolizumab and tofacitinib, and 47.0 % (95 % CI: 14.5–80.7 %) for vedolizumab and ustekinumab [23]. Pooled endoscopic remission rates among patients on TNF antagonists and vedolizumab 18.0 % (95 % CI: 1.6–41.8 %), and 24.6 % ((95 % CI: 6.4–47.6 %) for tofacitinib and vedolizumab. These studies preceded the approval of upadacitinib and filgotinib, hence the use of JAK inhibitors for UC was limited to tofacitinib and no JAK inhibitors were used in CD.

The pooled rates of adverse events and serious adverse events were 31.4 % (95 % CI: 12.9–53.7 %) and 6.5 % (95 % CI: 2.1–13.1 %) [22]. Significant heterogeneity between studies was noted for these outcomes. Rates of adverse events and serious adverse events were broadly comparable between individual treatment combinations [23]. Infections were the most reported serious adverse events. The pooled rate of adverse events in meta-analyses are impacted by the RCT of infliximab combined with natalizumab, where the adverse event rate was 92 %, reflecting the more thorough recording in this study, compared to retrospective observational data [27]. The commonest adverse events were headache, fatigue, worsening of CD (which was not captured as an adverse event by most observational studies), dizziness, and nasopharyngitis – the rates were not significantly different in the infliximab monotherapy study arm.

4. Clinical trials

4.1. State of the art

Key trials such as the VEGA [28], the EXPLORER [29], and the ongoing DUET—as well as the foundational study by Sands et al. [27] that focused on natalizumab and infliximab, clearly demonstrate both the significant potential and the inherent challenges of utilizing combination therapies (Table 2). In 2007 Sands et al. evaluated the efficacy and safety of a TNF-antagonist agent, infliximab, in conjunction with an anti-integrin, natalizumab, within a cohort of patients diagnosed with active CD despite ongoing infliximab treatment [30]. The trial encompassed 79 individuals with moderate-to-severe CD and primarily focused on assessing safety, driven by initial concerns regarding the risks associated with using concurrent biologic therapies. The findings indicated that the rates of adverse events were similar between the combination

Table 2
Summary of the RCTs on ACT in patients with IBD.

Trial	Study Focus	Phase	Participants	Primary Outcomes	Key Findings
Sands et al. (2007)	Infliximab combined with natalizumab in moderate to severe CD	Phase 4	79 patients with active CD despite ongoing Infliximab	Short-term safety and tolerability of natalizumab in patients concurrently receiving infliximab	Non-significant decrease in CDAI score for combination therapy. No major safety signals
Feagan et al. VEGA (2023)	Combination of guselkumab (IL-23p19 inhibitor) and golimumab (TNF antagonist) in moderate to severe UC	Phase 2b	214 biologic-naive participants with moderate-to-severe UC	Clinical response at week 12 (≥30 % decrease from baseline in the full Mayo score and a ≥3 points absolute reduction with either a decrease in rectal bleeding score of ≥1 point or a rectal bleeding score of 0 or 1)	Clinical response w12: 83.1 % (59/71) with ACT vs 61 % (golimumab monotherapy) and 75 % (guselkumab monotherapy). At least one AE at w50: 63 % with ACT vs 76 % (golimumab monotherapy) and 65 % (guselkumab monotherapy)
Colombel et al. EXPLORER (2024)	Triple therapy of vedolizumab, adalimumab, and methotrexate for biologic-naïve, newly diagnosed high-risk CD	Phase 4	55 participants with newly diagnosed high-risk CD	Endoscopic remission at 26 weeks (SES-CD ≤2)	Endoscopic remission at w26: 34.5 % with ACT Clinical remission w10 and 26: 61.8 % and 54.5. Post-Bayesian analysis: triple ACT likely outperformed placebo (99.9 %), vedolizumab monotherapy (86.3 %), and adalimumab monotherapy (71.4 %) in achieving endoscopic remission. 6 serious AEs with triple: small-intestine obstruction, CD, lymphadenopathy, pyrexia, gastroenteritis, perirectal abscess
DUET-UC (NCT05242484) DUET-CD (NCT05242471)	UC: Dual therapy of guselkumab and golimumab in moderate to severe UC CD: Dual therapy of Guselkumab and Golimumab in moderate to severe CD	UC: Phase 2b CD: Phase 2b	UC: Participants with moderately to severely active UC CD: Participants with moderately to severely active CD	UC: Percentage of Participants with Clinical Remission at Week 48 (mMS) CD: Percentage of Participants with Clinical Remission at Week 48 (CDAI). Percentage of Participants with Endoscopic Response at Week 48 (SES-CD)	UC: No results yet CD: No results yet
VICTRIVA (NCT06227910)	Short- and long-term efficacy and safety of ACT vedolizumab and oral upadacitinib in moderate to severe CD	CD: Phase 3	Participants with moderately to severely active CD	Percentage of Participants with Clinical Remission at Week 12 (CDAI) Percentage of Participants with Endoscopic Response at Week 12 (SES-CD)	No results yet
Target-CD (NCT06548542)	Efficacy and safety of different ACTs in moderate to severe CD Risankizumab and ABBV-382 Risankizumab and Lutikizumab	CD Platform Phase 2 trial	Participants with moderately to severely active CD	Percentage of Participants with Endoscopic Remission at Week 12 (SES-CD)	No results yet

Abbreviations: AE: adverse events; CD: Crohn's Disease; CDAI: mMS: modified Mayo Score; SES-CD: Simple Endoscopic Score for Crohn's Disease; UC: Ulcerative Colitis.

group (27 %) and the infliximab monotherapy group (30 %). This is reassuring about the safety of combination therapies. Additionally, although remission rates favored ACT (46 % compared to 41 %), this difference did not reach statistical significance. Importantly, this study underscored the necessity for rigorous monitoring of adverse events, considering that the application of combination biologics was innovative at that time. The limited statistical power for efficacy outcomes illustrated the challenges associated with early research on combination therapies, which predominantly concentrated on safety and tolerability. Nevertheless, the findings provided an essential foundation for future investigations, suggesting that with careful patient selection and monitoring, ACT could represent a viable treatment option.

The VEGA trial represents a milestone in ACT, assessing the efficacy of combining guselkumab (IL-23p19 inhibitor) with golimumab (TNF-antagonist) in moderate-to-severe UC [28]. This phase 2, proof-of-concept study enrolled biologic-naive patients who had failed conventional therapies, randomizing them to receive either ACT or monotherapy with guselkumab or golimumab. Clinical response at week 12 (defined as ≥30 % decrease from baseline in the full Mayo score and a decrease of ≥3 points with either a decrease in rectal bleeding score of ≥1 point or a rectal bleeding score of 0 or 1) was achieved in 83.1 % (59/71) of patients receiving ACT, noticeably higher than the 74.6 % (adjusted treatment difference 8.5 % [–0.2 to 17.1; nominal $p = 0.2155$) and 61.1 % (adjusted treatment difference 22.1 % [80 % CI: 12.9 to 31.3]; nominal $p = 0.0032$) observed in the guselkumab and golimumab monotherapy groups, respectively. ACT also showed a marked increase in rates of mucosal healing, a composite endpoint including endoscopic improvement and histologic remission (40.8 % for combination versus 26.8 % and 15.3 % for guselkumab and golimumab monotherapy, respectively). Safety outcomes in VEGA are noteworthy, given the dual modulation of immune pathways. Only one patient developed a serious infection (influenza complicated by sepsis) among the combination group, suggesting an acceptable safety profile within the study period. The genomic data added insight, with ACT yielding more extensive modulation of inflammatory genes than monotherapy. Specifically, combination treatment led to 4776 gene upregulations, compared to 495 and 633 in the guselkumab and golimumab arms, respectively, indicating a robust suppression of the inflammatory response and improved epithelial homeostasis [6]. This suggests that ACT may achieve deeper and sustained disease control, particularly in biologic-naive patients.

The EXPLORER trial built upon the VEGA approach by investigating a triple therapy regimen for CD [29]. This regimen combined vedolizumab, adalimumab, and methotrexate for patients with recent diagnoses and high-risk disease profiles. In this open-label phase 4 study, participants received vedolizumab infusions along with adalimumab and methotrexate during the induction phase, followed by vedolizumab monotherapy. The primary endpoint was endoscopic remission at 26 weeks, defined as a Simple Endoscopic Score for CD (SES-CD) of ≤2, while secondary endpoints included clinical remission at 10 and 26 weeks. Results showed that 34.5 % of patients achieved endoscopic remission, and 54.5 % were in clinical remission at 26 weeks, indicating

that ACT might provide a meaningful benefit in early CD by improving both mucosal healing and clinical outcomes. Since the trial lacked a placebo or monotherapy arm, statistical comparisons relied on a post hoc Bayesian analysis, which estimated the probability of achieving higher remission rates compared to historical benchmarks from prior studies of placebo, vedolizumab, and adalimumab monotherapy. This Bayesian framework allowed for robust probability assessments with credible intervals, facilitating comparisons even without a direct control group. The findings provide valuable insights into the safety and efficacy of tailored combination therapy in CD, underscoring its potential for specific patient subgroups.

The VEGA and the Sands studies highlight the potential of ACT to effectively manage complex cases of IBD, particularly in patients who do not respond to standard treatments. EXPLORER suggests that early ACT may improve outcomes in patients with recent-onset CD affecting the ileum and/or colon, meriting further exploration of this approach.

Most recently a systematic review including 10 RCT involving 1154 patients with IMID (not only IBD, but also RA and systemic lupus erythematosus) compared ACT with single-agent therapy (monotherapy) [31]. Eight of the ten trials focused on anti-TNF-α drugs (such as etanercept, infliximab, golimumab, and certolizumab) combined with another biologic (e.g., anti-IL-23, anti-integrin, anti-IL-1) or an oral small molecule. In patients with RA (n = 7 RCTs), there was no significant difference in achieving clinical remission between ACT and monotherapy (RR, 1.75 [95 % CI 0.60–5.13]; moderate heterogeneity [I^2 = 33 %]). For systemic lupus erythematosus (n = 1), the results were similar, showing no significant difference (RR, 1.20 [0.53–2.72]) with low certainty evidence (GRADE). Patients with RA receiving ACT experienced a higher likelihood of adverse events (RR, 1.07 [1.01–1.12]) compared to those on monotherapy. In patients with IBD (n = 2), ACT was associated with higher rates of clinical remission (RR, 1.68 [1.15–2.46]) and minimal heterogeneity (I^2 = 15 %) with low certainty evidence (GRADE). There were no differences in adverse events (RR, 0.92 [0.80–1.05]), nor in the risk of infections or serious infections in either rheumatological diseases or IBD. Based on these findings, authors concluded that ACT did not demonstrate a clinical benefit for patients with rheumatological IMIDs and was associated with a higher rate of adverse events in those with RA. Conversely, ACT may offer clinical benefit in patients with IBD without a clear safety signal, although further trials are warranted.

4.2. What is next?

The DUET-UC (NCT05242484) and DUET-CD (NCT05242471) trials are Phase 2 studies that evaluate the efficacy and safety of combining guselkumab and golimumab for treating moderate-to-severe UC and CD. These trials are designed as dose-ranging studies, testing high, medium, and low doses of the combination therapy for both induction and maintenance phases. Preliminary findings indicate improved rates of clinical remission and mucosal healing, particularly in patients who have not responded to single-agent therapies. The safety profile is still under evaluation, with a focus on monitoring for infections due to the risks associated with immune modulation.

A key trial in ACT development is the VICTRIVA trial (NCT06227910), a phase 3b randomized, double-blind, placebo-controlled trial investigating the combination of vedolizumab and upadacitinib for induction in patients with moderately to severely active CD. This trial compares the efficacy and safety of vedolizumab plus upadacitinib combination therapy with vedolizumab monotherapy, followed by vedolizumab maintenance therapy after induction. The VICTRIVA trial is the first to explore a combination therapy during the induction phase, followed by a monotherapy maintenance phase. This innovative design aims to capitalize on the potent effects of combination therapy during the induction period, while transitioning to vedolizumab monotherapy for sustained maintenance.

The Target CD trial (NCT06548542) is a platform study designed to evaluate multiple therapies for CD in parallel. Participants are randomized into various treatment arms for the first 24 weeks (induction and maintenance phases), with options including risankizumab monotherapy, ABBV-382 monotherapy, lutikizumab monotherapy, or combination therapies of risankizumab and ABBV-382 or risankizumab and lutikizumab. Following the initial phase, participants enter a long-term extension from week 24 to week 96, where they continue with risankizumab monotherapy. The platform design allows for the simultaneous testing of different therapies and combinations, providing flexible evaluation of their effectiveness and safety [32].

5. Summary

The continued development of ACT in IBD is promising. For patients with complex IBD who are refractory to multiple therapies, ACT offers a targeted approach to disease management. Selecting appropriate candidates—those with high-risk phenotypes or overlapping conditions like EIMs or IMIDs—is essential, as is balancing the potential risks of combination therapy against the risks of disease progression. However, it is important to emphasize that ACT remains entirely off-label, and as such, should be approached with caution. Due consideration must be given to alternative treatment strategies, including surgery, especially in patients with refractory disease. Shared decision-making with patients, considering the risks, benefits, and available options, is essential in guiding treatment decisions. Optimal initiation timing hinges on the severity of disease activity, often beginning when the threat of uncontrolled disease outweighs concerns of added therapeutic risk. This treatment should ideally occur in specialized centres with multidisciplinary teams, ensuring comprehensive care and access to clinical trials for patients with limited options. Various combination strategies, including recycling previously effective agents, simultaneous induction, or add-on approaches, offer flexibility based on patient history and disease presentation. Selection of agents, such as anti-TNFs for CD (especially with ileal involvement), vedolizumab for UC, or JAK inhibitors for overlapping conditions, is key to tailoring regimens with favourable safety profiles. Rigorous monitoring and reassessment every six months help ensure safety and efficacy, adjusting treatment as needed. Future research should focus on refining optimal drug combinations, duration of treatment, and cost-effectiveness, which will likely improve as more biosimilars become available, making these advanced treatments more accessible and economically viable. New classes of therapies are emerging to overcome existing limitations, particularly in patients who are refractory to conventional therapies. The incorporation of novel biomarkers to help identify responders to specific combinations will likely be necessary to realize the full potential of ACT. Meanwhile, ongoing clinical trials will be essential to evaluate the efficacy and safety of these advanced therapeutic approaches, particularly in well-defined cohorts. In conclusion, ACT shows potential as a new therapeutic paradigm in IBD, and promising results from preclinical, real-world studies warrant further exploration in carefully designed clinical trials. These studies suggest that targeting multiple immune pathways can lead to higher remission rates and better disease control markers, potentially raising the therapeutic ceiling (Fig. 1). However, the primary safety concerns associated with ACT include the risk of infections and potential long-term effects of immunosuppression. These risks underscore the importance of carefully selecting patients for this therapy, ensuring it is reserved for those with refractory disease, a high risk of complications, or concurrent immune-mediated conditions. Future research should focus on optimizing dosing regimens and identifying the patient profiles that would benefit most from these advanced therapies while minimizing risks. The findings from these trials advocate for a shift toward more personalized, multi-targeted treatment approaches in IBD, highlighting the need for ongoing research to fully realize the benefits of ACT in clinical practice.

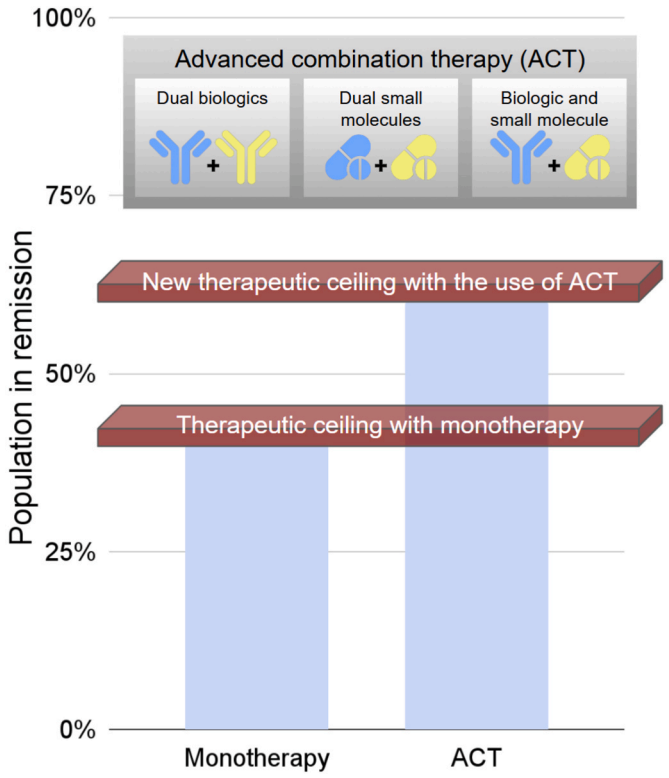

Fig. 1. Reaching the therapeutic ceiling in IBD: Can Advanced Combination Treatment (ACT) provide a solution? Targeting multiple immune pathways may enhance remission rates and optimize disease control.

CRediT authorship contribution statement

Virginia Solitano: Conceptualization, Writing – original draft, Writing – review & editing. **Jurij Hanžel:** Writing – original draft, Writing – review & editing. **Maria Manuela Estevinho:** Writing – original draft, Writing – review & editing. **Rocio Sedano:** Conceptualization, Writing – original draft, Writing – review & editing. **Luca Massimino:** Visualization. **Federica Ungaro:** Supervision. **Vipul Jairath:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Role of the funding source

This article/work received no external funding.

Declaration of competing interest

VS has received speaker's fees from Pfizer.

MME, LM, FU do not have conflict of interests.

JH has received consultancy fees from Alimentiv Inc, speaker's fees from AbbVie, Eli Lilly, and Takeda.

RS has received consultancy fees from Alimentiv Inc.

VJ has received has received consulting/advisory board fees from AbbVie, Alimentiv, Anaptyis Bio, Arena pharmaceuticals, Asahi Kasei Pharma, Asieris, Astra Zeneca, Bristol Myers Squibb, Celltrion, Eli Lilly, Endpoint Health, Enthera, Ensho, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Innomar, JAMP, Janssen, Merck, Metacrine, Mylan, MRM Health, Pandion, Pendopharm, Pfizer, Protagonist, Prometheus Biosciences, Reistone Biopharma, Roche, Roivant, Sandoz, Second Genome, Sorriso, Spyre, Synedgen, Takeda, Teva, Ventyx, Vividion; speaker's fees from, Abbvie, Ferring, Bristol Myers Squibb, Eli Lilly, Fresenius Kabi, Janssen, Pfizer, Shire, Takeda, Tillotts.

References

[1] Frolkis AD, Dykeman J, Negron ME, Debruyn J, Jette N, Fiest KM, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. Gastroenterology 2013;145(5):996–1006.
[2] Raine T, Danese S. Breaking through the therapeutic ceiling: what will it take? Gastroenterology 2022;162(5):1507–11.
[3] Ben-Horin S, Novack L, Mao R, Guo J, Zhao Y, Sergienko R, et al. Efficacy of biologic drugs in short-duration versus long-duration inflammatory bowel disease: a systematic review and an individual-patient data meta-analysis of randomized controlled trials. Gastroenterology 2022;162(2):482–94.
[4] Magro F, Moreira PL, Catalano G, Alves C, Roseira J, Estevinho MM, et al. Has the therapeutical ceiling been reached in Crohn's disease randomized controlled trials? A systematic review and meta-analysis. United European Gastroenterol J 2023;11(2):202–17.
[5] Mao R, Chen M. Precision medicine in IBD: genes, drugs, bugs and omics. Nat Rev Gastroenterol Hepatol 2022;19(2):81–2.
[6] D'Amico F, Fiorino G, Furfaro F, Allocca M, Roda G, Loy L, et al. Patient's profiling for therapeutic management of inflammatory bowel disease: a tailored approach. Expet Rev Gastroenterol Hepatol 2020;14(9):765–73.
[7] Noor NM, Lee JC, Bond S, Dowling F, Brezina B, Patel KV, et al. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. Lancet Gastroenterol Hepatol 2024;9(5):415–27.
[8] Solitano V, Ma C, Hanžel J, Panaccione R, Feagan BG, Jairath V. Advanced combination treatment with biologic agents and novel small molecule drugs for inflammatory bowel disease. Gastroenterol Hepatol 2023;19(5):251–63.
[9] Danese S, Solitano V, Jairath V, Peyrin-Biroulet L. The future of drug development for inflammatory bowel disease: the need to ACT (advanced combination treatment). Gut 2022;71(12):2380–7.
[10] Atreya R, Neurath MF. Mechanisms of molecular resistance and predictors of response to biological therapy in inflammatory bowel disease. Lancet Gastroenterol Hepatol 2018;3(11):790–802.
[11] Bendele AM, Chlipala Es Fau - Scherrer J, Scherrer J, Fau - Frazier J, Frazier J, Fau - Sennello G, Sennello G, Fau - Rich WJ, Rich Wj, Fau - Edwards 3rd CK, et al. Combination benefit of treatment with the cytokine inhibitors interleukin-1 receptor antagonist and PEGylated soluble tumor necrosis factor receptor type I in animal models of rheumatoid arthritis. Arthritis Rheum 2000;43(12):2648–59.
[12] Bendele A, Sennello G, Fau - McAbee T, McAbee T, Fau - Frazier J, Frazier J, Fau - Chlipala E, Chlipala E Fau - Rich B, Rich B. Effects of interleukin 1 receptor antagonist alone and in combination with methotrexate in adjuvant arthritic rats. J Rheumatol 1999;26(6):1225–9.
[13] Feige U, Hu Yl Fau - Gasser J, Gasser J, Fau - Campagnuolo G, Campagnuolo G, Fau - Munyakazi L, Munyakazi L, Fau - Bolon B, Bolon B. Anti-interleukin-1 and anti-tumor necrosis factor-alpha synergistically inhibit adjuvant arthritis in Lewis rats. Cell Mol Life Sci 2000;57(10):1457–70.
[14] Seki I, Takai-Imamura M, Kohara-Tanaka T, Shirae S, Sasano M, Matsuno H, et al. Concomitant treatment with etanercept and tacrolimus synergistically attenuates arthritis progression via inhibition of matrix metalloproteinase-3 production and osteoclastogenesis in human TNF-α transgenic mice. Mediat Inflamm 2019;2019:4176974.
[15] Llop-Guevara A, Porras M, Cendón C, Di Ceglie I, Siracusa F, Madarena F, et al. Simultaneous inhibition of JAK and SYK kinases ameliorates chronic and destructive arthritis in mice. Arthritis Res Ther 2015;17:356.
[16] Kang SE, Park JK, Yoo HJ, Kang HS, Park YW, Park BC, et al. Efficacy of novel bispecific antibody targeting TNF-α/CXCL10 in the treatment of experimental arthritis. Transl Res 2021;232:75–87.
[17] Schmitt H, Billmeier U, Dieterich W, Rath T, Sonnewald S, Reid S, et al. Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn's disease. Gut 2019;68:814–28.
[18] Perrigoue J, Muniz-Bongers L, Ong L, Chen Y, Chang L, Ngo K, et al. P328 in silico evaluation and pre-clinical efficacy of anti-TNF and anti-IL-23 combination therapy in Inflammatory Bowel Disease. J Crohn's Colitis 2022;16(1):i348–9.
[19] Roberts KJ, Cubitt MF, Carlton TM, Rodrigues-Duarte L, Maggiore L, Chai R, et al. Preclinical development of a bispecific TNFα/IL-23 neutralising domain antibody as a novel oral treatment for inflammatory bowel disease. Sci Rep 2021;11(1):19422.
[20] Wang J, Kang G, Lu HA-O, de Marco A, Yuan H, Feng Z, et al. Novel bispecific nanobody mitigates experimental intestinal inflammation in mice by targeting TNF-α and IL-23p19 bioactivities. Clin Transl Med 2024;4:e1636.
[21] Cui X, Teng Y, Hu Y, Li Q, Pei H, Yang Z. Therapeutic potential of a synthetic dual JAK1/TYK2 inhibitor in inflammatory bowel disease. Int Immunopharm 2024;126:111238.
[22] Ahmed W, Galati J, Kumar A, Christos PJ, Longman R, Lukin DJ, 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(3):e361–79.
[23] Alayo QA, Fenster M, Altayar O, Glassner KL, Llano E, Clark-Snustad K, et al. Systematic review with meta-analysis: safety and effectiveness of combining biologics and small molecules in inflammatory bowel disease. Crohns Colitis 2022;4(1):otac002.
[24] Berinstein EM, Sheehan JL, Jacob J, Steiner CA, Stidham RW, Shannon C, 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(6):2604–23.

[25] Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manip Physiol Ther 2004;27(1):26–35.
[26] Solitano V, Facciorusso A, Jess T, Ma C, Hassan C, Repici A, 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 : Official Clin Practice J Am Gastroenterol Associat 2023;21(4):907–21.
[27] Sands BE, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission whil receiving infliximab. Inflamm Bowel Dis 2007;13:2–11.
[28] Feagan BG, Sands BE, Sandborn WJ, Germinaro M, Vetter M, Shao J, 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(4):307–20.
[29] Colombel JF, Ungaro RC, Sands BE, Siegel CA, Wolf DC, Valentine JF, et al. Vedolizumab, adalimumab, and methotrexate combination therapy in Crohn's disease (EXPLORER). Clin Gastroenterol Hepatol 2024;22(7):1487–96.
[30] Sands BE, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, 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(1):2–11.
[31] Solitano V, Yuan Y, Singh S, Ma C, Nardone OM, Fiorino G, et al. Efficacy and safety of Advanced Combination Treatment in immune-mediated inflammatory disease: a systematic review and meta-analysis of randomized controlled trials. J Autoimmun 2024;149:103331.
[32] Ma C, Solitano V, Danese S, Jairath V. The future of clinical trials in inflammatory bowel disease. Clin Gastroenterol Hepatol 2024.