Advanced Combination Treatment With Biologic Agents and Novel Small Molecule Drugs for Inflammatory Bowel Disease

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Abstract: The use of combination therapy with a biologic agent and immunosuppressant has well-established efficacy and safety and is common practice in the management of inflammatory bowel disease (IBD). Current research has shifted focus toward the use of advanced combination treatment (ACT). This term was coined to describe combination therapy using 2 or more advanced treatments (biologic agents and/or oral small molecule drugs) with the aim of achieving optimal disease control in selected patients. An ACT approach may be particularly beneficial in patients with documented medically refractory IBD and in patients with a poor prognosis, extraintestinal manifestations, or concomitant immune-mediated inflammatory diseases. To date, the body of evidence for ACT strategies in IBD is largely comprised of uncontrolled retrospective case series and cohort studies in highly refractory patients. Recently, results from the VEGA trial have suggested that combination induction therapy with guselkumab and golimumab was more effective in ulcerative colitis than either agent alone. However, questions remain about issues such as related costs, ACT duration, and optimal combinations to adopt. Future randomized controlled trials are likely to evaluate rationally selected combinations of agents. This article summarizes the available literature on ACT, including comparisons with traditional combination therapy and the rheumatology field, and discusses practical recommendations, profiles of IBD patients who should be considered for combination approaches in clinical practice, and remaining knowledge gaps.

Keywords
Advanced combination treatment, dual biologic therapy, Crohn's disease, ulcerative colitis, inflammatory bowel disease, dual targeted therapy

Multiple new drug classes have recently become available for the treatment of inflammatory bowel disease (IBD), and the drug development pipeline is likely to continue to provide new therapeutic options. However, despite the availability of novel classes of monoclonal antibodies and targeted oral small molecule drugs, a high proportion of patients have an inadequate response or subsequent loss of response to existing advanced therapies. A striking observation is that most advanced therapies report 1-year clinical remission rates of only 30% to 50%,[1-4] even when administered under optimal circumstances in patients naive to conventional agents. These rates are substantially lower for patients who have previously failed 1 or more advanced therapies. Thus, a therapeutic ceiling may have been reached with the use of advanced therapies as monotherapies.

Multiple inflammatory pathways are involved in the development and progression of IBD. This is corroborated by the phenotypic heterogeneity in clinical presentations for both ulcerative colitis (UC) and Crohn's disease (CD). The existence of several cytokine patterns may be a contributing factor explaining why treatment with a single agent is usually not sufficient for durable induction of remission.[5] In clinical practice, therapeutic agents effective for luminal disease may not adequately control extraintestinal manifestations (EIMs), perianal fistulizing disease, or concomitant immune-mediated inflammatory diseases (IMIDs) requiring the use of additional agents.[6,7]

Advanced combination treatment (ACT) is an emerging therapeutic concept that specifies the combination of at least 2 biologic agents or a biologic agent and a small molecule drug with different mechanisms of action.[8] The concept is based upon the notion that simultaneously targeting several pathogenic pathways may provide an additive or even synergistic benefit and could be a promising strategy in a wide range of patients who have failed to achieve disease control with monotherapy alone. In several other fields, such as the treatment of HIV, hepatitis C virus, hypercholesterolemia, and epilepsy, the combination of 2 or more drugs with different mechanisms of action has already been used to rationally produce synergistic effects.[9-12] However, combination compounds should have similar pharmacokinetic characteristics, avoiding irrational polypharmacy that might lead to antagonistic effects or perhaps supra-additive side effects.

Preliminary evidence from clinical practice consisting of case series and uncontrolled observational studies has described the outcomes of ACT in IBD. Recently, the phase 2a VEGA trial demonstrated that combination induction therapy with guselkumab (Tremfya, Janssen) and golimumab (Simponi, Janssen) was more effective than monotherapy in patients with UC, with no increased safety concerns.[13]

This article summarizes the available literature on ACT, including comparisons with traditional combination therapy and the rheumatology field, and discusses practical recommendations, profiles of IBD patients who should be considered for combination approaches in clinical practice, and remaining knowledge gaps.

Traditional Combination Therapy in Inflammatory Bowel Disease

The landmark SONIC and UC-SUCCESS trials provided clear evidence for the use of traditional combination therapy consisting of a biologic agent plus azathioprine in patients with IBD. In both trials, combining the anti–tumor necrosis factor (TNF) agent infliximab with azathioprine was superior to monotherapy and associated with higher corticosteroid-free remission and mucosal healing rates in CD and UC.[14,15] The reason for the greater efficacy of combination therapy observed in these trials has been the subject of considerable debate. Although it is most plausible that dual therapy was more effective because of the previously described effects on multiple inflammatory pathways, other explanations have been proposed. Specifically, a post hoc analysis indicated that higher infliximab concentrations and lower antidrug antibody rates observed in patients who received concomitant azathioprine may have contributed to the additive effect.[16]

In PANTS, a prospective cohort study of 1610 patients with active CD that was conducted in the United Kingdom, the addition of a thiopurine or methotrexate was found to have a protective effect on the development of immunogenicity with similar effect sizes for infliximab-treated patients (hazard ratio [HR], 0.39; 95% CI, 0.32-0.46; $P<.0001$) and adalimumab-treated patients (HR, 0.44; 95% CI, 0.31-0.64; $P<.0001$).[17] Thiopurines were observed to reduce immunogenicity in participants treated with infliximab in a dose-dependent manner. Data from PANTS also suggested that higher remission rates observed at week 54 among patients receiving a concomitant immunosuppressive were independent of drug concentration or antidrug antibody development. This suggests that the addition of an immunosuppressive to anti-TNF therapy may enhance anti-inflammatory effects in distinction to improving pharmacokinetics alone.

The window of opportunity for preventing immunogenicity appears to be during the first months of traditional combination therapy. This observation raises the question of whether continued treatment for more than 6 to 12 months with a concomitant immunosuppressive is necessary. Moreover, observational studies have suggested the potential value of optimizing infliximab exposure by using therapeutic drug monitoring as an alternative

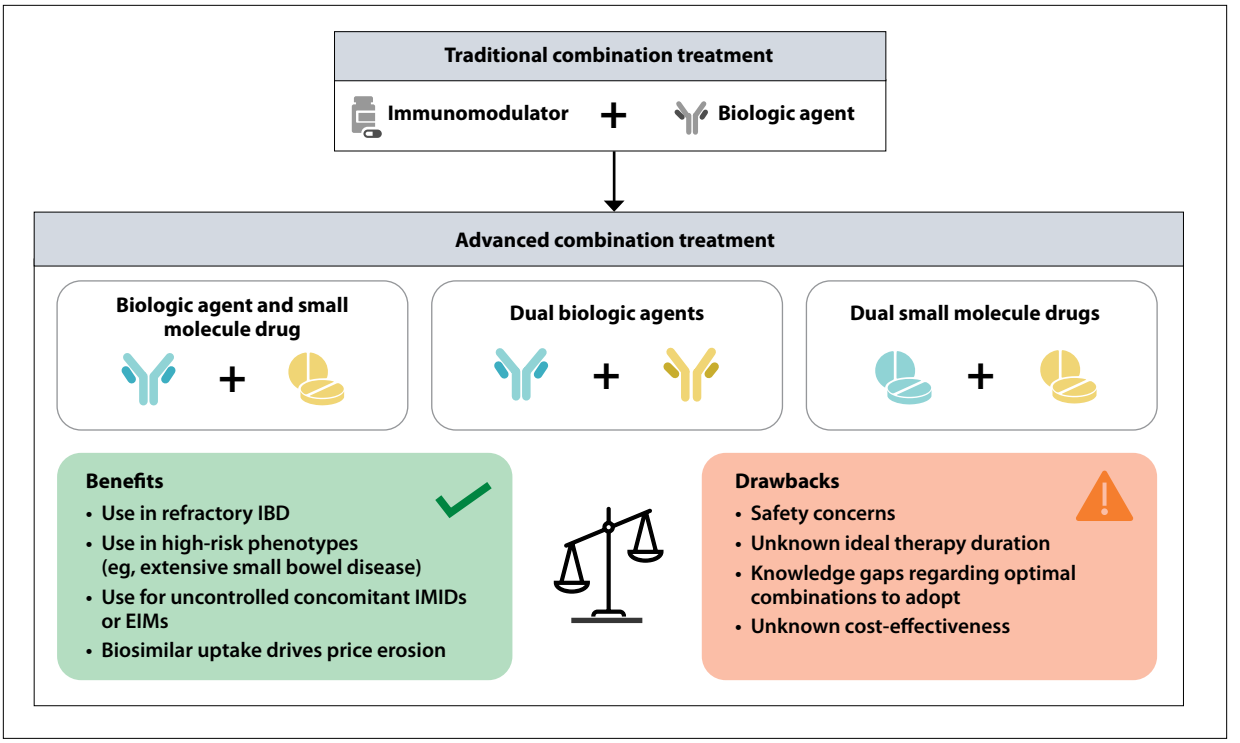

Figure 1. From traditional to advanced combination treatment: weighing benefits and drawbacks.

EIM, extraintestinal manifestation; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease.

strategy to concomitant immunosuppression for the prevention of immunogenicity.[18,19] Additional evidence regarding the role of drug discontinuation comes from the SPARE trial.[20] This open-label study enrolled patients with CD in sustained corticosteroid-free remission for at least 6 months who had received combination therapy with infliximab and either a thiopurine or methotrexate for at least 8 months. Patients were randomized into 3 arms: continuing combination therapy, discontinuing infliximab, or discontinuing immunosuppressive therapy. Withdrawal of immunosuppression did not appear to increase relapse rates (2-year relapse rate, 10%) in patients continuing infliximab monotherapy, whereas the risk of relapse was 36% at 2 years following withdrawal of infliximab.

Advantages of combining anti-TNF agents and immunosuppressive therapy should be weighed against potential safety risks of this approach, including the risk of serious and opportunistic infections. However, in PANTS, combination therapy was not associated with an increased risk of infection in the first year of treatment, even among patients older than 50 years.[17] This result aligned with the SONIC and UC-SUCCESS trials, in which the rates of serious adverse events were not significantly different between the combination arm and the infliximab monotherapy arm.[14,15] Furthermore, real-world data from long-term surveillance registries (eg, the TREAT registry) have not found an increased risk of infection in patients receiving traditional combination therapy compared with monotherapy.[21] Instead, disease activity, corticosteroids, and opiates were identified as key risk factors, highlighting that potential safety concerns associated with immunosuppressive therapy may be offset by improved treatment efficacy and disease control.[17] Accordingly, it is reasonable to speculate that any risks attributable to combined therapy may be offset by greater effects on disease activity and reduced exposure to corticosteroids. However, safety concerns associated with long-term immunosuppression (eg, risk of lymphoma) should always be considered. Following induction of remission with combination therapy, maintenance therapy with a biologic agent as monotherapy is recommended, especially in higher-risk populations such as patients older than 65 years.[22-24]

In summary, traditional combination therapy with a biologic agent and concomitant immunosuppressant therapy has well-studied efficacy and safety and is a common strategy for managing CD and UC. More recently, clinical and research interests have shifted toward the potential applications of ACT modalities with a combination of at least 2 biologic agents, or a biologic agent and a small molecule drug, with the aim of achieving optimal disease control (Figure 1).

Lessons From Rheumatology: From Bench to Bedside

The most robust experimental evidence for the use of ACT in IMIDs has emerged from studies in rheumatoid arthritis (RA), with the first preclinical investigations published more than 20 years ago. Combination therapy with an interleukin-1 (IL-1) receptor antagonist (Ra) and PEGylated soluble tumor necrosis factor receptor type I (PEG sTNFRI) was investigated in rat models of RA with established type II collagen–induced arthritis (CIA).[25] Dual targeted therapy with IL-1Ra and PEG sTNFRI was associated with greater-than-additive efficacy relative to monotherapy with either agent, providing preliminary support for further clinical investigations in patients with RA. In a preclinical study of anti–IL-1 and anti-TNF therapy in a rat model of autoimmune arthritic disease, the synergistic benefits of dual therapy were particularly evident when suboptimal doses of each agent were given.[26] Combination therapy was observed to have substantially superior efficacy over the use of a single class of anticytokine agent, even when combining relatively low doses of anti–IL-1 and anti-TNF agents that did not adequately control inflammation as monotherapy. This raises the possibility that reduced exposure to the individual agents might minimize adverse events.

This line of research led to initiatives to design novel bispecific antibodies that simultaneously target 2 different epitopes.[27] These molecules may improve immunogenic response through modulation of different signaling pathways in the same cell or by engaging different cells expressing either antigen. In addition, dual-affinity retargeting (DART) antibodies can be used to simultaneously bind the target receptors in vitro and in intact cells. Veri and colleagues reported construction of DART antibodies that simultaneously bind CD32B and CD79B on the same B cell, resulting in downregulation of B-cell activation, proliferation, and immunoglobulin secretion.[28] Treatment with a mouse-specific DART antibody reduced disease activity in a CIA murine model. Other bispecifics have been shown to ameliorate inflammation in murine models, providing further support for the concept of dual targeting for the treatment of RA.[29-31]

Despite promising preclinical results, safety concerns have been raised by attempts to treat patients with RA using a combination of at least 2 approved biologic disease-modifying antirheumatic drugs (bDMARDs), including infliximab, etanercept, certolizumab pegol (Cimzia, UCB), adalimumab, golimumab, anakinra (Kineret, Sobi), abatacept (Orencia, Bristol Myers Squibb), rituximab, and tocilizumab (Actemra, Genentech). A systematic review identified 5 randomized controlled trials (RCTs) and 1 observational cohort study that evaluated combination therapy in patients with RA using 2 of the following bDMARDs: anti-TNF agents, anakinra, abatacept, rituximab, and tocilizumab.[32] On meta-analysis, patients receiving combination therapy had a higher rate of serious adverse events compared with the control group (14.9% vs 6.0%; odds ratio, 2.51; 95% CI, 1.29-4.89; I^2 = 0%), particularly during the first 12 months of treatment and in patients receiving a full dose of both agents. Pooled efficacy data from RCTs showed no clear evidence that receiving combination bDMARD therapy was advantageous. Conversely, the single observational study found that combination therapy with rituximab and etanercept was associated with clinical and biological benefits.[33] In this study, patients had persistent, uncontrolled disease activity at enrollment despite previous treatment with up to 6 DMARDs and 3 anti-TNF therapies, denoting a very high-risk study population. After 2 months of rituximab and etanercept combination therapy, all clinical and serologic parameters improved significantly, and no serious infections requiring intravenous therapy or hospitalization were observed.

Of the RCTs included in the aforementioned meta-analysis, 2 evaluated the safety of abatacept, a cytotoxic T lymphocyte–associated antigen-4–immunoglobulin fusion protein, combined with background nonbiologic or biologic DMARDs in patients with active RA.[34,35] Although some improvement in physical function and patient-reported disease outcomes was detected, the rate of adverse events and serious adverse events in the combination therapy group was higher than in the background monotherapy groups. On the other hand, 2 RCTs comparing rituximab monotherapy vs combination rituximab with either an anti-TNF agent or tocilizumab found that combination therapy was generally well tolerated; however, no additive efficacy was observed.[36,37] Finally, a study by Genovese and colleagues of biologic-naive patients with active RA despite methotrexate therapy concluded that combination treatment with the anti–IL-1 agent anakinra and the anti-TNF agent etanercept was not justified owing to an increased risk of serious infection and neutropenia.[38]

In summary, the cumulative experience of ACT in rheumatology has been disappointing in that no clear efficacy signal has been observed and an increased risk of infection relative to monotherapy may have been identified for the combinations evaluated. Although these findings provide a cautionary message about safety outcomes, they do not preclude the possibility of future successful ACT regimens. Based upon the aforementioned RA experience, trial investigators recommend that candidate molecules for these regimens should have the following characteristics. First, strong efficacy as monotherapy should be demonstrated. This was not the case

Table 1. Studies on ACT in Patients With IBD

Authors (year)	Study design	Population	Combination (# of patients)	Safety	Efficacy
Clark-Snustad et al[71] (2020)	Retrospective cohort study	18 CD patients	Tofacitinib + ustekinumab (10) Tofacitinib + vedolizumab (7) Tofacitinib + certolizumab pegol (1)	No AEs reported	Clinical, endoscopic, and biochemical improvement
Dolinger et al[69] (2021)	Retrospective cohort study	16 pediatric IBD patients (9 UC/IBD-unspecified, 7 CD)	Tofacitinib + vedolizumab (9) Vedolizumab + ustekinumab (4) Tofacitinib + ustekinumab (3)	Serious AEs reported in only 1 patient (septic arthritis, deep vein thrombosis)	Corticosteroid-free remission at 6 months
Eronen et al[68] (2022)	Retrospective cohort study	16 IBD patients (1 UC, 15 CD)	Vedolizumab + anti-TNF agent (6) Vedolizumab + ustekinumab (5) Ustekinumab + anti-TNF agent (5)	No serious AEs reported 3 infection complications	Clinical benefit in half of patients
Glassner et al[62] (2020)	Retrospective cohort study	50 IBD patients (18 UC, 31 CD, 1 IBD-undetermined) 10 with concomitant IMID Median number of failed biologic agents=2	53 ACT regimens: Vedolizumab + ustekinumab (25) Tofacitinib + anti-TNF agent (9) Tofacitinib + vedolizumab (8) Vedolizumab + anti-TNF agent (7) Tofacitinib + ustekinumab (3) Anti-TNF agent + apremilast (1)	Serious AEs in 12%	Clinical remission (50% vs 14%; *P*=.0018; Δ36%; 95% CI, 0.13-0.53) and endoscopic remission (34% vs 6%; *P*=.0039; Δ28%; 95% CI, 0.09-0.47) at follow-up compared with baseline
Goessens et al[67] (2021)	Retrospective multicenter cohort study	98 IBD patients (40 UC, 58 CD) 41 with concomitant IMID Median number of failed biologic agents=3	104 ACT regimens: Vedolizumab + anti-TNF agent (41) Anti–IL-4/13, -5, -6, -12/23, -17A, or -23 agent + vedolizumab (21) Tofacitinib + vedolizumab (13) Anti-TNF agent + anti–IL-4/13, -5, -6, -12/23, -17A, or -23 agent (11) Tofacitinib + anti-TNF agent (1) Others (17)	AEs in 42%, mostly related to uncontrolled IBD (10 significant infections, 1 skin cancer)	Improvement of IBD disease activity in 70% Improvement of IMID/EIM activity in 81%
Goyal et al[70] (2020)	Retrospective cohort study	9 pediatric refractory CD patients (1 with concomitant sacroiliitis)	Vedolizumab + anti-TNF agent (8) Infliximab + anakinra (1)	1 serious AE (staphylococcal skin infection)	Clinical remission (44.4%)
Guillo et al[66] (2023)	Ambispective cohort study	213 IMIDs (91 CD, 54 axial spondyloarthritis, 20 UC, 13 rheumatoid arthritis, 9 psoriatic arthritis, 8 psoriasis, 18 others) 73 with 1 IMID 70 with ≥2 IMIDs	Vedolizumab + anti-TNF agent (73) Ustekinumab + anti-TNF agent (70) Vedolizumab + ustekinumab (12)	27 infections reported 3 serious infections leading to discontinuation (*Clostridioides difficile* colitis, *Pseudomonas aeruginosa* lung infection, hemophagocytic syndrome related to zoonosis)	Significant improvement in patient-reported outcomes (50%) Mild-to-moderate improvement (27%)
Kwapisz et al[63] (2021)	Retrospective cohort study	15 refractory IBD patients (1 UC, 14 CD) Median number of failed biologic agents=3.8	Vedolizumab + anti-TNF agent (8) Vedolizumab + ustekinumab (5) Ustekinumab + anti-TNF agent (2)	Infections requiring antibiotics in 27% 3 hospitalizations 3 surgeries 1 discontinuation	Symptomatic improvement in 73% Reduction of corticosteroid use in 67% Endoscopic or radiographic improvement in 44%
Llano et al[72] (2021)	Retrospective cohort study	14 IBD patients (10 UC, 3 CD, 1 indeterminate colitis)	Tofacitinib + vedolizumab (9) Vedolizumab + ustekinumab (3) Vedolizumab + anti-TNF agent (2)	No serious AEs (4 infections reported)	Clinical improvement and biochemical response (>50%)
Lee et al[73] (2022)	Retrospective cohort study	19 refractory CD patients 18 with prior failure of ≥2 biologic agents	Tofacitinib + ustekinumab (11) Tofacitinib + vedolizumab (7) Tofacitinib + certolizumab pegol (1)	AEs in 36.8% of patients (minor infections or CD flares) No serious AEs	Clinical response (80%) Clinical remission (60%) Endoscopic improvement (54.5%)

(Table continues on following page)

Table 1. *(Continued)* Studies on ACT in Patients With IBD

Authors (year)	Study design	Population	Combination (# of patients)	Safety	Efficacy
Privitera et al[64] (2020)	Retrospective cohort study	16 IBD patients (5 UC, 11 CD) 7 with uncontrolled IBD 9 with concomitant IMID	Vedolizumab + anti-TNF agent (6) Ustekinumab + anti-TNF agent (4) Vedolizumab + ustekinumab (3) Vedolizumab + secukinumab (2) Vedolizumab + apremilast (1)	AEs in 18.8% 1 discontinuation	Clinical response in 100%
Yang et al[65] (2020)	Retrospective cohort study	22 refractory CD patients Median number of failed biologic agents=4	24 ACT regimens: Vedolizumab + anti-TNF agent (13) Vedolizumab + ustekinumab (8) Ustekinumab + adalimumab (2) Ustekinumab + infliximab (1)	AEs in 13%	Endoscopic improvement in 43% Endoscopic remission in 26% Clinical response in 50% Clinical remission in 41% Significant posttreatment reduction in median SES-CD (from 14 to 6; $P<.05$) and PRO-2 (from 24.1 to 13.4; $P<.05$)

ACT, advanced combination treatment; AE, adverse event; CD, Crohn's disease; EIM, extraintestinal manifestation; IBD, inflammatory bowel disease; IL, interleukin; IMID, immune-mediated inflammatory disease; PRO-2, patient-reported outcome-2 score; SES-CD, Simplified Endoscopic Score–Crohn's Disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

with respect to the anakinra studies. Second, component agents should be selected for an optimal safety profile; thus, broad-spectrum immunosuppressives are less attractive for evaluation. Finally, proof of concept should be established in animal models and human translational medicine studies before phase 2 studies are conducted.

Use of Advanced Combination Treatment in Inflammatory Bowel Disease

In patients with IBD, there are at least 3 distinct clinical circumstances in which ACT may be considered: (1) patients with IBD that is refractory to multiple medical therapies, including investigational agents; (2) patients with very high-risk phenotypes such as extensive small bowel disease, and stricturing or fistulizing disease behavior; and (3) patients with severe EIMs or an IMID other than IBD such as psoriasis or ankylosing spondylitis that is inadequately controlled by a single mechanism of action alone. In the first scenario, patients with poorly controlled bowel disease refractory to multiple agents might benefit from combination treatment with agents to which they have previously been exposed and experienced partial or no response, provided there is no contraindication to reintroducing a prior therapy (eg, intolerance or the presence of antidrug antibodies). Alternatively, an add-on approach may be considered when there has been inadequate response (based upon signs, symptoms, and/or laboratory values) to a current biologic therapy, and a second agent that has not previously been used is added. In the second scenario, for patients with particular high-risk phenotypes, an ACT approach could offer more timely disease control and prevent complications or progression of bowel disease that could develop through inadequate suppression of inflammation with single agents. In the third scenario, the patient profile comprises patients with both intestinal and extraintestinal disease—or IBD and a concomitant IMID—where inhibiting a single mechanism of action has not provided adequate disease control across multiple organ systems. Here, selection of a second advanced therapy would be made with the goal of targeting potential pathways driving the uncontrolled concomitant disease.

Evidence From Case Series and Observational Studies in Inflammatory Bowel Disease

The body of evidence for the use of ACT in patients with IBD is growing. More than 20 case series and reports spanning a range of clinical scenarios have been published,[39-61] and several retrospective and uncontrolled observations[62-68] have investigated the outcomes of ACT approaches in patients with refractory intestinal disease, or IBD and a concomitant EIM or IMID (Table 1).

Yang and colleagues provided data on the use of ACT in a high-risk group of patients with medically refractory CD.[65] Of note, the majority of patients had undergone prior surgical resections, had stricturing or fistulizing disease, and failed a median of 4 biologic agents. The most common combinations included vedolizumab (Entyvio, Takeda) and ustekinumab (Stelara, Janssen). The majority

of ACT regimens (79%) included at least 1 biologic agent that had previously induced initial response with secondary nonresponse (recycling strategy), and 29% of ACT trials utilized a compound that had not been previously administered. Almost 50% of patients treated with dual therapy had clinical and endoscopic improvements (41% achieved clinical remission, 43% endoscopic improvement). Compared with baseline, significant post-treatment reductions were reported for median Simplified Endoscopic Score (SES)-CD (from 14 to 6; $P<.05$) and patient-reported outcome–2 score (from 24.1 to 13.4; $P<.05$).

A retrospective cohort study examined data from 50 patients in the United States with medically refractory IBD (31 with CD, 18 with UC, 1 with IBD-undetermined) who received ACT from 2015 to 2019.[62] Ten patients were affected by a concomitant IMID. Vedolizumab and ustekinumab were most frequently combined (47.2%). Twenty patients received a combination of the small molecule Janus kinase (JAK) inhibitor therapy tofacitinib (Xeljanz, Pfizer), with either an anti-TNF agent (16.9%), vedolizumab (15.1%), or ustekinumab (5.7%). The combination of vedolizumab and an anti-TNF agent was administered in 13.3%. At follow-up, increased rates of clinical remission (50% vs 14%; $P=.0018$; Δ36%; 95% CI, 0.13-0.53) and endoscopic remission (34% vs 6%; $P=.0039$; Δ28%; 95% CI, 0.09-0.47) were found when compared with baseline. With respect to safety outcomes, 23 adverse events were reported. Eight of these were serious infections that, according to the authors, may have been observed in the course of CD and were not necessarily related to combination treatment (eg, abdominal wall abscesses, peristomal cellulitis, peripherally inserted central catheter line infections).

More recently, the results of a large ambispective French cohort study of 143 patients with IMIDs treated with ACT were published.[66] This study provided examples of ACT use in cases of either highly refractory disease after the failure of multiple treatment lines or concomitant uncontrolled IMIDs. Patients with CD comprised the majority of the study population (63.6%), followed by patients with axial spondyloarthritis (37.7%), UC (14%), RA (9.1%), psoriatic arthritis (6.3%), and psoriasis (5.6%). Nearly half of the patients had 2 IMIDs. The 3 most frequent combinations were an anti-TNF agent and vedolizumab (30%), an anti-TNF agent and ustekinumab (28.7%), and vedolizumab and ustekinumab (8%). Corroborating previous results, this study found that ACT appeared to be effective in achieving significant (50%) and mild-to-moderate (27%) improvement in patient-reported outcomes at the end of follow-up. The authors also noted that ACT in patients with 2 diseases resulted in a numerically higher rate of significant improvement compared with patients with a single disease. Overall, 27 infections occurred during the study. Seven of these occurred in patients receiving an immunosuppressant, either azathioprine or methotrexate, in addition to ACT. Most infections were considered to be mild to moderate; however, there were 9 cases of serious infections, of which 3 were associated with methotrexate use.

Few studies have looked specifically at the effect of combination therapy in pediatric patients.[51,69,70] Although the available evidence is scarce, combination therapy (including 2 biologic agents or 1 biologic agent and tofacitinib) appears to be a promising strategy in younger populations, who have limited therapeutic options, and few serious adverse events have been reported.

Regarding the use of oral small molecule drugs, emerging evidence suggests that the combination of tofacitinib with a biologic agent, mainly vedolizumab or ustekinumab, induces clinical response and endoscopic improvements without triggering any new safety signals in patients with refractory active disease.[71-73]

A large amount of observational data has accumulated supporting a number of ACT regimens; however, these studies have been initiated by investigators and have lacked adequate controls and randomized designs.

Clinical Trials in Inflammatory Bowel Disease

The first RCT evaluating dual biologic drugs in IBD was conducted by Sands and colleagues in 2007 in which 79 patients with active CD (Crohn's Disease Activity Index score ≥150) receiving infliximab treatment were randomized to receive either an anti-integrin agent, natalizumab (Tysabri, Biogen), or placebo.[74] It should be noted that the primary objective was to evaluate safety and tolerability because regulatory authorities were concerned about the potential toxicity of overlapping the agents in clinical practice; therefore, the study was not statistically powered to evaluate any potential efficacy differences among the treatment regimens. The authors found that the proportion of patients experiencing adverse events was similar between the combination and monotherapy groups (27% vs 30%, respectively). A higher proportion of patients in the combination group achieved clinical remission over the course of the study compared with the infliximab monotherapy arm (46% vs 41%, albeit P=not significant).

The VEGA study was a phase 2 induction trial that evaluated the combination of an anti–IL-23 agent (guselkumab) and an anti-TNF agent (golimumab) in 214 patients who had moderately to severely active UC bio-naive to anti-TNF agents and who had a history of inadequate response or failure to conventional therapy.[13] Results supported both the efficacy and safety of ACT

Table 2. Key Recommendations for the Use of ACT in Clinical Practice

Who	Patients with IBD refractory to multiple medical therapies Patients with very high-risk phenotypes Patients with a concomitant EIM/IMID
When	The risk of doing nothing (eg, uncontrolled disease) is higher than the risk of adding a combination molecule
Where	Centers with clinical expertise and multidisciplinary teams
Why	Differential and combination mechanisms of action with dual targeted treatments Lack of available options for inducing and maintaining remission and response
How	• Recycling strategy (using at least 1 agent already administered) • Simultaneous induction (starting with 2 new agents) • Add-on strategy (adding a new compound later on)
	Preference for agents with the most favorable safety profiles (eg, vedolizumab, ustekinumab), especially in frail or elderly patients
	Preference for an anti-TNF agent in CD, especially in ileal CD or with bowel damage
	Preference for vedolizumab in UC patients
	Preference for an anti-TNF agent or ustekinumab (or anti–IL-23 blocker when approved) or a JAK inhibitor in patients with concomitant EIM or IMID
Unknown areas	Most appropriate combinations to administer Treatment duration Cost-effectiveness of combination regimens

ACT, advanced combination treatment; 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.

with guselkumab and golimumab in this population. A greater proportion of patients receiving combination therapy achieved the primary outcome of clinical response after 12 weeks (59/71; 83.1%) compared with monotherapy with either guselkumab (53/71; 74.6%) or golimumab (44/72; 61.1%). The comparison with golimumab monotherapy met the perceived criterion for significance. Clinical remission rates were higher for the combination group compared with either monotherapy. Furthermore, mucosal healing, a composite outcome defined as endoscopic improvement and histologic remission, was achieved in approximately twice as many patients treated with ACT (40.8%) compared with guselkumab (26.8%) or golimumab (15.3%) monotherapy. A favorable safety profile was reported, and only 1 patient developed a serious infection of influenza and sepsis of the 72 patients treated with ACT. Interestingly, a large change relative to baseline in genes associated with the T helper 17 axis, inflammation, and epithelial homeostasis was observed in the combination arm; the number of genes upregulated at week 12 was 633, 495, and 4776 for golimumab monotherapy, guselkumab monotherapy, and combination therapy, respectively, and the number of genes downregulated at week 12 was 709, 613, and 4867 in the 3 groups, respectively.[75] Genes modulated by anti-TNF and anti–IL-23 agents are suggestive of more robust suppression of inflammatory pathways, with decreased T helper 17 activity and increased epithelial modulation. Genes modulated by anti-TNF and anti–IL-23 agents are suggestive of more robust suppression of inflammatory pathways, with decreased T helper 17 activity and increased epithelial normalization.

Based upon these promising results, two phase 2 RCTs are currently investigating combination therapy with guselkumab and golimumab in moderately to severely active UC (DUET-UC; NCT05242484) and CD (DUET-CD; NCT05242471). In contrast to the VEGA trial, these are dose-ranging studies exploring 3 different doses of combination therapy (high, mid, and low) with either monotherapy or placebo for both induction and maintenance of remission.

The potential advantages of a vedolizumab-based triple combination therapy are being evaluated in the EXPLORER trial (NCT02764762) in patients with a diagnosis of CD established within 24 months of study entry. Participants were selected for increased risk of complications using a scoring system and had documented endoscopic disease activity (SES-CD score ≥7, or ≥4 if isolated ileal disease). In this open-label, phase 4 trial, all participants received vedolizumab infusions (at weeks 0, 2, 6, 14, and 22), adalimumab subcutaneous injections (every 2 weeks until week 26), and oral methotrexate (15 mg to week 34). After coinduction, all participants received vedolizumab monotherapy for a follow-up period of 102 weeks. An interim analysis showed that the primary outcome of endoscopic remission (SES-CD score 0-2) at 26 weeks was reached in 34.5% of patients and that more than 50% of patients were in clinical remission at this time point.[76] Over the 26-week period, more than one-third of patients (36%) developed an infection; however, only 2 cases (perirectal abscess, gastroenteritis) were considered serious, and it was not apparent that any increase in infectious complications was evident beyond the expected incidence in this patient population.

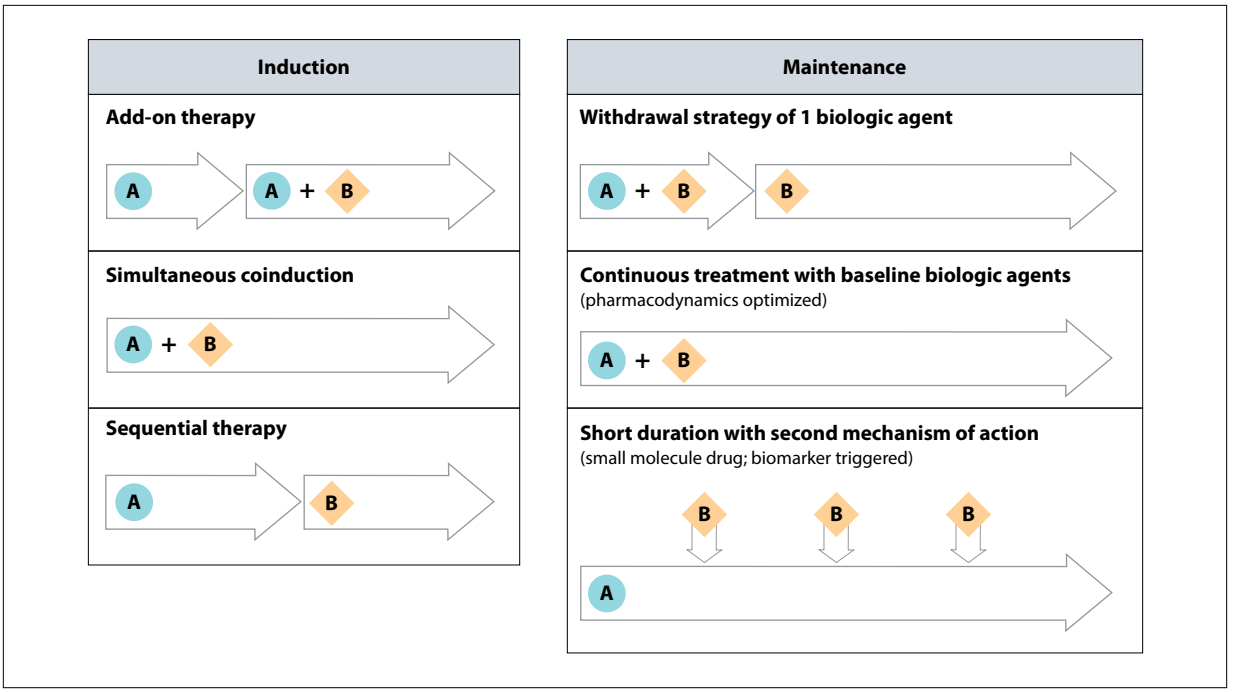

Figure 2. Potential advanced combination treatment trial designs. **A** represents the first drug and **B** represents the second drug in the combination.

Furthermore, the oral small molecule BI 706321 is currently being investigated as add-on treatment to biologic therapy in patients with CD receiving ustekinumab induction treatment (NCT04978493). Motivated by mechanistic hypotheses regarding potential additive or synergistic effects rather than opportunist combination based upon availability, agents targeting immune pathways (eg, vedolizumab) have been combined with strategies targeting the microbiome (eg, diet, fecal microbiota transplantation) in ongoing trials (NCT04231110, NCT03309865).

Practical Recommendations for Advanced Combination Treatment in Clinical Practice

There are specific clinical presentations in which ACT may be realistically considered after careful assessment of the patient's needs and potential safety issues. Key recommendations for clinical practice are summarized in Table 2.

To date, the most common ACT regimens investigated in patients with IBD have been based upon an anti-TNF agent and vedolizumab, followed by ustekinumab with vedolizumab.[77] For combinations of an oral small molecule drug with a biologic agent, therapy with tofacitinib and either vedolizumab or ustekinumab has most frequently been evaluated.

Given that the evidence available regarding the efficacy and safety of these ACT regimens is derived mainly from uncontrolled observational studies,[62-68] we highlight the recommendations below regarding cautious use in clinical practice.

This approach should be reserved for patients who have disease refractory to medical therapy, very high-risk phenotypes, or a concomitant EIM or IMID that cannot be controlled by a single agent. The practice of ACT is off-label and carries potential risks of serious infections and unknown longer-term complications. The risks of untreated disease should be weighed against the potential risks of ACT after careful discussion with the patient. Disease phenotype, comorbidities, prior drug failures, and drug pharmacodynamics are key considerations for the selection of appropriate combinations. Furthermore, targeting an alternative concomitant untreated inflammatory pathway should take into account agents with multiple cross-talk interactions that have previously caused immunogenicity. Choosing agents that are orthogonal to one another or further apart in the cross-talk maps may increase the chance of improved efficacy. Modulation of multiple pathways simultaneously through anti-TNF agents, JAK inhibitors, or anti–IL-12/23 agents should be favored. The VEGA study is a clear example of rationally combining an anti-TNF agent and anti–IL-23 agent based upon preclinical mechanistic data as well as

in-silico modeling, showing that distinct and complementary modes of action can increase the amplitude of response overall.[75]

Finally, preference should be given to agents with the most favorable safety profiles, such as vedolizumab or ustekinumab.[78,79] Data on the use of ACT in rheumatology have raised concerns about an increased risk of adverse or unknown effects that must be discussed with patients before shared decision-making. However, extrapolating these observations to IBD should be done with caution. Combination therapy in rheumatology literature included agents that are not approved or have been shown ineffective in IBD, including anakinra, abatacept, rituximab, and tocilizumab. Additionally, patients with IBD are typically younger with less comorbidity and are therefore less prone to developing serious infections.[32]

Combinations that include an anti-TNF agent and ustekinumab represent valid options in CD, whereas the use of vedolizumab should be considered in patients with UC. The presence of bowel damage in CD (eg, fistula, strictures) emphasizes the need to first evaluate anti-TNF agents. When choosing the second compound, both recycling strategies and simultaneous coinductions appear feasible.

Knowledge Gaps and Limitations

Despite increasing evidence on the use of ACT in the setting of IBD, key questions regarding this new approach remain unanswered and require further research to address (Table 2). For instance, the use of dual biologic therapy is off-label and experimental, and the most appropriate combinations for different indications within IBD have not yet been established.[80] Additionally, whether ACT should be continued indefinitely or used as an induction strategy with monotherapy maintenance therapy as a potential next step needs to be defined. Until more data become available, limiting the use of combination therapy to a short period of time, rather than extended or indefinite use, may be appropriate given the risk of adverse events reported in prior experiences. A recent systematic review and meta-analysis included 30 studies with 279 patients with IBD for a median follow-up of 32 weeks (interquartile range, 24-52 weeks).[77] The findings showed not only that ACT may be a viable therapeutic strategy in highly selected populations, but also that rates of adverse events, infections, and malignancy were similar to those reported on anti-TNF monotherapy (pooled rate of adverse events, 31.4%; 95% CI, 12.9%-53.7%).[81] In line with current strategies for de-escalation of therapy in IBD, a switch from combination therapy to monotherapy with a targeted agent should be considered after remission has been achieved.

The costs associated with administering ACT regimens are an important potential limitation for their use. However, the uptake of biosimilars under switching initiatives in clinical practice provides a favorable outlook. The introduction of biosimilars has already resulted in substantial cost savings, and as more biosimilars and biobetters (modified versions of a specific approved biologic agent) enter the IBD economic landscape, it is possible that further price erosion of available therapeutic options will occur.[82-84] Although the argument that dual biologic agents will be more costly than immunosuppressive combinations is valid, improved efficacy and possible savings associated with increased use of biosimilars may counterbalance these expenses for select difficult-to-treat, high-risk IBD patient populations, who are at high risk for other major cost drivers such as hospitalization and surgery. However, the potential for greater efficacy with ACT owing to better incremental cost-effectiveness ratios despite higher drug acquisition costs needs to be assessed by rigorous pharmacoeconomic analyses.

Conclusion

Given that a therapeutic ceiling may have been reached in IBD with limited remission rates through the use of single agents and that multiple pathways drive immune-mediated inflammatory processes, shifting focus toward the rational combination of well-established therapies is an important strategy for realizing optimal disease control. Combination with 2 targeted advanced therapies has been shown to induce a greater reduction in inflammation and improvement in epithelial homeostasis compared with monotherapy, suggesting differential and complementary mechanisms of action with a dual approach. Although less investigated in real-world settings, ACT with a small molecule drug and a biologic agent appears to be a promising option as well. Future well-controlled and adequately powered clinical trials exploring different strategies in both induction and maintenance phases are eagerly awaited to address remaining knowledge gaps (Figure 2). Potential designs for induction might include several approaches (eg, add-on therapy, simultaneous treatment, and sequential treatment). There is a growing interest in combination therapies leveraging ACT for early disease control during the induction phase, followed by monotherapy with likely a gut-selective and safe compound or with a short course of a recycled small molecule drug.

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