

Evolution of Advanced Combination Treatment in Inflammatory Bowel Disease

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Abstract: Despite multiple new advanced therapeutic options for the treatment of inflammatory bowel disease (IBD), almost half of patients do not achieve clinical remission and the number requiring intestinal resection has not significantly changed in over 20 years. To address the therapeutic ceiling seen with single-agent biologics or small molecules, clinicians have attempted combination therapy, known as advanced combination treatment (ACT), to target multiple inflammatory pathways involved in IBD pathogenesis. ACT may be particularly helpful for patients with long-standing refractory disease and those with extraintestinal manifestations. Initial trials have supported the safety and efficacy of ACT, showing clinical and endoscopic remission rates of 59% and 34%, respectively, and response rates of 69% and 43%, respectively, and few new safety signals. However, increased adverse events are seen in patients combining ACT and immunomodulators or corticosteroids. Conclusions are limited by the lack of robust randomized controlled trial evaluation and aggregate analysis of outcomes. This article will review the available data on the use of specific ACT regimens in IBD.

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, progressive immune-mediated disorders affecting the gastrointestinal tract. The armamentarium of advanced medical therapies for inflammatory bowel disease (IBD), which previously comprised only tumor necrosis factor (TNF) antagonists, has expanded over the past 10 years. New biologics include an $\alpha 4\beta 7$ integrin inhibitor vedolizumab (Entyvio, Takeda); interleukin (IL)-12/IL-23 antagonist ustekinumab (Stelara, Janssen); and pure IL-23 antagonists risankizumab (Skyrizi, AbbVie), guselkumab (Tremfya, Janssen), and mirikizumab (OmvoH, Lilly). New small molecules include sphingosine-1 phosphate (S1P) receptor modulators etrasimod (Velsipity, Pfizer) and ozanimod (Zeposia, Bristol Myers Squibb), and Janus kinase (JAK) inhibitors tofacitinib (Xeljanz, Pfizer) and upadacitinib (Rinvoq, AbbVie). Despite expanded

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Inflammatory bowel disease, Crohn's disease, ulcerative colitis, advanced combination treatment, dual biologic therapy, combination therapy

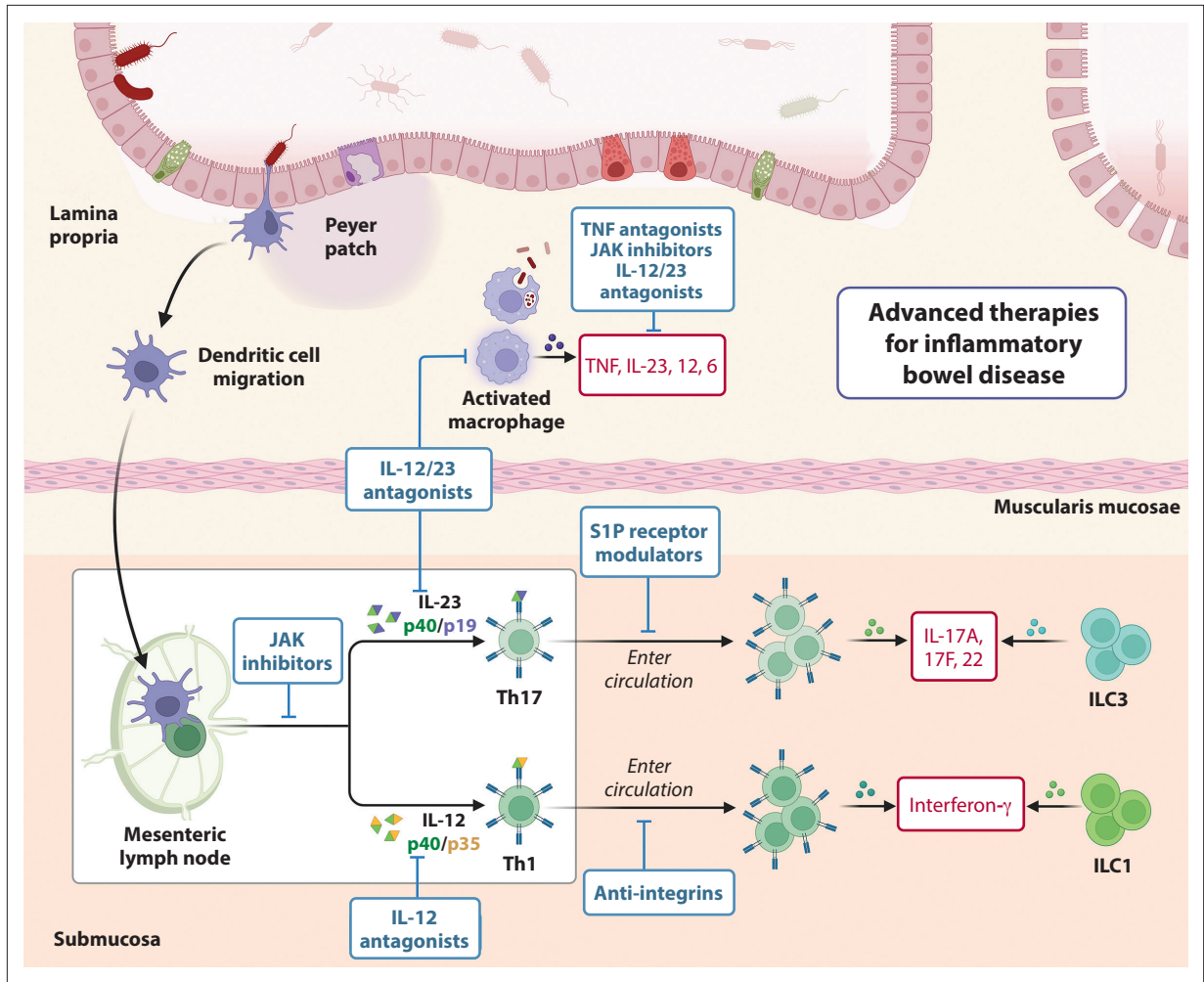


Figure. Mechanisms of action within the intestine of advanced therapies for inflammatory bowel disease.

Figure created in BioRender.com.

IL, interleukin; ILC1, group 1 innate lymphoid cells; ILC3, group 3 innate lymphoid cells; JAK, Janus kinase; S1P, sphingosine-1 phosphate; Th, T helper cell; TNF, tumor necrosis factor.

options, clinical remission rates at 1 year following any new agent do not exceed 50%, and rates of intestinal resection have not changed significantly in over 20 years,¹ raising concern for a therapeutic ceiling with single-agent advanced therapies.

New drug mechanisms have yet to solve this problem, suggesting a different approach may be needed. IBD involves a complex interplay of inflammatory pathways²; therefore, to achieve adequate remission, multiple pathways may need to be suppressed (Figure). The SONIC³ and UC-SUCCESS⁴ trials demonstrated superiority in combining infliximab with thiopurines in CD and UC, respectively. The availability of multiple targeted and safer biologics raises the possibility of advanced combination treatment (ACT) to target multiple inflammatory pathways while limiting adverse events (AEs).⁵

Initial systematic reviews and case series offer support for efficacy and safety of ACT.⁶⁻¹⁰ Ahmed and colleagues analyzed 279 patients on 288 various ACT regimens, primarily TNF antagonists and anti-integrins (48%), and reported pooled results.⁶ The majority of patients had CD (76%) and extraintestinal manifestations (EIMs) (52%). Patients had a mean disease duration of 12.3 years, median number of 2 prior biologics, and approximately half had undergone prior IBD-related surgery (47%). The main reason for ACT was medically refractory disease (81%), followed by concurrent EIM (12%). Pooled rates of clinical and endoscopic remission were 59% and 34%, respectively, and response rates were 69% and 43%, respectively. In patients on ACT for EIM indications, 73% achieved EIM remission with higher rates of luminal healing. Infections were reported in 19% (52/281). Few serious

AEs or malignancies were reported. Several systematic and narrative reviews have demonstrated similar findings.^{1-5,11} Since publication of these reviews, several studies addressing specific ACT combinations have been published. This article will review the available literature on individual ACT regimens in the treatment of IBD.

Tumor Necrosis Factor Antagonists + Anti-Integrins

Recent studies and clinical data highlight the promise of combining TNF antagonists with anti-integrins. TNF antagonists in IBD neutralize TNF- α , a key cytokine driving inflammation,⁵ by inducing apoptosis of lamina propria T cells and promoting wound-healing macrophages, contributing to mucosal healing and inflammation resolution. Integrin inhibition blocks leukocyte migration to the intestines while preserving systemic immune defenses against infections and malignancies.⁷ Anti-integrins may have a slower onset of action; however, vedolizumab has higher gut selectivity with decreased AEs and infection risks.

Combining TNF antagonist and anti-integrin therapies enhances mucosal healing, sustains remission, and maintains a safety profile comparable to monotherapy.⁸ Sands and colleagues performed the first randomized controlled trial (RCT) investigating combination anti-integrin therapy (natalizumab) and infliximab compared with infliximab monotherapy in 79 CD patients.⁹ Although not powered for superiority, remission rates were numerically higher with ACT over 10 weeks without an increase in AEs. A smaller 2019 systematic review described outcomes of 18 patients treated with ACT (15 TNF antagonist and vedolizumab, 3 vedolizumab and ustekinumab).¹⁰ Despite the limited sample size, 100% of patients reported clinical improvement, with 14/15 patients who received a TNF antagonist and vedolizumab achieving endoscopic improvement. The majority (15/18) received ACT for refractory IBD; 3 patients received ACT for EIMs. The AEs were self-limited illnesses after 14 months of ACT.

A systematic review and meta-analysis of 13 studies by Alayo and colleagues included 8 studies with 53 therapeutic trials of vedolizumab and a TNF antagonist.¹² In patients who received this combination, the authors found a 55.1% clinical remission rate, 24.1% AE rate, and 9.6% serious AE rate, with no new safety concerns. A smaller case series further supported the efficacy of this combination but was limited by sample size. Buer and colleagues reported 100% clinical remission in 10 IBD patients (6 UC, 4 CD) with combination TNF antagonist and vedolizumab.⁸ After a median of 6 months on ACT, 8 patients were able to de-escalate to vedolizumab monotherapy and maintain clinical remission. AE rates were

similar to TNF antagonist monotherapy, and no serious AEs were reported. Although encouraging, these findings require validation in larger, controlled cohorts.

With increased data suggesting earlier top-down therapy improves outcomes and decreases disease complications,¹³ Colombel and colleagues published on triple therapy (vedolizumab, adalimumab, and methotrexate) in newly diagnosed CD patients.¹⁴ Triple therapy achieved endoscopic remission in 33.5% at 26 weeks compared with benchmarked placebo rates calculated by the authors from RCT data for vedolizumab and adalimumab monotherapy (14%), with a similar safety profile. The study (EXPLORER) de-escalated triple therapy to single-agent vedolizumab at week 26 and then patients entered a maintenance phase extending to week 52, with vedolizumab infusions scheduled to week 102. This is the first study to evaluate ACT for first-line induction, rather than salvage.

The TNF antagonist and anti-integrin combination offers promising results with improved efficacy and similar safety profile to monotherapy. The gut specificity of vedolizumab makes it an attractive component of ACT. However, the lack of efficacy in EIMs or concomitant rheumatologic conditions requires pairing with broader therapies like TNF antagonists. The use of TNF antagonists during induction quickly decreases inflammatory burden to induce rapid remission. De-escalation to anti-integrin monotherapy may lead to improved long-term medication persistence rates and fewer AEs. This combination would be most beneficial in refractory patients with concomitant inflammatory arthritis plus IBD, or in patients with perianal fistulizing CD in whom monotherapy has not yielded disease control.^{8,12,14}

Tumor Necrosis Factor Antagonist + Interleukin-12/23 or Interleukin-23 Antagonist

A TNF antagonist plus IL-12/23 or IL-23 antagonist is another promising combination for refractory IBD cases based on the favorable safety profile of the IL-12/23 and IL-23 antagonists. Ustekinumab targets the p40 subunit of IL-12 and IL-23. IL-12 inhibition suppresses Th1 by reducing interferon gamma, which is critical for cell-mediated immunity against intracellular pathogens. IL-23 inhibition decreases the Th17 inflammatory response, a key driver of chronic intestinal inflammation.¹⁵ Several small studies support the efficacy of this combination, showing improved clinical outcomes with minimal AEs.¹⁶⁻¹⁸ The most robust evidence to date comes from the VEGA study, an RCT that evaluated combination guselkumab and golimumab (Simponi, Janssen) induction therapy in the treatment of 214 UC patients naive to TNF antagonists and IL-12/23 or IL-23 antagonists.¹⁹

At week 12, clinical response was significantly higher in the combination group (83%) compared with the golimumab group (61%), but not significantly higher than guselkumab monotherapy (75%). Week 12 endoscopic and histologic remission rates were significantly higher in the combination group than either group alone. Combination therapy reached faster symptomatic remission than either monotherapy (41% at week 2 with combination vs 29% with golimumab and 14% with guselkumab). At week 38, after mandatory de-escalation to guselkumab monotherapy, the symptomatic remission rates equalized; however, calprotectin levels remained lower in the initial combination group (118 µg/g) than in both monotherapy groups (>250 µg/g). AEs were similar across all groups. Thus, induction with a TNF antagonist and IL-23 antagonist may induce a faster, more robust clinical and endoscopic remission. Combination therapy was not permitted beyond 12 weeks, but this raises the question for future studies if patient- and disease-related factors should dictate timing of de-escalation in order to maintain remission.

Smaller observational studies and case series suggest potential efficacy of TNF antagonist and ustekinumab combinations in refractory IBD. In a multicenter study, Eronen and colleagues reported that among 8 patients on adalimumab and ustekinumab, 5 experienced clinical response, 1 had fistula remission, 3 required surgery, and 1 developed an infection.¹⁸ In the same study, 2 patients on golimumab and ustekinumab saw symptom improvement (1) or reduced corticosteroid use (1).

Pure IL-23 antagonists (risankizumab, guselkumab, and mirikizumab) target the p19 subunit. Isolated IL-23 inhibition is more effective and potentially safer in IBD treatment^{15,20-22} owing to the more central role of IL-23 in driving chronic intestinal inflammation and preservation of protective immunity by avoiding IL-12 inhibition. A case report found risankizumab and certolizumab pegol ACT safe and effective for CD and spondyloarthritis.²³ The patient's CD was uncontrolled on certolizumab pegol alone, and spondyloarthritis worsened after switching to risankizumab. ACT ultimately controlled both with minor AEs.

In summary, ACT with a TNF antagonist and IL-12/23 or IL-23 antagonist appears promising, particularly for rapid induction of remission. The VEGA study supports the hypothesis that ACT may improve both short-term outcomes and markers of disease control.¹⁹ Larger trials should be conducted with long-term follow-up to monitor remission rates and optimal de-escalation strategies. Current data suggest this combination may be most beneficial in refractory patients with concomitant psoriasis and IBD or in patients with perianal fistulizing CD not achieving remission with monotherapy.

Tumor Necrosis Factor Antagonist + Janus Kinase Inhibitor

Given the limitations of targeting a single cytokine with biologic therapy and risks of immunogenicity with additional biologic agents, clinicians have utilized small molecules inhibiting enzymes involved in multiple cytokine signaling pathways, such as JAK inhibitors. JAK inhibitors target the JAK Signal Transducers and Activators of Transcription pathway, thereby mediating the signaling effects of multiple inflammatory cytokines. Tofacitinib predominantly inhibits JAK1 and JAK3, whereas upadacitinib modulates JAK1 and the specific downstream signaling effects of IL-2, IL-4, IL-7, IL-9, IL-15, IL-21, and type I and II interferons.²⁴ The JAK inhibitor and TNF antagonist combination has been trialed for refractory and corticosteroid-unresponsive IBD to regulate multiple inflammatory mediators.

Small studies assessing anywhere from 1 to 9 patients on a TNF antagonist and JAK inhibitor combination provide evidence of potential efficacy in UC, although evaluation with larger cohorts is required (Table 1). Glassner and colleagues' assessment of 9 patients on tofacitinib and TNF antagonist therapy in pooled analysis with 53 patients on other combinations showed clinical remission in 89% at a median of 8 months.²⁵ In a study by Alayo and colleagues, of 6 patients on tofacitinib and infliximab, 60% had clinical response as soon as 2 months, and 66.7% had endoscopic response.^{12,26} Gilmore and colleagues' prospective evaluation of 5 patients with active, severe corticosteroid-refractory UC on the tofacitinib and TNF antagonist combination showed clinical remission in 60% and endoscopic remission in 40% at 3 months.²⁷ Taken together, these studies suggest that response and even remission may be obtained rapidly and durably with this combination.

In addition to encouraging efficacy data, this combination is associated with relatively few AEs, with only self-limited illnesses not requiring therapy discontinuation in these small trials (Table 2). Of patients on the tofacitinib and TNF antagonist combination, Glassner and colleagues showed only 1 episode of strep throat,²⁵ Alayo and colleagues reported only 1 patient with *Clostridioides difficile* infection and later *Candida* esophagitis,²⁶ Gilmore and colleagues noted 1 varicella zoster infection.²⁷ Thus, the expansive immunosuppression with this ACT did not appear to contribute to an increase in severe infectious safety concerns.

Studies analyzing JAK inhibitor and TNF antagonist combinations appear to demonstrate efficacy for UC, particularly as a corticosteroid-sparing agent in acute severe UC, but most studies are limited by small sample sizes and short follow-up times. Insufficient data exist to

recommend the combination TNF antagonist and JAK inhibitor in CD. The broad immunosuppression achieved with these agents led to mostly infectious AEs, but relatively few of these required hospitalization and most patients tolerated combination therapy without infections or other side effects. Combination of these agents may be limited to a brief induction course to avoid significant immunosuppression and infection risk. It may be most beneficial in severe, refractory IBD patients who require a rapidly acting agent, may have concomitant inflammatory arthritis and/or severe fistulizing perianal CD, and are not at high risk for venous thromboembolism. This combination should be used with caution for long-term maintenance and in patients older than 60 years. More investigation into the efficacy, safety, and duration of this combination is warranted.

Anti-Integrin + Interleukin-12/23 or Interleukin-23 Antagonist

Combinations targeting integrins and IL-12/23 or IL-23 attempt to reduce the AEs associated with TNF antagonists, particularly in severe or refractory CD. Studies have shown success in several CD patients treated with combination anti-integrin (vedolizumab) plus IL-12/23 antagonist (ustekinumab) or IL-23 antagonist (risankizumab), although conclusions are limited by small sample size and lack of controlled trials.

Glassner and colleagues' work represents the only studies on this combination with relatively robust sample size, although conclusions are limited by their retrospective nature. Their initial retrospective cohort study included 25 patients (23 CD, 1 UC, 1 IBD-undetermined) treated with vedolizumab and ustekinumab in a cohort of 50 patients receiving ACT.²⁵ Patients had failure of a median of 2 biologics, and ACT efficacy for clinical and endoscopic remission was assessed at a median of 4 and 8 months, respectively. Seven of 15 (46.7%) patients achieved clinical remission with adequate follow-up, a relatively high proportion given the medical refractoriness of IBD in the participants; however, 10/25 (40%) reported an AE, 5 of which were serious. Concomitant immunomodulator use predisposed to a 3-fold increased likelihood of serious AE development, and the authors suggest infection risk was confounded by baseline disease severity and health care exposure, indicating AEs may not be related to ACT.

A subsequent study that focused on the vedolizumab and ustekinumab combination in 30 patients with active, refractory CD supported these conclusions, finding an average 2-point reduction in Harvey-Bradshaw Index and biochemical response.²⁸ Although endoscopic response was not significant, half of the participants had not yet

had follow-up. Serious AEs occurred in 17% of patients, and 10% experienced nonserious infections. Multivariate analysis found immunomodulator use, disease duration, and age as risk factors for serious infection. All patients with complications had severe refractory disease, and 78% were taking corticosteroids with ACT, again indicating other factors likely influenced the AE rate beyond combination biologics. These 2 trials support the efficacy of ACT with an anti-integrin and IL-12/23 or IL-23 antagonist, particularly in medically refractory patients.

All other studies on this combination are limited by their small sample size (5-14 participants) and retrospective nature, and results must be interpreted with caution. Most studies demonstrate similar or better efficacy (63%¹¹-81%¹⁶ endoscopic response, 25%¹¹ endoscopic remission), potentially contributed to by longer duration of follow-up (≥ 1 year in both studies), for those with medically refractory disease or those with concomitant EIMs. In particular, Goessens and colleagues evaluated 16 patients on this combination among 70 patients with active IBD on other combinations and demonstrated the anti-integrin and IL-12/23 antagonist to be the most effective combination tested.¹⁵ Similar or fewer AEs were reported in these studies (12.5%-42% AEs, 0%-10% serious AEs), partially related to the smaller proportion of patients on concomitant immunomodulators or corticosteroids. Eronen and colleagues published a notable exception to these findings, with only partial response in 1/5 (20%) of patients,¹⁸ although participants were only followed for a median of 9 months and were younger than other studies (27 years vs 40 years), indicating a possibly more severe disease phenotype. Still, small sample size and pooled analyses, rather than those specific to anti-integrin and IL-12/23 antagonist combination, limit interpretability of these findings.

In addition to these small retrospective cohort studies, several case reports have been published touting the success of the vedolizumab and ustekinumab combination. Huff-Hardy and colleagues presented the first case of severe penetrating vulvo-perianal CD refractory to multiple therapies, successfully treated with ustekinumab, vedolizumab, and methotrexate.²⁹ Clinical response was seen at 8 weeks, and deep remission was achieved at 1 year, with 1 self-limited rotavirus infection. Subsequent reports similarly described patients with penetrating CD refractory to biologics and surgical intervention who improved with combination ustekinumab and vedolizumab with minimal AEs (most often self-limited mild infections).³⁰⁻³⁹ One case described a favorable safety profile when vedolizumab and ustekinumab were combined during pregnancy.³⁴

Using this combination to avoid TNF antagonists is appealing to limit serious infection risk while still targeting

Table 1. Efficacy of ACT for Inflammatory Bowel Disease in Studies With 18 or More Patients

Authors	N, notes	Combination ^a	Clinical remission	Clinical response	Endoscopic remission	Endoscopic response
Colombel et al ¹⁴	55 CD Biologic-naive population	55 ADA+VDZ+MTX	30/55 at week 26	24/55	19/55	31/55
Ribaldone et al ¹⁰	10 CD, 8 UC 9/18 pts treated with corticosteroids or immunosuppressants	15 TNF (9 IFX, 3 GOL, 2 ADA, 1 CZP) +VDZ 3 VDZ+USK	NR	18/18	NR	14/18
Sands et al ⁹	79 CD RCT	52 IFX+NAT (27 placebo)	19/52	7/24	NR	NR
Glassner et al ²⁵	31 CD, 18 UC	25 VDZ+USK 9 TOF+TNF (4 IFX, 4 GOL, 1 CZP) 8 VDZ+TOF 7 VDZ+TNF (3 ADA, 2 CZP, 2 GOL) 1 ADA+APR	18/36 (5/36 in clinical remission at baseline)	12/36	11/32 (2/32 in endoscopic remission at baseline)	13/32
Alayo et al ²⁶	10 CD, 25 UC All failed ≥1 biologic, 60% failed ≥2 biologics	24 VDZ+TOF 6 IFX+TOF 5 USK+TOF	3/28 at 8 weeks 7/10 at 26 weeks	14/28 at 8 weeks 9/10 at 26 weeks	8/23	13/23
Feagan et al ²¹	71 UC Numerically more clinical response with dual therapy than with either GUS or GOL monotherapy	71 GUS+GOL	31/71	49/71	36/71	35/71
Goessens et al ¹⁶	58 CD, 40 UC 80 with active inflammatory bowel disease (10/80 with IMID/EIM)	36 TNF+VDZ 8 TNF+anti-IL 16 Anti-IL+VDZ 1 TOF+TNF 12 TOF+VDZ 1 Anti-IL+anti-IL 6 Other combination	21/80	35/80	NR	19/39
Yang et al ¹¹	22 CD (24 combinations)	13 VDZ+TNF 8 VDZ+USK 3 USK+TNF	4/7 ^b 4/12 ^b 1/3	5/7 ^b 5/12 ^b 1/3	2/8 3/12 ^c 1/3 ^c	5/8 4/12 ^c 1/3 ^c
Glassner et al ²⁹	30 CD Median 2 failed prior biologics, 20% had concomitant rheumatologic or dermatologic disease	30 VDZ+USK	NR	NR	4/14	NR
Kolar et al ⁴²	21 UC	21 VDZ+TOF	NR	10/21	NR	NR
Lee et al ⁴³	19 Refractory CD Mean disease duration was 16.9 years, 47.3% had penetrating or stricturing disease, 100% failed prior TNF, 94% failed ≥2 biologics	11 TOF+USK 7 TOF+VDZ 1 TOF+CZP	6/10	8/10	2/11	6/11
Kellar et al ⁴⁷	30 (30% CD) >60% flare after monotherapy All with flares achieved remission after re-escalating dual therapy	11 USK+TOF 9 VDZ+TOF 4 USK+VDZ 5 USK+UPA 1 VDZ+OZA	11/11 6/9 3/4 5/5 1/1	NR	NR	NR

^aIndividual ACTs are shown if stratified data were reported. For aggregate data reports, combinations are grouped by mechanism of action. Case reports and those including only pediatric patients were excluded.

^bPatient-reported outcomes unable to be calculated in 2 trials owing to presence of an ostomy (1 in VDZ+USK and 1 in VDZ+TNF).

^cEndoscopic endpoint data not yet available in 4 trials; 3 were considered failure of ACT owing to surgery or entering a clinical trial (2 VDZ+TNF, 1 USK+TNF), 1 was awaiting follow-up but achieved clinical response (VDZ+TNF).

ACT, advanced combination treatment; ADA, adalimumab; anti-IL, interleukin-12/23 antagonist or interleukin-23 antagonist; APR, apremilast; CD, Crohn's disease; CZP, certolizumab pegol; EIM, extraintestinal manifestation; GOL, golimumab; GUS, guselkumab; IFX, infliximab; IMID, immune-mediated inflammatory disease; MTX, methotrexate; NAT, natalizumab; NR, not reported; OZA, ozanimod; Pts, patients; RCT, randomized controlled trial; RIS, risankizumab; TNF, tumor necrosis factor antagonist; TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib; USK, ustekinumab; VDZ, vedolizumab.

Table 2. Safety of ACT for Inflammatory Bowel Disease in Studies With 18 or More Patients

Authors	Combination	Nonserious AEs ^a	Serious AEs ^b	Total no. of infections
Colombel et al ¹⁴	55 ADA+VDZ+MTX	4 UTI 6 Nasopharyngitis	3 Small-intestine obstruction 1 Lymphadenopathy 1 Gastroenteritis	10
Ribaldone et al ¹⁰	15 TNF (9 IFX, 3 GOL, 2 ADA, 1 CZP) +VDZ 3 VDZ+USK	3 URI requiring Abx 1 Dyspnea 1 Rotavirus	0	4
Sands et al ⁹	52 IFX+NAT	3 URI 5 Nasopharyngitis	0	8
Glassner et al ²⁵	25 VDZ+USK 9 TOF+TNF (4 IFX, 4 GOL, 1 CZP) 8 VDZ+TOF 7 VDZ+TNF (3 ADA, 2 CZP, 2 GOL) 1 ADA+APR	14 Infections (3 <i>Escherichia coli</i> , 3 <i>Clostridium difficile</i> , 1 viral enteritis, 1 URI, 2 acute bronchitis, 3 sinusitis, 1 strep throat)	8 Infections ^c (1 bacterial enteric infection, 2 abdominal wall abscesses, 1 peristomal cellulitis, 2 pelvic abscesses, 1 PICC line infection, 1 sepsis)	22
Alayo et al ²⁶	24 VDZ+TOF 6 IFX+TOF 5 USK+TOF	1 <i>Candida</i> esophagitis 1 Rash (VDZ+TOF)	1 <i>C difficile</i> colitis No Tx discontinued because of AE	2 (Same patient on IFX+TOF had <i>C difficile</i> colitis, then <i>Candida</i> esophagitis)
Feagan et al ²¹	71 GUS+GOL	6 URI 3 Neutropenia	2 Infections 7 Tx discontinued because of AE 1 Death	8
Goessens et al ¹⁶	36 TNF+VDZ 8 TNF+anti-IL 16 Anti-IL+VDZ 1 TOF+TNF 12 TOF+VDZ 1 Anti-IL+anti-IL 6 Other combination	NR	10	NR
Yang et al ¹¹	13 VDZ +TNF 8 VDZ+USK 3 USK+TNF	2	1 Pneumonia 1 Malignancy (recurrent BCC) 1 <i>C difficile</i> infection 1 Acinetobacter bacteremia 1 Drug-induced lupus from ADA	3
Glassner et al ²⁹	30 VDZ+USK (CD)	3 infections	5 infections requiring hospitalization	8
Kolar et al ⁴²	21 VDZ+TOF	4 Disease flares	1 Liver lesion	0
Lee et al ⁴³	11 TOF+USK 7 TOF+VDZ 1 TOF+CZP	7/19 (36.8%) (including 1 acne, 1 rash, 2 URI)	1 Malignancy (BCC)	2
Kellar et al ⁴⁷	11 USK+UPA 5 USK+TOF	0 for USK+UPA 1 mild leukopenia that resolved with TOF de-escalation	0	0

^aNonserious and serious AEs are mutually exclusive, whereas infections overlap with nonserious and serious AEs to demonstrate the severity of infection.

^bSerious AEs include those requiring hospitalization or leading to death.

^cIn the Glassner et al study, serious AEs were significantly more common in patients on concomitant immunomodulators compared with those on ACT alone. Concomitant immunomodulator use was reported in 57% of the ACTs with serious AEs compared with 17.4% of the other combinations where a serious AE did not occur ($P=.019$).²⁵

Abx, antibiotics; ACT, advanced combination treatment; ADA, adalimumab; AE, adverse event; anti-IL, interleukin-12/23 antagonist or interleukin-23 antagonist; APR, apremilast; BCC, basal cell carcinoma; CD, Crohn's disease; CZP, certolizumab pegol; GOL, golimumab; GUS, guselkumab; IFX, infliximab; MTX, methotrexate; NAT, natalizumab; PICC, peripherally inserted central catheter; TNF, tumor necrosis factor antagonist; TOF, tofacitinib; Tx, treatment; UC, ulcerative colitis; UPA, upadacitinib; URI, upper respiratory infection; USK, ustekinumab; UTI, urinary tract infection; VDZ, vedolizumab.

pathways that propagate IBD. Most serious infections with combination vedolizumab and ustekinumab occurred in patients using a triple combination with an immunomodulator. Use of anti-integrins and IL-12/23 antagonists without additional nonspecific immunomodulation appears to be well tolerated and mitigates infection risk in patients with CD. This combination may be beneficial to treat concomitant immune-mediated inflammatory diseases such as psoriasis and psoriatic arthritis and skin-related EIMs of IBD. Data on UC efficacy are limited. In a single-center case series, none of 3 patients with UC responded to combination ustekinumab and vedolizumab,³⁷ whereas in 2 other retrospective case series, 1 UC patient achieved clinical remission and biomarker improvement,³³ and 1 UC patient achieved clinical improvement and extraintestinal remission.³⁶ Clinical trials across IBD subtypes are needed to elucidate the true impact of combination anti-integrin and IL-12/23 antagonist therapy. Data thus far suggest this combination would be most beneficial in refractory patients with a higher risk for AEs or infectious risks who may have already had failure of or are intolerant to TNF antagonists and in patients with concomitant psoriasis. This ACT will not adequately treat patients with inflammatory arthritis and will have a longer onset of action than other ACTs.

Anti-Integrins + Small Molecule Inhibitors

The combination of anti-integrin and JAK inhibitor is attractive to target 2 separate inflammatory pathways and balance the slower onset of action of vedolizumab with the rapid onset of action of the JAK inhibitor. The excellent safety profile and gut specificity of vedolizumab pairs well with JAK inhibitors that have higher rates of infections and AEs but can target EIMs and concomitant inflammatory joint disease. Both medications modulate chronic inflammation via the Th1/Th17 adaptive immune response through separate complementary mechanisms. Vedolizumab plays a larger role in repairing intestinal barrier disruption, and both medications modulate tissue remodeling through different pathways. This combination could both separately and synergistically modulate a large array of effectors altered in CD.⁴⁰

An abstract on 21 acute severe UC or medically refractory UC patients treated with vedolizumab and tofacitinib reported a 50% mucosal healing rate (extended Mayo score of 0-1), with 1 patient terminating early owing to a liver lesion.⁴¹ Llano and colleagues reported on combining vedolizumab with other biologics (n=5) or tofacitinib (n=9) for active luminal disease.³³ Six of 7 (1 CD, 6 UC) patients achieved clinical response. There were 4 infectious events, 2 of which were serious requiring hospitalization (rotavirus and *C difficile*). Otherwise, this

ACT was well tolerated and effective, and 1 patient de-escalated to vedolizumab monotherapy. Additional studies have confirmed similar results of improved efficacy without increased serious AEs using combination vedolizumab and tofacitinib.^{25,26} Triple therapy with vedolizumab, ustekinumab, and tofacitinib in a refractory UC patient was safe and efficacious.⁴² After achieving remission, the patient stepwise de-escalated to vedolizumab every 8 weeks without any AEs.

Although tofacitinib lacks a CD indication, studies have examined its use in refractory patients.^{43,44} As described in the retrospective study by Lee and colleagues of 19 refractory CD and/or pyoderma gangrenosum patients, treatment with tofacitinib and a biologic agent—either ustekinumab (n=11), vedolizumab (n=7), or certolizumab pegol (n=1)—contributed to clinical remission in 60%, clinical response in 80%, and endoscopic remission in 54%.⁴³ All 4 patients with pyoderma gangrenosum experienced visual resolution. AEs were noted in 36.8% of patients, including 2 CD flares and 1 basal cell carcinoma. A pediatric study with 9 patients (5 UC, 4 CD) on vedolizumab and tofacitinib found a 77.8% corticosteroid-free remission rate at 6 months.⁴⁴ One serious AE, septic arthritis with deep vein thrombosis, occurred in a child on vedolizumab, tofacitinib, and 30 mg/day prednisone. After anticoagulation and corticosteroid tapering, full remission was reached allowing de-escalation of tofacitinib to vedolizumab monotherapy, which maintained his remission.

The newest JAK inhibitor upadacitinib has greater JAK1 selectivity and approval for both UC and CD. Greater JAK1 selectivity may portend improved safety compared with a pan-JAK inhibitor, and studies have suggested upadacitinib is more efficacious than tofacitinib for UC,^{45,46} making upadacitinib the preferred agent. The VICTRIVA study, currently recruiting patients, will investigate combination vedolizumab and upadacitinib vs vedolizumab and placebo for 12 weeks, followed by vedolizumab monotherapy for 40 additional weeks in a double-blind RCT. This study will provide valuable data regarding the safety and efficacy of ACT when used as an induction strategy.

Data on S1P receptor modulators for ACT are limited to an adolescent case series that included 1 patient treated with vedolizumab and ozanimod who was refractory to dose-optimized vedolizumab and achieved remission, and successful de-escalation to ozanimod monotherapy was performed.⁴⁷ No AEs were noted. Additional data are required to better understand the role of S1P receptor modulators in ACT. The synergistic use of a JAK inhibitor with vedolizumab addresses a key limitation of vedolizumab monotherapy—its delayed onset of action. In patients with an incomplete or slow response

to vedolizumab, or in those requiring immediate symptom control, a JAK inhibitor can be initiated to rapidly induce remission. Following this induction phase, the JAK inhibitor can be tapered once remission is reached, thereby leveraging its rapid efficacy while maintaining the long-term, gut-selective benefits of vedolizumab.

Interleukin-12/23 Antagonist + Small Molecule Inhibitors

IL-12/23 antagonist and small molecule JAK inhibitor combination may similarly yield synergistic immunomodulatory effects. JAK inhibitors' rapid onset balances IL-12/23 antagonist's slower onset, whereas the more targeted immunoregulatory properties of IL-12/23 antagonists may decrease infectious complications and contribute to intestinal healing. As with other combinations including small molecule inhibitors, data on the IL-12/23 antagonist and small molecule inhibitor combination are limited by retrospective design and small sample size.

Although many small reports show clinical response rates ranging from 90% to 100%,^{25,26,43,47,48} even in patients who demonstrated sufficient medical refractoriness, with failure of 4 prior biologics including TNF antagonists, clinical remission rates were far more variable, ranging from 0% to 83%.^{25,26,43,47,48} Differences in response may be attributable to duration of study follow-up, with shorter follow-up intervals less likely to show clinical remission. Miyatani and colleagues identified 10 CD patients treated with ustekinumab and upadacitinib, 2 of whom had EIMs, and both of these patients experienced joint symptom resolution, and 1 patient with a perianal fistula achieved fistula closure.⁴⁸

Despite potential indications that sustained IL-12/23 antagonist and JAK inhibitor therapy may aid disease control, long-term tolerability may be limited by AEs (Table 2). Although some studies reported no²⁶ or few^{25,47} AEs with this combination, others note AEs in 45%²⁶ to 70%⁴⁸ of participants, ranging from cutaneous fungal infections to respiratory distress and bowel obstruction. In 2 patients, sufficient nausea developed that required dose reduction or discontinuation, according to the retrospective, observational study by Miyatani and colleagues.⁴⁸ Most studies reported no serious AEs with this combination.

Although limited by retrospective data and small samples, studies show potential efficacy for combination IL-12/23 antagonist and JAK inhibitor in both luminal and extraintestinal IBD treatment. Case reports have similarly shown that combination ustekinumab and tofacitinib provides clinical benefit with minimal AEs, particularly in TNF antagonist failures.^{6,26,49-51} These case reports suggest that mild AEs are common, few serious

AEs occur, and the AEs may not preclude long-term use of this ACT. Although de-escalation to either IL-12/23 antagonist or JAK inhibitor monotherapy caused disease recurrence in the majority of patients treated with this combination, most regained remission after resumption of dual therapy.⁴⁷ One case report describes maintenance of remission on vedolizumab after tapering ustekinumab and tofacitinib.⁴² Additionally, most patients tolerate the combination with few serious AEs, fewer infections compared with TNF antagonists, and minor AEs that often respond to dose reduction.^{8,10,15,26,28,35,47,48,52} Although more literature is needed to strengthen efficacy and safety signals, data thus far are encouraging. This combination would be most beneficial in patients with incomplete response to IL-23/23 or IL-23 antagonists or for induction of remission with plans to taper a JAK inhibitor once remission is reached. This combination is also beneficial for patients with concomitant psoriasis or inflammatory arthritis.

De-escalation of Advanced Combination Treatment

The research described confirms that ACT is efficacious and offers refractory patients an additional medical option. Emerging data also suggest that ACT may provide therapeutic benefit during induction early in the disease course to rapidly suppress disease activity and decrease the risk of disease-related complications (strictures, fistulas).¹⁴ However, ACT may come at the risk of increased AEs and higher costs. Questions then arise as to whether treatment can be de-escalated to monotherapy and when it is safe to de-escalate.

Several studies report the successful de-escalation of ACT after achieving remission.^{8,30,42,53} Although exact details on the type of remission (clinical, endoscopic, histologic) are not mentioned, evidence from monotherapy de-escalation suggests that the deeper the healing prior to de-escalation, the higher the chances of success.⁵⁴ Lower fecal calprotectin level and longer duration of remission are also associated with lower rates of relapse in TNF antagonist cessation.⁵⁵ Therefore, deep endoscopic healing and a normal fecal calprotectin level are recommended prior to de-escalation. Although severely refractory patients may experience recurrence after de-escalation, most are able to recapture remission upon reinitiation of ACT.⁴⁷ When de-escalating, discontinuation of corticosteroids should be prioritized first, followed by immunomodulators.²⁹ Subsequently, de-escalating the high-risk medications (ie, JAK inhibitors) while maintaining the more gut-selective therapies (vedolizumab, ustekinumab, and IL-23 antagonists) can limit serious AEs and infectious complications. However, in patients

Table 3. Proposed Criteria for De-escalation of ACT^a

Combination	Endpoint	De-escalation strategy ^b
Any ACT + immunomodulator	Clinical or endoscopic response	Discontinue immunomodulator to limit AEs
Any ACT + corticosteroid	Clinical or endoscopic response OR 3 months of nonresponse	Discontinue corticosteroid to limit AEs If no response after 3 months, consider alternate ACT agents
Any biologic + JAKi	Biochemical or endoscopic response	Discontinue or taper JAKi to limit AEs Over half of participants may need to re-escalate to dual therapy, but most can re-achieve response after re-escalation
Any ACT with 2 biologics	Biochemical or endoscopic remission	Discontinue 1 biologic to limit AEs; choice of biologic to discontinue is dependent on patient factors Given that there are fewer AEs with biologic use than with small molecule inhibitor use, de-escalation is not recommended until objective measures of remission are achieved (biochemical, endoscopic) rather than clinical measures
Any biologic + TNF antagonist	Control of EIMs (eg, erythema nodosum, peripheral polyarticular arthritis, Sweet syndrome, oral aphthous ulcers, episcleritis) shown to correlate with intestinal activity	Discontinue TNF antagonist, ^c given that other biologics may be sufficient to maintain intra-intestinal disease or are better tolerated/exhibit longer persistence than TNF antagonists This approach does not work for EIMs whose activity is independent of intra-intestinal disease activity
	Endoscopic or biochemical remission with history of inflammatory arthritis or perianal/fistulizing disease	Discontinue non-TNF biologic, given the requirement of a TNF antagonist to maintain inflammatory arthritis/perianal disease/fistulizing disease control
Any biologic + anti-integrin	Endoscopic or biochemical remission with history of psoriasis or psoriatic arthritis	Discontinue anti-integrin, as anti-integrin monotherapy will be insufficient to address psoriatic disease

^aData supporting these recommendations are limited, and therapy should be adjusted according to patient-specific factors.

^bDe-escalation without deep healing may lead to disease flares.

^cWeigh the risk of anti-drug antibody formation with discontinuation of the TNF antagonist.

ACT, advanced combination treatment; AE, adverse event; EIM, extraintestinal manifestation; JAKi, Janus kinase inhibitor; TNF, tumor necrosis factor.

with concomitant inflammatory arthritis, TNF antagonists or JAK inhibitors will be required to adequately control the joint disease, and in patients with concomitant psoriasis, vedolizumab monotherapy will not adequately control their skin disease. Lastly, de-escalating a TNF antagonist may increase the risk of immunogenicity, and inability to restart this medication in the future should be weighed in the decision-making process (Table 3).

Outcomes of several pivotal studies using ACT up-front as induction therapy with de-escalation to monotherapy at specified time frames or once remission is reached may help answer questions about how to de-escalate therapy. This new top-down approach may be a promising option for patients at high risk for severe disease (younger age at diagnosis, more extensive disease burden, perianal fistula). Extrapolating on the missed endpoints in the VEGA study wherein mandatory de-escalation after an arbitrary time period (12 weeks) may have decreased efficacy, de-escalation may best be done based on patient-specific criteria proving remission (ie, fecal calprotectin normalization, deep mucosal healing), rather than based on a set time frame.

Concerns About Safety and Cost

Overall, the safety data in the few RCTs evaluating ACT have not shown any new safety signals.^{14,19} The case series and systematic reviews have not suggested any new AEs but have suggested an increased risk of infection, especially with the concomitant use of immunomodulators and corticosteroids. One must consider whether the infections were caused by exposure to any biologic agent or as a direct consequence of ACT. Based on the VEGA study, the former is likely, as comparable infection rates were found in patients on monotherapy and ACT.¹⁹ Nonetheless, long-term follow-up is required to demonstrate the safety of ACT over time.

Combination therapy of biologics with immunomodulators and corticosteroids has been well studied and accepted as appropriate treatment in IBD, with the benefits outweighing the risks. However, ACT has raised concerns over safety and cost based on its use in oncology and rheumatology. The increased risk of infectious AEs reported in rheumatology and oncology literature⁵⁶ may not apply to the IBD population, as IBD treatments tend

to be less immunosuppressive and exhibit greater gut specificity. In addition, biologic use currently contributes to rising IBD costs,^{57,58} without significant recent decreases in hospitalization costs after those seen with the introduction of TNF antagonists.⁵⁸ However, early ACT may increase response and remission rates beyond those seen with monotherapy—particularly for patients with refractory disease who contribute to a disproportionate amount of hospitalizations and IBD-related costs. The overall reduction in morbidity, long-term complications (eg, fistulas, strictures, and intestinal cancer), and absenteeism from work and school may reduce long-term health care expenditures and increase productivity. As evidence supporting the efficacy of ACT continues to grow, payors may become increasingly willing to provide coverage, diminishing cost- and access-related barriers to care.

Conclusion

The rising prevalence of IBD, combined with higher rates of refractory disease, contributes to a growing health care burden. The chronic nature and long-term complications of IBD often necessitate surgical intervention and lead to significant loss of productivity. The armamentarium of biologics and small molecules for IBD continues to grow; nonetheless, their efficacy remains capped at approximately 50%, highlighting a critical therapeutic gap. ACT may break that ceiling; a systematic review with meta-analysis of pooled ACT combinations in refractory IBD (76% CD) demonstrated pooled clinical remission rates of 59% and clinical response rates of 69%.⁶

The use of ACT in IBD can be 3-fold: to control EIMs not responsive to treatment for luminal disease, to treat medically refractory patients, and to initiate early intensive therapy in high-risk patients with planned de-escalation upon remission. Overall, ACT has pushed the therapeutic ceiling with improved efficacy seen across all medication combinations studied.

The decision for which medication combinations to use will have to be individualized based on the patient's prior response to therapy and prior AEs experienced. Current data are insufficient to recommend specific regimens; however, general recommendations include utilization of two distinct mechanisms of action and consideration of the patient's comorbid conditions. For patients without penetrating or concomitant extraintestinal disease, vedolizumab and IL-23 antagonists are attractive options based on their excellent safety profile and gut specificity. Vedolizumab alone may be insufficient to target psoriasis and can be paired with other biologics. Patients with perianal or fistulizing disease or inflammatory arthritis may benefit from a TNF antagonist or JAK inhibitor as one component of ACT. Combining TNF antagonists with JAK inhibitors

may be associated with higher AEs and infections based on their broader immunosuppression, but these agents may be appropriate choices for induction or during flares given the quick onset of action. JAK inhibitors particularly offer the ability to discontinue treatment with quick clearance from the blood and without risk of antibody development.

The majority of data for ACT in IBD currently are limited to small case reports or case series with aggregated data across all ACT combinations. Within these reports, data are inconsistent on concomitant corticosteroid or immunomodulator use, which is known to increase AEs and infections, clouding the safety of ACT. Final results of pivotal RCTs (VEGA, EXPLORER, and VICTRIVA) should provide more precise estimates of the safety and efficacy of ACT. Future positioning for ACT must be supported by larger clinical trials evaluating distinct ACT mechanisms, separating corticosteroid and immunomodulator use, establishing biomarkers or other endpoints to guide ACT initiation and de-escalation, and examining long-term safety in diverse populations. As with all medical decisions, the risks and benefits for the individual patient should be weighed and shared decision-making with the patient performed.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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