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ADVANCED COMBINATION THERAPY IN IBD: CAN IT BE ACHIEVED WITH SUCCESS?

Introduction

Conventional combination therapy in inflammatory bowel disease (IBD), which consists of an immunosuppressant agent and an anti-TNF agent, is a well-integrated strategy in clinical practice. The landmark SONIC and UC SUCCESS trials demonstrated that combining a thiopurine and infliximab was more effective than monotherapy and was associated with higher corticosteroid-free remission and mucosal healing rates.^{1,2}

The primary advantage of this traditional combination therapy derives from the immunomodulator's effect on the pharmacokinetics of anti-TNFs, with a lower rate of anti-drug antibodies detected in subjects administered combination therapy.³ Despite the growing therapeutic armamentarium and clinical study development pipeline for IBD, clinical remission rates at one year continue to range from 30% to 50%⁴⁻⁷ indicating that a therapeutic ceiling may have been reached with the use of single agents. In addition, agents that have proven effective for luminal disease may not be helpful for extraintestinal manifestations (EIMs) or for concurrent immune-mediated diseases (IMIDs).⁸ In light of this, the concept of advanced combination treatment (ACT), which entails the simultaneous administration of at least two biologic agents, or a biologic and a small-molecule drug, is emerging as a therapeutic approach for patients with refractory IBD, as well as for those with IBD and a concurrent IMID, or IBD with EIMs.⁹

Clinical Evidence for ACT

Previous clinical trials and reports

Several case series and small-cohort studies have provided interesting examples of successful use of ACT in patients with refractory IBD, or those with concomitant IMIDs (e.g., psoriatic disease, rheumatoid arthritis [RA], spondylarthritis [SpA]) or EIMs (e.g., erythema nodosum, pyoderma gangrenosum, uveitis).

Among cohort studies, Yang et al reported the results of 22 patients with long-standing Crohn's disease (CD) in a Canadian and U.S. centre, of whom the majority had undergone prior surgical resections and failed a median number of four biologics.¹⁰ The most common combination administered was vedolizumab plus ustekinumab, likely due to their favourable individual safety profiles.

An Italian retrospective cohort study reported improved outcomes in all 16 patients with either active IBD or active EIMs (e.g., active SpA and psoriatic disease), treated with ACT.¹¹ In this case series, only three adverse

events were reported (cutaneous reaction following certolizumab administration, a drug-induced liver injury, and a perianal abscess); however, none of these were serious.

A systematic review with meta-analysis including 30 studies involving 279 IBD patients found that the primary indication for ACT was refractory IBD, followed by concurrent EIMs or rheumatologic disease.¹² The most common combination was anti-TNF therapy plus anti-integrins (48%), followed by ustekinumab plus an anti-integrin. Over a median follow-up of 32 weeks, pooled rates of clinical and endoscopic remission were 59% (95% CI, 42%-74%), and 34% (95% CI, 23%-46%), respectively. Interestingly, rates of success were higher in those receiving ACT due to concomitant EIMs, corroborating the hypothesis that inhibiting more than a single mechanism of action might provide adequate disease control across multiple organ systems. The safety data revealed 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%)¹³.

The RCT conducted by Sands et al in 2007 represents the first attempt of ACT in IBD.¹⁴ In this study, 79 patients with active CD (Crohn's Disease Activity Index [CDAI] score $\geq$ 150) while on infliximab treatment were randomized 2:1 to receive three intravenous infusions of natalizumab (300 mg; n = 52) or placebo (n = 27) every four weeks. Patients received infliximab (5 mg/kg) every eight weeks for at least ten weeks prior to randomization and throughout the study. The percentage of patients experiencing adverse events was similar between the combination and the monotherapy groups (27% vs 30%, respectively). Although the trial was not powered to detect statistical differences in terms of efficacy, a higher proportion of patients in the combination group achieved clinical remission over the entire length of the study compared to the monotherapy arm. However, the use of natalizumab is associated with increased risk for developing progressive multifocal leukoencephalopathy and it is approved only for moderate-to-severe CD by the FDA.

The Phase 2, randomized, double-blind, controlled VEGA trial, whose results were published online in February 2023, demonstrated that the combination of the anti-TNF golimumab with the anti-interleukin-23 guselkumab was more effective for short-term induction treatment in UC than either agent alone.¹⁵

VEGA was a proof-of-concept trial conducted at 54 hospitals, academic medical centers, or private

practices in nine countries. Eligibility criteria included: Adults age ≥ 18 to 65 years with a confirmed diagnosis of UC at least three months before screening and moderately-to-severely active UC (Mayo score 6-12) with a centrally-read baseline endoscopy subscore of 2 or higher.

Three-hundred fifty-eight patients were randomly assigned (1:1:1) to combination therapy (subcutaneous golimumab 200 mg at Week 0, subcutaneous golimumab 100 mg at Weeks 2, 6, and 10, and intravenous guselkumab 200 mg at Week 0, 4, and 8, followed by subcutaneous guselkumab monotherapy 100 mg every 8 weeks for 32 weeks, $n=71$); golimumab monotherapy (subcutaneous golimumab 200 mg at Week 0 followed by subcutaneous golimumab 100 mg at Week 2 and every 4 weeks thereafter for 34 weeks, $n=72$); or guselkumab monotherapy (intravenous guselkumab 200 mg at Weeks 0, 4, and 8, followed by subcutaneous guselkumab 100 mg every 8 weeks thereafter for 32 weeks, $n=71$).

The study's primary endpoint was clinical response at Week 12 (defined as a $\geq 30\%$ 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). A greater proportion of patients receiving combination therapy achieved clinical response (59/71, 83.1%) after 12 weeks vs monotherapy with either guselkumab (53/71, 74.6%, nominal $p=0.2155$) or golimumab (44/72, 61.1%, nominal $p=0.0032$). Interestingly, the composite outcome, including endoscopic improvement and histologic remission, was achieved in approximately twice as many patients with ACT vs monotherapy (40.8% vs 26.8% and 15.3% with guselkumab and golimumab, respectively). Consistent with safety data from real-world experiences, only one patient reported a serious infection of influenza and sepsis among 71 subjects on ACT. Infections were reported in 14% of patients receiving combination therapy or guselkumab monotherapy vs a rate of 22% in those receiving golimumab monotherapy.

Ongoing clinical trials

Several clinical trials on ACT in IBD are currently ongoing. EXPLORER is an open-label, uncontrolled study, investigating the role of triple combination therapy with vedolizumab, adalimumab and oral methotrexate in inducing endoscopic remission in selected patients with a recent CD diagnosis (within 24 months) and at high risk for complications (SES-CD score ≥ 7 , or ≥ 4 if isolated ileal disease).¹⁶ An interim analysis showed that the primary outcome of endoscopic remission (SES-CD 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. DUET-CD and DUET-UC are ongoing Phase 2b randomized, active-and placebo-controlled studies evaluating the efficacy and safety of induction and maintenance ACT with guselkumab and golimumab in participants with moderate-to-severe CD and UC, respectively.

ACT should be administered only in specific clinical situations following a comprehensive examination of the patient's needs and any potential safety issues. Specifically, ACT should be considered for treatment of luminal disease, which is medically refractory to all available monotherapy, in cases of concomitant EIMs or IMIDs, or in extremely high-risk phenotypes such as extensive small bowel disease, as well as structuring and penetrating disease at high risk of developing complications. When using ACT for an alternative concomitant, untreated inflammatory pathway, clinicians should take into account inflammatory pathways and downstream cascades that are targeted with potential ACT, avoiding agents with multiple crosstalk interactions (such as an anti-12/23 combined with an anti-IL-23). Finally, biologics that have previously resulted in immunogenicity should be avoided. Due to their favorable safety profiles, vedolizumab and ustekinumab appear to be the most suitable anchor biologics based on the clinical evidence currently available^{17,18}

An individualized approach to treatment is paramount in cases where there is a paucity of clinical data to support what appears to be the optimal combination. For instance, in individuals with concomitant EIMs/IMIDs who have shown response from one tissue target, such as the skin or joints with an anti-TNF or an (IL-12)/23 antagonists, the addition of a gut-selective compound such as vedolizumab seems reasonable in the setting of active luminal disease. The addition of vedolizumab or an oral small-molecule drug such as tofacitinib in UC should be considered in very high-risk phenotypes with partial response to IL-12/23-axis-blockade and a history of loss of response, intolerance to therapy with one or more TNF inhibitors, or both. Decisions should also be made based on the mode of delivery selected (e.g., subcutaneous vs oral), individual comorbidities, prior treatment failures, and disease subtype.

Despite the growing number of observational studies, the practice of ACT remains off-label and larger real-world clinical studies and RCTs are needed to better evaluate the effectiveness and safety of this treatment approach.

Conclusion

The concept of ACT has appeal as a method to raise the therapeutic ceiling for IBD. At present, its use is strictly off-label, and it should be used only in specific scenarios as discussed in this article (**Table 1**). Potential risks and benefits should be clearly documented, and ideally the decision to initiate should be made by a multidisciplinary team. In addition to traditional combination therapy, ACT including at least two advanced targeted therapies has proven to be useful for specific clinical scenarios following careful evaluation of the patient's needs, as well as potential safety issues. With the addition of ozanimod, upadacitinib, and other anti-IL-23 medications (such as risankizumab, guselkumab, and mirikizumab), it is anticipated that new drug combinations with varied effectiveness and safety profiles will be investigated in the near future, enhancing the current IBD treatment armamentarium. All of the available evidence should be considered hypothesis-generating for future well-controlled and adequately powered clinical trials, ideally in high-risk subjects.

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References

- Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. <http://dx.doi.org/10.1056/NEJMoa0904492>. 2010;362(15):1383-1395. doi:10.1056/NEJMoa0904492
- Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology*. 2014;146(2). doi:10.1053/J.GASTRO.2013.10.052
- Colombel JF, Adedokun OJ, Gasink C, et al. Combination Therapy With Infliximab and Azathioprine Improves Infliximab Pharmacokinetic Features and Efficacy: A Post Hoc Analysis. *Clin Gastroenterol Hepatol*. 2019;17(8):1525-1532.e1. doi:10.1016/J.CGH.2018.09.033
- Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT 1 randomised trial. *Lancet*. 2002;359(9317):1541-1549. doi:10.1016/S0140-6736(02)08512-4
- Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65. doi:10.1053/J.GASTRO.2006.11.041
- Rosario M, Dirks NL, Gastonguay MR, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther*. 2015;42(2):188-202. doi:10.1111/APT.13243
- Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med*. 2016;375(20):1946-1960. doi:10.1056/NEJMoa1602773
- Schett G, McInnes IB, Neurath MF. Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs. *N Engl J Med*. 2021;385(7):628-639. doi:10.1056/NEJMRA1909094
- 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*. Published online 2022. doi:10.1136/GUTJNL-2022-327025
- Yang E, Panaccione N, Whitmire N, et al. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. *Aliment Pharmacol Ther*. 2020;51(11):1031-1038. doi:10.1111/APT.15719
- Privitera G, Onali S, Pugliese D, et al. Dual Targeted Therapy: a possible option for the management of refractory Inflammatory Bowel Disease. *J Crohns Colitis*. 2020;15(2):335-339. doi:10.1093/ECCO-JCC/JJAA149
- Ahmed W, Galati J, Kumar A, et al. Dual Biologic or Small Molecule Therapy for Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. Published online 2021. doi:10.1016/J.CGH.2021.03.034
- Lichtenstein GR, Feagan BG, Cohen RD, et al. Infliximab for Crohn's Disease: More Than 13 Years of Real-world Experience. *Inflamm Bowel Dis*. 2018;24(3):490-501. doi:10.1093/IBD/IZX072
- Sands BE, Kozarek R, Spainhour J, 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. doi:10.1002/IBD.20014
- Feagan BG, Sands BE, Sandborn WJ, 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*. Published online February 2023. doi:10.1016/S2468-1253(22)00427-7
- Colombel JF, Ungaro RC, Sands BE, et al. 885: TRIPLE COMBINATION THERAPY WITH VEDOLIZUMAB, ADALIMUMAB, AND METHOTREXATE IN PATIENTS WITH HIGH-RISK CROHN'S DISEASE: INTERIM ANALYSIS FROM THE OPEN-LABEL, PHASE 4 EXPLORER TRIAL. *Gastroenterology*. 2022;162(7):S-215. doi:10.1016/S0016-5085(22)60514-6
- Schreiber S, Dignass A, Peyrin-Biroulet L, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. *J Gastroenterol*. 2018;53(9):1048-1064. doi:10.1007/S00535-018-1480-0
- Sandborn WJ, Rebutck R, Wang Y, et al. Five-year Efficacy and Safety of Ustekinumab Treatment in Crohn's Disease: the IM-UNITI trial. *Clinical gastroenterology and hepatology*. Published online 2021. doi:10.1016/j.cgh.2021.02.025

Population	Patients with IBD refractory to all medical therapy Patients with high-risk phenotypes (extensive small bowel disease, and stricturing or fistulizing disease behaviour) Patients with a concomitant IMID (e.g., psoriatic disease, RA, SpA) or EIMs (e.g., erythema nodosum, pyoderma gangrenosum, uveitis)
ACT	Preference for agents with the most favorable safety profile (e.g., vedolizumab and ustekinumab as anchor) Preference for anti-TNF agents in CD, especially in ileal CD or with bowel damage (eg, fistula, strictures, complex perianal disease) Preference for vedolizumab in UC patients Preference for anti-TNF agents or ustekinumab (or anti-IL-23 blocker); or a JAK inhibitor in patients with concomitant EIMs or IMIDs
Setting	Potential risks and benefits should be clearly documented; ideally the decision to initiate should be made by a multidisciplinary team

Table 1. Practical recommendations for the use of ACT in clinical practice; courtesy of Vipul Jairath, MD and Virginia Solitano, MD