Ther Adv Gastroenterol

2024, Vol. 17: 1–9

DOI: 10.1177/
17562848241272995

Advanced combination therapy: is it the best way to break the therapeutic ceiling?

Panu Wetwittayakhlang and Peter L. Lakatos

***Abstract*:** Current therapeutic strategies for inflammatory bowel disease (IBD) have reached a plateau in the rates of response and/or remission achieved with a single therapeutic agent. Consequently, the advanced combination therapy (ACT) strategy has emerged as a novel treatment concept for IBD. ACT involves the use of two different targeted therapies, whether biologic or small molecules, with the primary goal of overcoming the therapeutic plateau. Real-world evidence is accumulating among patients undergoing ACT, especially those dealing with concurrent IBD and extraintestinal manifestations or grappling with medically refractory IBD. The recently conducted VEGA study, a randomized clinical trial, has provided crucial insights by demonstrating that the short-term combination of dual biological agents can lead to superior disease control compared to single agents in patients diagnosed with ulcerative colitis (UC). This suggests that ACT holds promise as a therapeutic option to enhance disease control effectively. However, there is still limited evidence of ACT in UC patients who have proven refractory to biologic therapy and patients with Crohn's disease. This review aims to discuss whether ACT represents the optimal approach for overcoming the therapeutic ceiling in IBD.

Video Abstract Please click on the image to play the video (also available as supplemental material).

Keywords: advanced combination therapy, biologic, Crohn's disease, inflammatory bowel disease, ulcerative colitis, small molecule

Received: 18 March 2024; revised manuscript accepted: 13 May 2024.

Correspondence to:
Peter L. Lakatos
McGill University Health Centre, Montreal General Hospital, 1650 Ave. Cedar, D16.173.1, Montreal, QC H3G 1A4, Canada

Department of Oncology and Medicine, Semmelweis University, Budapest, Hungary
Peter.Lakatos@muhc.mcgill.ca
peter.lakatos@mcgill.ca
kislakpet99@gmail.com

Panu Wetwittayakhlang
Gastroenterology and Hepatology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand

Division of Gastroenterology and Hepatology, McGill University Health Center, Montreal, QC, Canada

Introduction

In the contemporary landscape, biological therapies have become the established standard of care for managing moderate to severely active inflammatory bowel disease (IBD), encompassing both Crohn's disease (CD) and ulcerative colitis (UC).[1,2] Despite these advancements, current therapeutic approaches in IBD have reached stagnation in response and/or remission rates. The existing arsenal of advanced therapies for IBD, comprising biologic and small-molecule options, yields overall clinical remission rates hovering around a modest 50%.

In the context of CD, anti-tumor necrosis factor (anti-TNF) therapy's induction of remission has been reported in only 18%–48% of patients.[3] Meanwhile, a meta-analysis comparing gut-selective anti-integrin α4β7 (vedolizumab) with anti-TNFs in UC revealed pooled rates of mucosal healing ranging from 18% to 33% after 54 weeks of maintenance treatment.[4] The VARSITY study mirrored this trend, reporting clinical remission rates of a mere 31.3% for vedolizumab and 22.5% for adalimumab at 52 weeks.[5] The Janus kinase inhibitor tofacitinib demonstrated induction of clinical remission in UC patients at rates between 16.6% and 18.5% at 8 weeks, with remission rates at 52 weeks varying from 34.3% to 40.6% in initial responders.[6] Similarly, only 47.8% of UC patients treated with ozanimod in the True North study achieved clinical response at week 10, with only 37.0% of induction responders attaining clinical remission at week 52.[7,8]

Notably, approximately 50% of patients who initially respond to biological or small-molecule therapy ultimately lose their response over time.[9,10] Consequently, IBD patients who had refractory or lost response to a specific biologic therapy need to switch to a different molecule, diminishing their prospects of achieving long-term disease remission.

The new concept "advanced combination therapy" in IBD

The novel approach known as "advanced combination therapy" (ACT) has emerged as a prospective management strategy for IBD.[11] This proposal is grounded in several key considerations: (1) Low clinical remission rate of biologic therapy as a single agent. (2) Significant number of patients experience a decline in responsiveness to mono-biologic treatment over the course of time. (3) The immune-mediated inflammatory process in IBD involves the concurrent activation of multiple inflammatory pathways. Blocking only one pathway may not suffice for optimal inflammation control in each patient. (4) Monotherapy with a biologic agent effective for luminal disease may prove less effective in managing coexisting extraintestinal manifestations (EIMs) or other immune-mediated inflammatory diseases (IMIDs).[12,13]

In light of these considerations, the prospect of combined advanced therapy with diverse mechanisms of action arises. This could encompass a combination of biologics (dual biologic therapy), a combination of biologic and small molecules, or a combination of small molecules (dual small molecules). Such combinations represent a potential avenue for surpassing the therapeutic limitations of IBD.

Recently, accumulating data on ACT has been gleaned from a noteworthy randomized controlled trial, the VEGA study. This review aims to discuss the current evidence surrounding ACT and its impact on breaking the therapeutic ceiling in the treatment of IBD.

Methodology

A literature search was conducted on PubMed up until February 2024, using search terms such as "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," "advanced combination therapy," and "dual biologic." Publications were selected for inclusion based on their relevance and study design. Priority was given to data from clinical trials and meta-analyses whenever available, followed by prospective and retrospective observational studies. In this review, we specifically address the question "Does ACT have the potential to break the therapeutic ceiling?" based on the currently available data.

Evidence from randomized controlled trials of ACT

Combination of gulselkumab and golimumab

The VEGA study, the most recent ongoing phase IIa RCT, evaluated the efficacy of a combination induction therapy with selective interleukin (IL)-23, guselkumab, and anti-TNF,

golimumab compared to guselkumab or golimumab monotherapy in patients with moderately to severely active UC.[14] A total of 214 patients naïve to an anti-TNF and refractory or intolerant to conventional therapy were randomly assigned to receive guselkumab 200 mg IV at weeks 0, 4, and 8 ($n=71$); golimumab 200 mg subcutaneous (SC) at week 0, then 100 mg SC at weeks 2, 6, and 10 ($n=72$); or combination with guselkumab 200 mg IV plus golimumab 200 mg SC at week 0, golimumab 100 mg SC at weeks 2, 6, and 10, and guselkumab 200 mg IV at weeks 4 and 8 ($n=71$). In the maintenance phase, patients in the combination therapy arm were switched to guselkumab monotherapy at the beginning of week 12.[14]

During the induction, at week 12, 59 (83%) of 71 patients in the combination therapy group had clinical response compared with 44 (61%) of 72 patients in the golimumab monotherapy group (adjusted treatment difference 22.1%; 80% confidence interval (CI): 12.9–31.3; $p=0.0032$) and 53 (75%) of 71 patients in the guselkumab monotherapy group (adjusted treatment difference 8.5%; 80% CI: −0.2 to 17.1; $p=0.2155$). However, statistical significance was not achieved between the combination therapy group and both monotherapy groups. Similarly, 26 (37%) of 71 patients in the combination therapy group had achieved clinical remission compared with 16 (22%) of 72 patients in the golimumab monotherapy group ($p=0.0578$) and 15 (21%) of 71 patients in the guselkumab monotherapy group ($p=0.0412$). In addition, the proportion of patients who had achieved endoscopic improvement (49% vs 25% vs 30%) and endoscopic remission (18% vs 10% vs 8%) was significantly higher in the combination therapy group than either the golimumab or guselkumab monotherapy groups, respectively.

In the maintenance phase, the clinical response and remission rates were largely sustained with guselkumab maintenance in the group that initially received combination therapy. At week 38, 49 (69%) of 71 patients in the combination therapy group had clinical response compared to 42 (58%) of 72 patients in the golimumab monotherapy group (adjusted treatment difference 10.8%; 80% CI: 1.1–20.5) and 51 (72%) of 71 patients in the guselkumab monotherapy group (adjusted treatment difference −2.8%; 80% CI: −11.9 to 8.3). Furthermore, 31 (44%) of 71 patients in the combination therapy group had achieved clinical remission compared to 16 (22%) of 72 patients in the golimumab monotherapy group (adjusted treatment difference 21.5%; 80% CI: 11.9–31.2) and 22 (31%) of 71 patients in the guselkumab monotherapy group (adjusted treatment difference 12.7%; 80% CI: 2.7–22.7). The proportion of patients who achieved endoscopic improvement (49% vs 22% vs 32%) and endoscopic remission (25% vs 7% vs 15%) in the combination group was higher compared to both the golimumab monotherapy and guselkumab monotherapy groups, respectively. Adverse event (AE) rates were comparable among the treatment groups.[14]

Combination of anti-integrin α4 antibody (natalizumab) and anti-TNF (infliximab)

This was the first RCT to evaluate the safety and efficacy of the combination of natalizumab and infliximab in patients with active CD despite ongoing infliximab treatment.[15] In this study of 79 CD patients (52 receiving natalizumab plus infliximab and 27 receiving placebo plus infliximab), the patients receiving combination therapy showed a trend to have higher rates of clinical remission throughout 32 weeks of follow-up compared with patients receiving infliximab monotherapy, but these differences were not statistically significant. It is important to note that the primary objective of this study was to assess safety. Therefore, the study may have been underpowered to detect statistically significant differences between mono- and combination therapy. However, there were concerns about the safety of natalizumab due to the possibility of progressive multifocal leukoencephalopathy, especially in patients who have had prior immunosuppressive treatment.[16,17] Due to this, the use of natalizumab in CD treatment has been extremely low.[18]

The open-label phase IV "EXPLORER trial," assessed the efficacy of the triple combination of vedolizumab, adalimumab, and methotrexate therapy in biologic-naïve

The open-label phase IV "EXPLORER trial" assessed the efficacy of triple combination therapy comprising vedolizumab, adalimumab, and methotrexate in biologic-naïve patients with moderate to high-risk Crohn's disease (CD), determined by an endoscopic score for CD (SES-CD) >7 (or >4 if isolated ileal disease)

Table 1. The current RCT evidence on ACT in the treatment of IBD.

Combination	Study population	Main result	Limitation in clinical implication
GUS + GOL vs GUS vs GOL monotherapy (VEGA study)	Biologic naïve moderately to severely active UC patients ($n = 214$)	At week 12 Clinical remission: GUS + GOL (37%) vs GUS (21%) vs GOL (22%) Endoscopic remission: GUS + GOL (18%) vs GUS (8%) vs GOL (10%) At week 38 Clinical remission: GUS + GOL (44%) GUS (31%) vs GOL (22%) Endoscopic remission: GUS + GOL (25%) vs GUS (15%) vs GOL (7%)	The study did not include patients with previously exposed to anti-TNF
VDZ + ADA + MTX (EXPLORER study)	Biologic-naïve CD patients with moderate to high risk of complications ($n = 55$)	Clinical remission 54.4% Endoscopic remission 34.5%	-No placebo-controlled group -The study included only anti-TNF-naïve CD patients. -Small sample size (preliminary analyses)
IFX + natalizumab vs IFX monotherapy	Active CD patients with inadequate response to anti-TNF ($n = 79$)	Clinical remission at weeks 2, 6, and 10 was 15.4%, 23.1%, and 36.5%, respectively Higher decrease in mean CDAI score in the IFX + natalizumab group vs IFX + placebo, but no significant difference.	-No significant difference in decrease of CDAI score -Safety concerns of natalizumab

ADA, adalimumab; CD, Crohn's disease; CDAI, Crohn's disease activity index; GOL, golimumab; GUS, gluselkumab; IFX, infliximab; MTX, methotrexate; TNF, tumor necrosis factor; UC, ulcerative colitis; VDZ, vedolizumab.

[ClinicalTrials.gov identifier: NCT02764762]. Eligible patients with CD were considered to be at moderate to high risk of complications based on clinical assessment by investigators, the CDPATH tool, or criteria outlined in the 2014 American Gastroenterological Association CD Clinical Care Pathway.[19] An interim analysis was undertaken of 55 patients treated with triple therapy (vedolizumab 300 mg IV on day 1 and week 2, week 6 and then every 8 weeks, adalimumab 160 mg SC on day 2, 80 mg at week 2, and then 40 mg every 2 weeks until week 26, methotrexate 15 mg orally weekly until week 34); after the triple therapy and by week 34, every patient received vedolizumab monotherapy until week 102. At week 26, endoscopic response and endoscopic remission were observed in 54.4% and 34.5%, respectively. There were no safety signals related to the triple therapy [ClinicalTrials.gov identifier: NCT02764762].[20] The current RCT evidence on ACT in the treatment of IBD is summarized in Table 1.

Evidence from real-world studies

In clinical settings, the rationale behind employing ACT, utilizing either biologics or small molecules, for the treatment of IBD within two distinct clinical scenarios.

First, in "complicated IBD patients" experiencing poorly controlled luminal disease, the approach involves initial co-induction or the addition of a second agent sequentially if there is a partial or inadequate response to the first agent. Moreover, for high-risk patients previously exposed to multiple biologic agents, the recommendation is to employ induction therapy with two agents simultaneously as a concomitant induction strategy.[13]

The second scenario, "double indication," pertains to patients with concomitant EIMs or IMIDs. In such cases, the addition of a second agent is suggested to control either active intestinal inflammation or symptoms associated with

EIMs. Specifically, in IBD patients presenting with uncontrolled luminal symptoms alongside quiescent EIM symptoms,[13] the most commonly utilized combination involves a gut-selective agent (vedolizumab) combined with ustekinumab or anti-TNFs, followed by a combination of ustekinumab with anti-TNFs in cases of the "double indication."[21–25]

Regarding real-world observational data, a large multicenter study reported 98 patients who started combination therapy for active IBD (67%), active IMID or EIMs (22%), or both (10%), in the setting of multiple biologic failures. IBD disease activity was clinically improved in 70% of patients, and IMID/EIM activity was clinically improved in 81%.[25] Another retrospective study reported on 92 patients receiving combined biologic therapy for active IBD or EIMs. The most common combinations were vedolizumab and ustekinumab (32%), or vedolizumab and anti-TNF (31%). The clinical response rates at 3 and 6 months were 46% and 34%, respectively.[26] A retrospective study by Glassner et al.[27] evaluated 50 patients with IBD who were treated with various combinations of biologics or small molecule therapy; approximately 50% were vedolizumab plus anti-IL-12 and IL-23 (ustekinumab) for persistent disease activity ($n = 47$) or concomitant rheumatological or dermatological disease ($n = 3$). There were significantly more patients in clinical remission at 4 months (50% vs 14%, $p = 0.0018$) and endoscopic remission at 8 months (34% vs 6%, $p = 0.0039$) compared to baseline.[27]

Another case series revealed that dual biologic therapy was safe and effective in 22 CD patients with severe refractory CD who had a total of 24 dual biologic treatments after multiple failed biologics. Clinical response and clinical remission were seen in 50% and 41% of patients, respectively. Endoscopic improvement and remission were found in 43% and 26%, respectively. The presence of active perianal fistula decreased from 50% at baseline to 33% after treatment.[28] Similarly, the efficacy of combining tofacitinib with other biological therapies was reported in two retrospective cohorts.[29,30]

In a 2021 meta-analysis by Ahmed et al., 30 studies involving 279 IBD patients (76% CD) were analyzed. The median treatment duration was 24 weeks. The most common dual biologic therapies were anti-TNFs and vedolizumab (48%) and ustekinumab and vedolizumab (19%). A total of 61% of patients had previously failed at least one of the two therapies used in combination. Over a median follow-up of 32 weeks (interquartile range 24–52), clinical remission and endoscopic remission rates were pooled at 59% (95% CI: 42%–74%) and 34% (95% CI: 23%–46%), respectively. The pooled rates of AEs and serious AEs were 31% (95% CI: 13%–54%) and 6.5% (95% CI: 2.1%–13.1%), respectively. The proportions of patients experiencing infections and malignancy were 19% and 1%, respectively.[31]

In another meta-analysis by Alayo et al., the efficacy of ACT with different combination regimens was assessed. Among patients receiving vedolizumab plus tofacitinib, the pooled clinical response and remission rates were 59.9% (95% CI: 37.2–80.8) and 47.8% (95% CI: 19.0–77.4), respectively. For vedolizumab plus ustekinumab, the pooled clinical response and remission rates were 83.9% (95% CI: 66.4–96.8) and 47.0% (95% CI: 14.5–80.7), respectively. Patients on vedolizumab plus anti-TNF had pooled endoscopic/radiologic response and remission rates of 38.2% (95% CI: 19.5–58.4) and 18.0% (95% CI: 1.6–41.8), respectively. For patients on tofacitinib plus vedolizumab, the corresponding rates were 46.2% (95% CI: 20.4–73.0) and 24.6% (95% CI: 6.4–47.6).[32]

Ongoing clinical trial of ACT in IBD

JNJ-78934804 (combination of guselkumab and golimumab)

The DUET-CD and DUET-UC trial—studies of an ongoing phase IIb randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe active CD and UC. The patients are being randomized into six arms, including guselkumab, golimumab, and JNJ-78934804 (combination guselkumab and golimumab, high dose, mid dose, and low dose) and a placebo arm. The primary outcome of this study is to compare clinical remission and endoscopic response at week 48 among the treatment arms. Both studies are recruiting patients. ClinicalTrials.gov identifiers: NCT05242471 (DUET-CD) and NCT05242484 (DUET-UC).

Combination of vedolizumab and upadacitinib

The VICTRIVA trial—a phase IIIb, a randomized, double-blind, placebo-controlled study of vedolizumab with and without upadacitinib in patients with moderately to severely active CD. The study will enroll approximately 396 patients. Participants will be assigned in a 1:1 ratio to one of the two treatment groups (vedolizumab plus upadacitinib vs vedolizumab plus placebo) in the 12-week induction period. Participants who achieve a Crohn's disease activity index reduction of 270 points from baseline at week 12 will progress into the 40-week maintenance period of the study to receive vedolizumab monotherapy [ClinicalTrials.gov identifier: NCT06227910].

Is the ACT strategy able to improve the therapeutic ceiling in IBD?

Addressing the pivotal clinical question of whether we can overcome the therapeutic ceiling in IBD through the utilization of ACT, the current evidence from the VEGA study provides insightful observations. In biologic-naïve patients with UC, the study indicates a higher rate of clinical remission and endoscopic improvement in the combination therapy group (golimumab and guselkumab induction therapy) compared to monotherapy with golimumab or guselkumab. However, the VEGA study did not include UC patients with prior exposure or failure to previous biologics. Consequently, there remains a scarcity of clinical trial data regarding the effectiveness of ACT in UC patients refractory to biologic treatment. Expanding the scope to patients with CD, the available data on ACT are limited. The EXPLORER study hints at the efficacy of a combination involving vedolizumab, adalimumab, and methotrexate in improving endoscopic response and remission in biologic-naïve CD patients with moderate to high risk of complication. Nevertheless, the absence of a controlled arm in the study hinders a clear demonstration of the therapeutic efficacy of ACT in CD.

Despite the increasing volume of real-world data on ACT in the treatment of IBD, the evidence is weak at the moment to achieve a definite conclusion on whether ACT can surpass the therapeutic ceiling. This limitation arises from the fact that the majority of patients in real-world observational studies have already experienced a loss or inadequate response to one or more agents used in combination therapy and outcome measures of the benefit are often based on clinical judgment. In addition, ACT may have been employed to manage co-existing EIMs, rather than addressing active luminal IBD. As a result, it is not feasible to assume the true therapeutic efficacy in biologic-naïve patients based solely on this data. Therefore, to address the question of whether ACT can overcome the therapeutic ceiling, we must rely on the most reliable data available, which is primarily derived from a limited number of clinical trials involving ACT in patients naïve to biologic agents at the moment.

The use of ACT has emerged as a potential new therapeutic strategy aiming to improve therapeutic efficacy and overcome the plateau observed with currently available therapies. In highly selected patients with a high-risk disease phenotype, such as those with extensive small bowel involvement in CD or those refractory to multiple therapies, employing ACT may be reasonable for early disease control to prevent disease progression and complications. During the induction phase, simultaneous co-induction with a combination of biologics or small molecules can be utilized to achieve maximum disease control through synergistic effects. Once disease remission is achieved, monotherapy with one of the combined agents may be used to maintain disease remission.[12]

Another aspect to consider in the application of the ACT strategy in clinical practice is the potential for shifts in safety signals with prolonged exposure to multiple immunosuppressants. While safety concerns have not been prominent thus far, it is important to recognize that existing data come from small studies with limited follow-up durations. To truly understand the efficacy and safety of this strategy, further large prospective studies with extended follow-up periods are needed. Uncertainties also persist regarding whether combination therapy should be used solely for the induction period or extended to maintenance therapy. In addition, the financial implications of long-term treatment with the ACT strategy may pose a burden, requiring careful consideration.

In the future, there is a need for larger prospective-controlled clinical trials to investigate the efficacy and safety of ACT, particularly focusing on subgroups of patients such as those with CD and fistulizing disease, perianal fistula, and patients refractory to biologic therapy. Given the increasing number of available biologic and small

molecule therapies with varying mechanisms of action, there is a need to identify optimal combination regimens. This includes determining which biologics should be used in combination therapy, as well as establishing the optimal doses and durations of treatment. In line with the principles of precision medicine, pre-treatment patient stratification may aid physicians in selecting the most suitable biologic for each patient. Finally, patient stratification based on safety risk is crucial to minimize drug toxicity and side effects associated with ACT.

Conclusion

Recent findings from the VEGA study highlight that the combination of novel biologics (guselkumab and golimumab) achieves superior therapeutic efficacy, both clinically and endoscopically, compared to mono-biologic therapy in biologic-naïve, moderately to severely active UC patients. This study establishes the feasibility of ACT in IBD, suggesting it as a potential future treatment strategy to break the therapeutic ceiling in IBD. However, the VEGA study did not include refractory UC patients who had failed or been exposed to biologic therapy, resulting in limited data on ACT in this specific population. Moreover, there is a notable absence of RCTs investigating ACT in patients with CD, which poses unique challenges, especially in those with complicated diseases. Observational real-world studies, while informative, fall short in addressing whether ACT can elevate the therapeutic ceiling in IBD within the complexities of real-life clinical settings, as most patients receiving ACT have experienced failure or inadequate response to biologic therapy. Looking ahead, ongoing studies such as DUET-CD and DUET-UC trials (examining the combination of guselkumab and golimumab in refractory IBD patients) and the VICTRIVA trial (evaluating the combination of vedolizumab and upadacitinib) hold promise for providing additional data on the efficacy of ACT in CD and UC patients who have failed biologic therapy.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Panu Wetwittayakhlang: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Peter L. Lakatos: Conceptualization; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Disclaimer

The article processing charges for this publication have been waived under an educational grant from Takeda Pharmaceuticals Limited.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

P.L.L. has been a speaker and/or advisory board member: AbbVie, Amgen, BioJamp, Bristol Myers Squibb, Fresenius Kabi, Genetech, Gilead, Janssen, Merck, Mylan, Organon, Pendopharm, Pfizer, Roche, Sandoz, Takeda, Tillots, and Viatris and has received unrestricted research grant: AbbVie, Gilead, Takeda, and Pfizer. P.W. has been a speaker for Takeda, Pfizer, Janssen, Ferring, A. Menerini, and MSD, and an advisory board member for Pfizer, Takeda, and Sanzdos (Norvatis).

Availability of data and materials

Not applicable.

ORCID iDs

Panu Wetwittayakhlang https://orcid.org/0000-0002-5962-4112

Peter L. Lakatos https://orcid.org/0000-0002-3948-6488

Supplemental material

Supplemental material for this article is available online.

References

1. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2020; 14: 4–22.

2. Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohns Colitis* 2022; 16: 2–17.

3. Peyrin-Biroulet L and Lémann M. Review article: remission rates achievable by current therapies for inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; 33: 870–879.

4. Cholapranee A, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther* 2017; 45: 1291–1302.

5. Sands BE, Peyrin-Biroulet L, Loftus EV, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med* 2019; 381: 1215–1226.

6. Sandborn WJ, Panés J, D'Haens GR, et al. Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. *Clin Gastroenterol Hepatol* 2019; 17: 1541–1550.

7. Sandborn WJ, Feagan BG, Wolf DC, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. *N Engl J Med* 2016; 374: 1754–1762.

8. William S, Geert D, Doug W, et al. P025 ozanimod efficacy, safety, and histology in patients with moderate-to-severe ulcerative colitis during induction in the phase 3 True North Study. *Am J Gastroenterol* 2020; 115: S6–S7.

9. Marsal J, Barreiro-de Acosta M, Blumenstein I, et al. Management of non-response and loss of response to anti-tumor necrosis factor therapy in inflammatory bowel disease. *Front Med* 2022; 9: 897936.

10. Chen C, Hartzema AG, Xiao H, et al. Real-world pattern of biologic use in patients with inflammatory bowel disease: treatment persistence, switching, and importance of concurrent immunosuppressive therapy. *Inflamm Bowel Dis* 2019; 25: 1417–1427.

11. Danese S, Solitano V, Jairath V, et al. The future of drug development for inflammatory bowel disease: the need to ACT (advanced combination treatment). *Gut* 2022; 71: 2380–2387.

12. Solitano V, Ma C, Hanžel J, et al. Advanced combination treatment with biologic agents and novel small molecule drugs for inflammatory bowel disease. *Gastroenterol Hepatol* (*NY*) 2023; 19(5): 251–263.

13. Privitera G, Pugliese D, Onali S, et al. Combination therapy in inflammatory bowel disease—from traditional immunosuppressors towards the new paradigm of dual targeted therapy. *Autoimmun Rev* 2021; 20: 102832.

14. 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* 2023; 8: 307–320.

15. 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: 2–11.

16. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012; 366: 1870–1880.

17. Vukusic S, Rollot F, Casey R, et al. Progressive multifocal leukoencephalopathy incidence and risk stratification among natalizumab users in France. *JAMA Neurol* 2020; 77: 94–102.

18. Gold SL and Steinlauf AF. Efficacy and safety of dual biologic therapy in patients with inflammatory bowel disease: a review of the literature. *Gastroenterol Hepatol* (*NY*) 2021; 17: 406–414.

19. Sandborn WJ. Crohn's disease evaluation and treatment: clinical decision tool. *Gastroenterology* 2014; 147: 702–705.

20. Colombel J-F, Ungaro RC, Sands BE, et al. Vedolizumab, adalimumab, and methotrexate combination therapy in Crohn's disease (EXPLORER). *Clin Gastroenterol Hepatol* 2024; 22: 1487–1496.e12.

21. 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* 2021; 15: 335–339.

22. Olbjørn C, Rove JB and Jahnsen J. Combination of biological agents in moderate to severe pediatric inflammatory bowel disease: a case series and review of the literature. *Pediatr Drugs* 2020; 22: 409–416.

23. Biscaglia G, Piazzolla M, Cocomazzi F, et al. Landmarks for dual biological therapy in inflammatory bowel disease: lesson from two case reports of vedolizumab in combination with ustekinumab. *Eur J Gastroenterol Hepatol* 2020; 32: 1579.

24. Fumery M, Yzet C and Brazier F. Letter: combination of biologics in inflammatory bowel

diseases. *Aliment Pharmacol Ther* 2020; 52: 566–567.

25. Goessens L, Colombel J, Outtier A, et al. Safety and efficacy of combining biologics or small molecules for inflammatory bowel disease or immune-mediated inflammatory diseases: a European retrospective observational study. *United European Gastroenterol J* 2021; 9: 1136–1147.
26. McShane C, Varley R, Fennessy A, et al. P695 effectiveness and safety of combination biologic or small molecule therapy in inflammatory bowel disease. *J Crohns Colitis* 2023; 17: i825–i826.
27. Glassner K, Oglat A, Duran A, et al. The use of combination biological or small molecule therapy in inflammatory bowel disease: a retrospective cohort study. *J Dig Dis* 2020; 21: 264–271.
28. 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: 1031–1038.
29. Alayo QA, Khatiwada A, Patel A, et al. Effectiveness and safety of combining tofacitinib with a biologic in patients with refractory inflammatory bowel diseases. *Inflamm Bowel Dis* 2021; 27: 1698–1702.
30. Lee SD, Singla A, Harper J, et al. Safety and efficacy of tofacitinib in combination with biologic therapy for refractory Crohn's disease. *Inflamm Bowel Dis* 2022; 28: 309–313.
31. 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* 2022; 20: e361–e379.
32. Alayo QA, Fenster M, Altayar O, et al. Systematic review with meta-analysis: safety and effectiveness of combining biologics and small molecules in inflammatory bowel disease. *Crohns Colitis 360* 2022; 4: otac002.