Efficacy and Safety of Dual Biologic Therapy in Patients With Inflammatory Bowel Disease: A Review of the Literature

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Abstract: Using 2 or more treatment modalities to achieve a synergistic effect in patients with refractory inflammatory bowel disease (IBD) has been an area of focus for many years. This methodology, known as combination therapy, has been proposed for various therapeutic agents, most commonly biologics and immunomodulators. Although the mainstay of biologic therapy for IBD has traditionally focused on agents targeting tumor necrosis factor, the development of newer biologics with different targets, such as vedolizumab and ustekinumab, has introduced the possibility of concomitant dual biologic therapy. Dual biologic therapy has been proposed in the treatment algorithm for 2 types of patients with IBD: those with well-controlled luminal IBD and uncontrolled extraintestinal symptoms (secondary indications such as arthritis or psoriasis) and those with refractory, uncontrolled IBD. Thus far, the data on the efficacy and safety of dual biologic therapy as a treatment for Crohn's disease or ulcerative colitis remain quite limited. In fact, the overwhelming majority of the literature consists of case reports and case series. Given this paucity of high-level data, physicians have looked to larger studies on dual biologic therapy in other fields of medicine, such as rheumatology and dermatology. The goal of this article is to summarize the current literature on the use of dual biologics in IBD, address the potential adverse effects or risks associated with combination therapy, and highlight future directions in the use of this therapeutic modality.

Keywords
Inflammatory bowel disease, biologic therapy, combination therapy, dual biologics, Crohn's disease, ulcerative colitis, extraintestinal manifestations

Combination therapy for the treatment of inflammatory bowel disease (IBD) gained popularity in 2010 when the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) trial was first published.[1] The SONIC trial results suggested that patients with mild to moderate Crohn's disease (CD) treated with infliximab plus azathioprine were more likely to achieve corticosteroid-free remission than those receiving azathioprine alone.

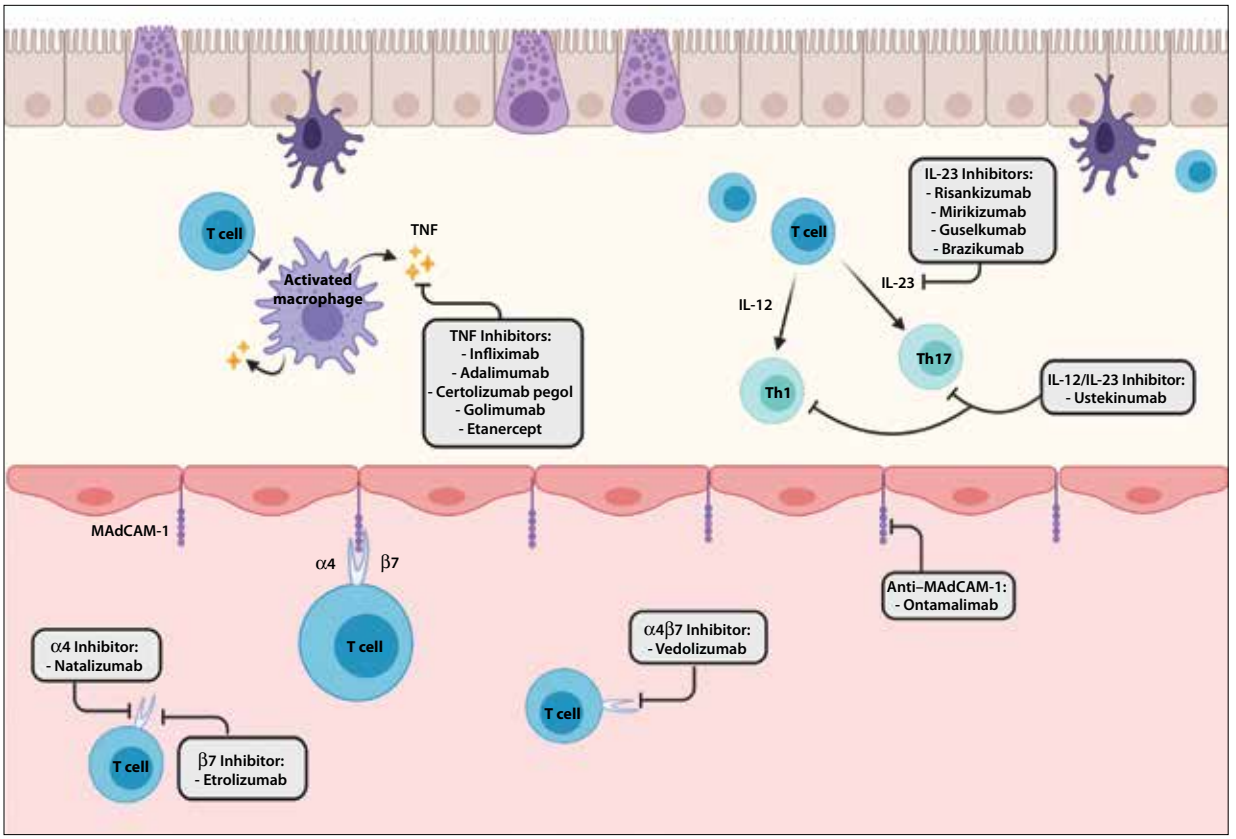

Figure. Overview of biologics used for the management of inflammatory bowel disease and their mechanisms of action. Figure created with BioRender.com.

IL, interleukin; MAdCAM-1, mucosal addressin cell adhesion molecule 1; Th, T-helper; TNF, tumor necrosis factor.

Although the efficacy and safety of combination therapy with a biologic and immunomodulator have been well studied and such treatment is common practice for many physicians, more recently, researchers and clinicians have proposed the use of dual biologic therapy in patients with refractory disease. Dual biologic therapy has been proposed in the treatment algorithm for 2 types of patients with IBD: those with well-controlled luminal IBD and uncontrolled concomitant extraintestinal symptoms (secondary indications such as arthritis or psoriasis) and those with refractory, uncontrolled IBD.[2]

Traditional biologic therapy has focused on the use of monoclonal antibodies directed against tumor necrosis factor (TNF). Newer biologics have novel targets and include ustekinumab (Stelara, Janssen), a monoclonal antibody that targets interleukin (IL)-12/IL-23, and vedolizumab (Entyvio, Takeda), a monoclonal antibody that prevents leukocyte trafficking to the small bowel by inhibiting the $\alpha_4\beta_7$ integrin (Figure).

The role of combination therapy with an anti-TNF agent and a novel biologic has become an area of great interest. The first study demonstrating the safety of dual biologic therapy was published in 2007.[3] However, little research on this topic has been published since, and there is no clear consensus on whether biologics can or should be used in tandem or which patients would benefit most. Therefore, the goal of this article is to summarize the current literature on the use of dual biologics in IBD, address the potential adverse effects or risks associated with combination therapy, and highlight future directions in the use of this therapeutic modality.

Combination of Tumor Necrosis Factor Inhibitors With Vedolizumab, Ustekinumab, or Natalizumab

The introduction of biologics with targets other than TNF has stimulated discussion about whether an improved clinical response can be achieved in patients with refractory IBD by combining a traditional anti-TNF agent with a novel biologic agent with a different mechanism of action. The data on such combined use are quite

limited. To date, only 1 randomized controlled trial (RCT) evaluating the safety and efficacy of combination biologic therapy in patients with IBD has been conducted.[3] The remaining published literature includes retrospective studies, case series, and case reports. Details about many of these studies, including the number of patients, the therapeutic agents used, and findings, can be found in Table 1.

Randomized Controlled Trial

The largest study and only multicenter RCT in this field evaluated the safety and tolerability of combination natalizumab (Tysabri, Biogen) and infliximab in patients with uncontrolled CD despite ongoing infliximab monotherapy.[3] In this study, 79 patients with active CD (defined as a CD Activity Index >150) were included, with 52 patients ultimately receiving natalizumab plus infliximab and 27 patients receiving placebo plus infliximab. Patients in the 2 groups were similar in terms of age, sex, body mass index, CD activity, and disease location. Of note, more than half of the patients in each treatment group were receiving concomitant therapy with an immunomodulator such as methotrexate or azathioprine. In terms of safety, adverse events were reported in 48 (92%) of the 52 patients treated with infliximab plus natalizumab and every patient in the placebo group. The most common events included headache and worsening of the underlying CD. No increased rate of infection was observed in patients receiving infliximab plus natalizumab in comparison with patients receiving infliximab monotherapy (27% vs 30%).

After 10 weeks in the study, patients were able to enroll in an open-label extension designed to better understand the long-term safety of combination therapy. Among the 64% of patients who continued on infliximab plus natalizumab therapy, no serious adverse events (eg, serious infections, malignancy, or death) were reported.

The study also looked at clinical outcomes, including disease activity and serum inflammatory markers. Overall, the patients receiving combination therapy with infliximab plus natalizumab tended to have improved clinical outcomes, including higher rates of clinical remission at all time points throughout the study compared with patients receiving infliximab plus placebo; however, these differences were not statistically significant. Despite the groundbreaking findings of this RCT, few physicians prescribe natalizumab for the treatment of IBD given its adverse-event profile, specifically the risk of progressive multifocal leukoencephalopathy, an opportunistic infection caused by the human polyomavirus 2. Researchers have, therefore, begun evaluating the safety and utility of combination therapy using newer biologics, which have improved safety profiles.

Retrospective Studies

In 2020, Yang and colleagues published a retrospective study from 2 referral centers that evaluated the safety and efficacy of dual biologic therapy in adults with refractory CD.[4] This study included 22 patients (who had a total of 24 dual biologic therapeutic trials). The primary outcome was endoscopic improvement, defined as a greater than 50% reduction in the Simplified Endoscopic Score–Crohn's Disease after 1 year of therapy. The patients included in this study had severe, refractory disease. Ninety-one percent had a prior IBD-related surgery, 59% had stricturing disease, and 55% had a history of perianal fistula in the setting of an average of 4 failed biologics prior to enrollment. Seven different combinations of biologics were evaluated. These included a traditional anti-TNF agent (infliximab, adalimumab, golimumab [Simponi, Janssen], or certolizumab pegol [Cimzia, UCB]) combined with vedolizumab or ustekinumab.

The study found endoscopic improvement and endoscopic remission in 43% and 26%, respectively, of dual biologic trials. Clinical response, as measured by patient-reported outcome scores, was seen in 50% of the dual therapy trials. Although the incidence of perianal fistula improved from 50% at baseline to 33% posttreatment, roughly one-third of the study patients ultimately required surgery and, therefore, were considered medical treatment failures. Endoscopic improvement and clinical remission were seen in 4 (33%) of 12 patients treated with vedolizumab plus a TNF inhibitor and in 1 (33%) of 3 patients treated with ustekinumab plus a TNF inhibitor. Adverse events were seen in 15% of those treated with vedolizumab plus a TNF inhibitor and none of the patients treated with ustekinumab plus a TNF inhibitor. Adverse events included infection (*Clostridioides difficile* infection, *Acinetobacter* bacteremia, and pneumonia) as well as 1 report of basal cell skin cancer. Although this study was small, the findings suggested that dual biologic therapy with an anti-TNF agent and a biologic such as ustekinumab or vedolizumab may offer promise for clinical and endoscopic remission in patients with severe, refractory CD.

Two additional retrospective studies published in 2020 evaluated dual biologic therapy in patients with CD and ulcerative colitis (UC).[5,6] The first, an Italian study, included 16 patients (11 with CD and 5 with UC).[5] Seven patients received dual therapy for uncontrolled luminal disease, and the remaining 9 patients were treated for uncontrolled extraintestinal manifestations despite quiescent gastrointestinal disease. Patients in this trial were treated with anti-TNF agents in addition to vedolizumab or ustekinumab, and 2 patients were treated with vedolizumab plus ustekinumab. The patients were monitored for 8 weeks. All patients on dual biologic therapy reported

Table 1. Primary Literature on Dual Biologics for the Treatment of IBD

Study	Year	Study Type	Biologics	Number of Patients	Disease	Findings
Sands et al[3]	2007	RCT	IFX + natalizumab	79	CD	Combination therapy was well tolerated. Combination therapy was superior to IFX alone.
Glassner et al[6]	2020	Retrospective cohort study	Various	50	CD, UC	Increased risk of infection was seen in patients on combination therapy compared with biologic monotherapy; however, the risk was lower in those not on a concomitant immunomodulator.
Kwapisz et al[7]	2021	Retrospective study	Various	15	CD, UC	Combination biologics with different mechanisms may be safe and effective; an anti-TNF or VDZ plus UST was most effective.
Privitera et al[5]	2020	Retrospective study	Various	16	CD, UC	Three adverse events were reported; however, none of them were serious. Clinical response was seen in all patients.
Yang et al[4]	2020	Retrospective study	Various	22	CD	Dual biologic therapy was associated with clinical, biomarker, and endoscopic healing in patients with refractory CD.
Olbjørn et al[11]	2020	CS	IFX + UST IFX + VDZ	13	CD, UC	This pediatric study demonstrated safety of combination therapy and clinical remission in 9 of the 13 patients.
Buer et al[8]	2018	CS	Anti-TNF + VDZ	10	CD, UC	Dual biologic therapy in this study was safe and may represent a long-term treatment option for patients with refractory IBD.
Mao et al[27]	2018	CS	Various	4	CD	Dual biologic therapy with VDZ appears to be safe and effective.
Yzet et al[23]	2016	CS	Anti-TNF + UST	3	CD, UC	Use of dual biologics appears to be safe and well tolerated. Use of UST was not effective in the treatment of paradoxical psoriasis.
Fischer et al[24]	2017	CR	VDZ + CZP	1	UC	No side effects were reported; spondyloarthritis symptoms and colitis improved with clinical remission.
Roblin et al[10]	2018	CR	GOL + VDZ	1	UC	After 1 year of combined therapy, the patient had clinical and endoscopic remission of UC.
Liu, Loomes[15]	2017	CR	UST + VDZ	1	CD	No adverse events were reported; the patient had mucosal healing.
Huff-Hardy et al[14]	2017	CR	UST + VDZ	1	CD	There were no infectious complications. Perianal disease significantly improved.
Afzali, Chiorean[25]	2016	CR	VDZ + ADA	1	CD	Six months of combination therapy resulted in endoscopic and clinical improvement in a patient with refractory disease.
Hirten et al[26]	2015	CR	IFX + VDZ	1	CD	Combination therapy resulted in improved symptomatology and endoscopic findings.
Bethge et al[9]	2017	CR	VDZ + ETN	1	UC	Combination therapy with VDZ and ETN was safe with no adverse events after 40 weeks of treatment.

ADA, adalimumab; CD, Crohn's disease; CR, case report; CS, case series; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; IBD, inflammatory bowel disease; IFX, infliximab; RCT, randomized controlled trial; TNF, tumor necrosis factor; UC, ulcerative colitis; UST, ustekinumab; VDZ, vedolizumab.

Table 2. Systematic and Other Recent Reviews on Dual Biologics for the Treatment of IBD

Study	Year	Type of Review	Findings
Ahmed et al[13]	2021	Systematic review with meta-analysis	This review included 30 studies with 288 patients on dual biologic therapy. The review also included combination therapy with a small molecule and a biologic. No severe safety concerns were identified. The authors concluded that dual biologic or other combination therapy may be an option for patients with severe, refractory IBD.
Ribaldone et al[12]	2019	Systematic review with pool analysis	This review included 7 studies (18 patients) with a combination of TNF inhibitors and VDZ as well as VDZ with UST. Clinical improvement was seen in all patients, and endoscopic improvement was reported in 93% of patients. No safety concerns were identified.
Hirten et al[17]	2018	Narrative review	This review included data on combination biologic therapy in patients with IBD, dermatologic conditions, rheumatologic conditions, and other immune-mediated inflammatory conditions.

IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab.

clinical improvement in luminal and extraluminal symptoms. Three patients reported adverse events, none of which were severe.

Data from a similar US study showed increased rates of clinical and endoscopic remission (based on clinical disease activity scores and endoscopic scores) after 2 months of treatment.[6] This study included 50 patients with IBD (32 with CD and 18 with UC) who were treated with combination therapy. The majority were on a concomitant immunomodulator (39%) or corticosteroids (78%). Only 29 patients in this study were treated with dual biologic therapy. Adverse events were reported in 13 (26%) patients. The majority of adverse events were infectious in nature, and 8 (35%) were considered serious.

The most recent retrospective study on this topic included 15 patients treated with various combinations of biologics, the most common (53.3%) of which was an anti-TNF agent plus vedolizumab.[7] Following a median 24 months of follow-up after a median duration of dual biologic therapy of 6 months, 11 (73%) of the 15 patients had symptom improvement, 10 (67%) were able to reduce their dose of corticosteroids, and 4 (26%) had endoscopic or radiologic improvement in disease status. Infection requiring antibiotic therapy developed in 4 patients, the details of which were not provided, and surgical intervention for IBD was required in 3 patients.

Case Reports and Small Case Series

Numerous case reports and small case series have reported on the use of dual biologics for the treatment of refractory IBD. The majority of these case reports and case series focus on the use of an anti-TNF agent with vedolizumab. The largest of these case series in adults includes 10 patients (6 with a diagnosis of UC and 4 with a diagnosis of CD) and suggests that combination therapy with vedolizumab and either infliximab (9/10 patients) or adalimumab (1/10 patients) may represent a safe, long-term treatment regimen for those with medically refractory disease.[8]

One of the more unique case reports evaluated the use of vedolizumab in combination with etanercept in a patient with pouchitis and spondyloarthritis.[9] This patient had a history of UC treated with proctocolectomy and ileal pouch–anal anastomosis and had enteropathic seronegative spondyloarthritis. A combination of vedolizumab and etanercept resulted in endoscopic and histopathologic remission of refractory pouchitis and complete resolution of the patient's joint symptoms with no significant adverse events.

Similarly, in a letter to the editor, Roblin and colleagues describe a case of a patient with severe, refractory UC treated with vedolizumab in whom severe, disabling HLA-B27–positive spondyloarthropathy subsequently developed.[10] The patient responded well to the addition of golimumab to the treatment regimen. The patient's UC and spondyloarthropathy remained quiescent following 1 year of combination therapy with vedolizumab and golimumab.

Although the majority of these studies focus on the use of dual biologic therapy in adults with IBD, 1 case series looked specifically at the effect of combination therapy in pediatric patients.[11] In this study, 8 patients (4 with CD and 4 with UC), ages 14 to 17.5 years, were treated with a combination of infliximab and vedolizumab

for refractory disease. Fifty percent of the patients achieved clinical remission, and 50% required colectomy. This study also included 5 patients with CD, ages 11 to 17 years, who were treated initially with infliximab; however, paradoxical psoriasis resistant to topical therapy developed. These 5 patients were started on ustekinumab in combination with the anti-TNF agent. Interestingly, all achieved clinical remission of CD and skin symptoms. No serious adverse events were reported in any of the children treated with combination therapy; however, the authors concluded that long-term studies are needed to fully assess the safety of dual biologic therapy in pediatric patients with IBD.

Systematic Reviews With Meta-Analyses

Furthermore, 2 recent systematic reviews with meta-analyses that examine the safety and efficacy of dual biologic therapy in patients with IBD have been published (Table 2).[12,13] The first systematic review, from 2019, examined 7 studies with a total of 18 patients.[12] Fifteen of these patients were treated with an anti-TNF agent in combination with vedolizumab. Clinical improvement was seen in all patients, and endoscopic improvement was documented in 93%. No serious adverse events were reported. The second, more recent systematic review with meta-analysis evaluated the effect of both dual biologic therapy and combination biologic with small molecule therapy in patients with refractory IBD.[13] Although various combination therapies were included in this study, 48% of patients were treated with an anti-TNF agent plus vedolizumab, 7% with an anti-TNF agent plus ustekinumab, and 19% with vedolizumab plus ustekinumab. Although the efficacies of the various combination therapies were not delineated for each drug combination, the study did note that clinical response, clinical remission, endoscopic response, and endoscopic remission were more likely in patients treated with dual therapy because of concomitant extraintestinal manifestations than in patients who simply had refractory intestinal disease. Both of these recent systematic reviews concluded that dual biologic therapy poses a potential therapeutic option for patients with refractory disease or those with extraluminal manifestations not controlled on a single agent.[12,13] However, the authors of both reviews noted that more data from high-quality studies are needed prior to widespread adoption of this treatment approach.

Combination of Ustekinumab and Vedolizumab

Combination biologic therapy most commonly has been described as consisting of an anti-TNF agent and a newer biologic; however, combination ustekinumab and vedolizumab has been presented as a possible treatment for refractory IBD. Very limited primary evidence supporting the use of ustekinumab and vedolizumab exists; however, retrospective studies, case series, and case reports have suggested that this treatment regimen may be effective in CD and UC and should be an area of future research.

In 2 of the retrospective studies previously mentioned that looked at the use of a TNF inhibitor plus a novel biologic, the efficacy and safety of ustekinumab in combination with vedolizumab were also evaluated.[4,7] In the study by Yang and colleagues, 8 (33%) of the 24 dual biologic therapeutic trials that were reviewed described concomitant use of ustekinumab and vedolizumab.[4] The combination resulted in higher rates of endoscopic improvement (68%) but similar rates of endoscopic remission (25%) and adverse events (13%) compared with combination therapy with a TNF inhibitor and either ustekinumab or vedolizumab. The other study included 5 (33%) patients on ustekinumab and vedolizumab therapy.[7] Within this small group of patients, 4 (80%) had a clinical response, 1 (20%) required surgical intervention, 2 (40%) were able to reduce their corticosteroid dosing, and none had any severe adverse events.

In addition, 2 published case reports describe the use of ustekinumab plus vedolizumab in adult patients with refractory CD.[14,15] The first report describes the case of a woman, age 22 years, with severe, stricturing, fistulizing CD following a subtotal colectomy and end ileostomy that remained refractory to traditional medical therapy.[14] The patient presented on ustekinumab; however, she had breakthrough symptoms with fistula formation to the rectal stump and vulvo-perianal disease. Following 8 weeks of vedolizumab plus ustekinumab therapy, her perianal disease had significantly improved. Deep remission was achieved after 1 year of treatment; however, the patient underwent completion proctectomy during that year, which potentially contributed to her clinical remission.

The second case report describes a woman, age 27 years, with ileocolonic CD that was refractory to traditional medical interventions.[15] The patient was treated with combination vedolizumab and ustekinumab and achieved mucosal healing after 6 months of therapy. The authors mentioned that, given her remission, the plan was to stop ustekinumab and continue vedolizumab as long-term monotherapy.

A pediatric study also has been published that evaluated the use of various combination therapies in 16 children with CD and UC.[16] The study included 4 patients treated with ustekinumab and vedolizumab. (The remaining 12 patients were treated with a combination of biologic and small molecule agents.) Of the 4 patients

treated with ustekinumab and vedolizumab, 3 (75%) achieved corticosteroid-free remission after 6 months of therapy. One patient with CD required a diverting loop ileostomy despite dual biologic therapy for ongoing symptoms.

Additional Data From the Rheumatology and Dermatology Literature

Given the limited data on the use of dual biologics in patients with IBD, physicians have relied on data from other immune-mediated diseases to further understand the safety and efficacy of combination therapy.[17] Numerous case reports have been published evaluating the use of ustekinumab plus another biologic in patients with psoriasis and psoriatic arthritis refractory to topical treatment and biologic monotherapy. In addition, patients with refractory palmoplantar pustulosis have been successfully treated with dual biologics, including ustekinumab plus a TNF inhibitor.[18] Although the majority of these case studies describe ustekinumab use in combination with a TNF inhibitor, a few report the use of etanercept with secukinumab (Cosentyx, Novartis) or guselkumab (Tremfya, Janssen).[19,20]

Overall, these case reports demonstrate significant clinical improvement in dermatologic and joint symptoms in patients with refractory disease who are started on a second biologic. In one case report, treatment with ustekinumab and etanercept improved skin symptoms but not joint pain in a female patient.[19] Etanercept was replaced with adalimumab, but the combination of adalimumab and ustekinumab also failed to control the patient's arthritis. Autoimmune hemolytic anemia ultimately developed. It was unclear whether emergence of the anemia was treatment-related.

Compared with the IBD literature, in which few adverse events have been reported, an increase in infectious adverse events has been seen in the dermatologic literature regarding combination biologic therapy.[17] These adverse events include a case of retrotonsillar abscess (ustekinumab + etanercept), a case of erysipelas and bacterial pneumonia (ustekinumab + adalimumab), and a putative case of increased upper respiratory tract and urinary tract infections (ustekinumab + etanercept).[19,21]

Of interest, the majority of the data on the use of dual biologic therapy stems from the rheumatologic literature in which this technique is not uncommonly used to capture disease control in patients with persistent symptoms on a biologic.[17] Compared with the literature in IBD or psoriasis, the rheumatology literature includes multiple RCTs, an open-label study, and numerous retrospective studies as well as case series.[17] However, extrapolating data from the rheumatoid arthritis literature to better understand the utility and safety of dual biologic therapy in patients with IBD is difficult, as the majority of the RCTs in the rheumatology literature includes biologics that are not approved for the treatment of IBD (etanercept, anakinra [Kineret, Sobi], abatacept [Orencia, Bristol Myers Squibb], and rituximab).

In 2019, a systematic review with meta-analysis evaluated the safety of dual biologic therapy in the treatment of rheumatoid arthritis.[22] This review identified 6 studies with a total of 410 patients on combination biologic therapy. After a median follow-up of 9.5 months, there was a significant increase in the rate of serious adverse events in patients who received combination biologics compared with patients on monotherapy (14.9% vs 6.0%; odds ratio [OR], 2.51; 95% CI, 1.29-4.89) as well as in total adverse events (94.6% vs 89.1%; OR, 2.07; 95% CI, 1.11-3.86) after 12 months of treatment. As mentioned, given that many of these rheumatology-focused studies included the use of biologics not approved for use in the setting of IBD, the generalizability of these data to other immune-mediated conditions, such as IBD, is unclear.

Dual Biologic Safety Concerns and Adverse Events

Although combining 2 biologics with different mechanisms of action is quite logical for patients with refractory luminal disease or those with extraintestinal manifestations not treated with a single agent, the biggest concern is safety. It initially was not clear whether the risk of giving 2 monoclonal antibodies with different mechanisms of action was the same as that of each drug separately or whether the risk would be cumulative. These concerns continue to limit the use of dual biologic therapy, especially in smaller, nontertiary care centers. In analyzing data from the 5 largest studies in this field, Privitera and colleagues reported that adverse events were seen with dual biologic therapy in 13% to 30% of patients, with infection being the most commonly reported event.[2] This is supported by the most recently published systematic review with meta-analysis, which identified a 31% pooled rate of adverse events.[13] Overall, in terms of serious adverse events, no deaths were reported, and a single malignancy (basal cell skin cancer) was documented.

Given that dual biologic therapy in patients with IBD commonly includes either vedolizumab or ustekinumab or both agents, the lower rate of adverse events seen in the IBD literature compared with that seen in the dermatology and rheumatology literature is secondary to the observation that each of these agents has a very favorable safety profile.[2] Although patients on dual biologics should always be monitored for adverse events, including rare and potentially life-threatening infections, use of

biologics with excellent safety data when used as monotherapy perhaps reduces the risk of adverse events when used in combination with other agents. Looking forward, larger, prospective studies are needed to better understand the risk profile associated with dual biologic therapy to better guide patients who present with refractory disease.

Looking Forward: Future Novel Combination Therapies

Recent studies looking at dual biologic combination therapy have begun to evaluate the use of small molecule therapies, such as tofacitinib (Xeljanz, Pfizer), in combination with biologics. Given the safety concerns associated with small molecule therapies alone, the safety profile of the 2 agents in combination will need to be well studied before such a therapeutic regimen will become adopted as a common practice.

Looking at the evolution from the SONIC trial, which supported the use of combination therapy with infliximab and an immunomodulator, to the current plethora of literature, which support de-escalation therapy, it remains unclear whether dual biologic therapy should be recommended solely for an induction period or if it should have a role in maintenance therapy.[1] Perhaps, similar to concomitant immunomodulator therapy, the second biologic will eventually be stopped with a plan for long-term maintenance monotherapy. If so, which biologic to stop and when to de-escalate therapy are currently unknown and will require larger, prospective studies to clarify.

With the introduction of an increasing number of novel biologics to treat patients with IBD, the question of whether new drugs with novel mechanisms of action can be used in combination with more traditional therapies remains unanswered. New biologics under study that have similar mechanisms of action to the currently available biologics include anti–IL-23 agents such as mirikizumab, risankizumab (Skyrizi, AbbVie), brazikumab, and guselkumab as well as newer anti-integrin medications such as etrolizumab and ontamalimab. Drugs with novel targets are also in the pipeline, including phosphodiesterase-4 inhibitors and sphingosine-1-phosphate receptor agonists. Although these agents are all being studied as monotherapy at the present time, whether they ultimately work best in combination with other IBD therapeutics as a part of a combination therapy technique remains to be seen.

Conclusion

For over a decade, the use of 2 therapeutic agents with different mechanisms of action in patients with IBD has been an area of interest. Although the use of an immunomodulator in combination with a biologic such as infliximab or adalimumab has become common practice for many physicians, the use of 2 biologics with different targets is increasingly being studied to treat refractory patients with CD or UC. To date, evidence for the use of dual biologic therapy is quite limited, and there is only 1 RCT from 2007 looking at the use of infliximab with natalizumab. The introduction of biologics with novel targets has increased the use of dual biologic therapy, and case reports as well as case series have described the use of vedolizumab or ustekinumab with a TNF inhibitor and vedolizumab with ustekinumab. Although further studies are certainly needed to better elucidate the effectiveness of dual biologic therapy, preliminary reports from the previously discussed studies suggest that dual biologic therapy may be effective at inducing remission in patients with refractory luminal symptoms and/or ongoing extraintestinal manifestations. The majority of these reports suggest that no severe adverse events have been associated with combination biologic therapy in the setting of IBD management. As more and more biologics with different targets are brought to the market, the possibilities for dual therapy will become endless. Whether the efficacy of these agents will increase when used in conjunction with another biologic and whether the safety profile will change if used in combination with another drug will be determined by future studies.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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