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Observations and Research

Favorable Outcomes Combining Vedolizumab With Other Biologics or Tofacitinib for Treatment of Inflammatory Bowel Disease

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Background: Combining advanced therapies may improve outcomes in inflammatory bowel disease (IBD), but there are little data on the effectiveness and safety of this approach.

Methods: We examined outcomes of patients who received vedolizumab in combination with another biologic or tofacitinib between 2016 and 2020.

Results: Fourteen patients (10 ulcerative colitis [UC], 3 Crohn disease, 1 indeterminate colitis) received a combination of advanced therapies. Vedolizumab was combined with tofacitinib in 9 patients, ustekinumab in 3, and adalimumab in 2. Median follow-up on combination therapy was 31 weeks. Normalization of C-reactive protein (CRP) or fecal calprotectin (<5 mg/L and <150 μg/g, respectively) was achieved in 56% (5/9) and 50% (4/8) of patients. Paired median CRP decreased from 14 mg/L to <5 mg/L with combination therapy (n = 9, $P = 0.02$), and paired median calprotectin from 594 μg/g to 113 μg/g (n = 8, $P = 0.12$). Among patients with UC, paired median Lichtiger score decreased from 9 to 3 (n = 7, $P = 0.02$). Prednisone discontinuation was achieved in 67% (4/6) of prednisone-dependent patients. There were 4 infections: 2 required hospitalization (rotavirus, *Clostridium difficile*), and 2 did not (pneumonia, sinusitis). During follow-up, 5/14 patients discontinued combination therapy (2 nonresponse; 1 improvement and de-escalation; 1 noninfectious adverse effect; 1 loss of coverage).

Conclusions: In this retrospective case series of a cohort with refractory IBD, combining vedolizumab with other biologics or tofacitinib improved inflammatory markers, reduced clinical disease activity and steroid use, and was well tolerated.

Lay Summary

Fourteen patients with refractory IBD were treated with vedolizumab at the same time as another advanced therapy (tofacitinib or another biologic). Patients had improvement in their inflammatory markers and clinical scores, as well as tolerable side effects.

Key Words: combination, vedolizumab, tofacitinib

Introduction

The treatment options for inflammatory bowel disease (IBD) have expanded dramatically over the past 2 decades. Since the introduction in 1998 of infliximab, the first antitumor necrosis factor (anti-TNF) agent to treat IBD, additional anti-TNF (adalimumab, certolizumab pegol, golimumab) and anti-integrin agents (natalizumab, vedolizumab), as well as an anti-IL12/23 antibody (ustekinumab) and a small molecule Janus kinase (JAK) inhibitor (tofacitinib) have become available to patients.[1–3] Despite this progress, medical therapy still often fails to control IBD. For example, 15% of ulcerative colitis (UC) patients ultimately require colectomy, and 50% of Crohn disease (CD) patients require surgery within 10 years of diagnosis.[4,5] Additionally, CD remains one of the most common reasons for chronic intestinal failure requiring long-term parenteral nutrition, and approximately 50% of UC patients who undergo colectomy with ileal pouch-anal anastomosis develop pouchitis.[6,7] In clinical trials, administering these advanced therapies individually induced remission in 30%–50% of patients, reflecting the difficulty of medically controlling IBD with a single agent.[8–10]

In an effort to improve these outcomes, biologic agents are frequently combined with immunomodulators such as thiopurines or methotrexate. In clinical trials, combining an anti-TNF agent with an immunomodulator outperforms either medication alone.[10,11] Immunomodulators may prevent loss of response to anti-TNF agents via mitigation of antidrug antibody formation and by increasing serum anti-TNF concentrations.[1,2,10] In addition, because immunomodulators and biologics inhibit inflammation via different mechanisms, it is possible there may be an additive treatment effect when combined.[10] In these cases, patients and gastroenterologists accept the risks of immunomodulator use; these are not insignificant and include opportunistic infection and an increased risk of lymphoma.[12,13] Despite assuming these risks, patients nonetheless have suboptimal response rates with induction of steroid-free clinical remission achieved in less than half of patients.[10,11]

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In contrast to combining biologics with immunomodulators, gastroenterologists rarely combine 2 biologics or a biologic with a small molecule therapy such as tofacitinib. Among the primary concerns regarding such an approach is that the additive risk of infection and/or malignancy from the 2 agents would be unacceptable. However, in the only randomized, placebo-controlled trial examining the combination of 2 biologics to treat IBD, concurrent administration of infliximab and natalizumab did not lead to an increased risk of infection when compared to infliximab monotherapy.[14] Natalizumab is currently rarely used for IBD due to the risk of progressive multifocal leukoencephalopathy (PML) from JC virus reactivation.[15,16] In contrast, vedolizumab, a gut-selective antiintegrin agent, has not been found to be associated with PML and has a favorable safety profile with low incidence of infection, malignancy, and infusion reactions.[8,17,18] Because of this safety profile, vedolizumab may have promise as a therapy used in combination with another biologic or with a JAK inhibitor for patients who do not adequately respond to a single agent. Here, we report a retrospective case series of such an approach.

Methods

We examined the outcomes of treatment with vedolizumab in combination with another advanced therapy (biologic or JAK inhibitor) for IBD in patients who initiated such a combination between March 1, 2016 and March 1, 2020. Vedolizumab was either added to the first advanced therapy or a second advanced therapy was added to vedolizumab. Data were retrospectively extracted from electronic medical records at a single, large academic medical center under an IRB-approved protocol.

For each patient, information collected included demographic data, clinical characteristics, prior medications, endoscopies, biomarkers, imaging studies, and steroid use, as well as information regarding hospitalizations, surgeries, and infections. Disease phenotype was described using the Montreal classification. Disease activity indices obtained prospectively in routine care were recorded; the Harvey–Bradshaw index (HBI) was used for CD and indeterminate colitis (IC), whereas the Lichtiger score was used for UC. An HBI score ≤4 and a Lichtiger score ≤3 defined clinical remission. We considered a C-reactive protein (CRP) <5 mg/L and fecal calprotectin (FC) <150 µg/g to be normal. For UC patients, the Mayo endoscopic subscore was documented prospectively at the time of endoscopy. Baseline colonoscopy, CRP, and FC consisted of the most recent value prior to initiation of combination therapy. Reported CRP and FC while on combination therapy consist of the lowest value obtained within the first 6 months after starting combination therapy. Duration of therapy for patients who remained on combination therapy at the time of this report was determined to be the time between the combination start date and the most recent clinical visit. Wilcoxon signed rank test was used to determine differences between paired pre- and postcombination therapy CRP, FC, and clinical scores.

Results

Patient Characteristics

A total of 14 patients received vedolizumab in combination with another advanced therapy (Table 1). The median age was 37 years (interquartile range [IQR] 28–53), the median duration of disease was 7 years (IQR 5–14), and 29% (4/14) of patients were diagnosed prior to 16 years of age. The majority of patients had UC (71%, 10/14), whereas a minority had CD (21%, 3/14) or IC (7%, 1/14). Of the 3 patients with CD, 2 had perianal disease, and 1 had upper gastrointestinal disease. All 3 patients with CD had previously undergone bowel surgery; 1 had undergone small bowel resection with stricturoplasty, another a small bowel resection with temporary loop ileostomy, and the third a total abdominal colectomy with end ileostomy. Extraintestinal manifestations were present in 29% of patients (4/14). All patients had been previously treated with anti-TNF agents and the median number of failed advanced therapies prior to combination therapy was 2 (range 1–4).

Table 1. Demographics and baseline clinical characteristics

Median age in years (IQR)	37 (28–53)
Median duration of disease in years (IQR)	7 (5–14)
Age at diagnosis <16 y old	29% (4/14)
Female gender	50% (7/14)
IBD type	
Crohn disease	21% (3/14)
Ulcerative colitis	71% (10/14)
Indeterminate colitis	7% (1/14)
Extraintestinal manifestations	29% (4/14)
Median number of failed advanced therapies (range)	2 (1–4)
Previous bowel surgery	21% (3/14)
Prednisone dependence	43% (6/14)

All patients were undergoing treatment with 1 advanced therapy when a second advanced therapy was added, with vedolizumab as either the initial or the added drug. As the initial advanced therapy, 7/14 were treated with tofacitinib, 4/14 with vedolizumab, 2/14 with ustekinumab, and 1/14 with adalimumab (Table 2). Vedolizumab was added as a second advanced therapy in 10/14 cases, tofacitinib in 2/14, ustekinumab in 1/14, and adalimumab in 1/14. The most common combination was vedolizumab and tofacitinib (9/14).

Prior to initiating combination therapy, 13/14 patients were on the maximum maintenance dose of the initial drug (defined as 300 mg every 4 weeks for vedolizumab, 90 mg every 4 weeks for ustekinumab, 80 mg weekly for adalimumab, 10 mg twice daily for tofacitinib); the remaining patient had just completed vedolizumab induction and recently tapered off cyclosporine when tofacitinib was added. Patients had received the first agent for a median of 40 weeks (IQR 33–63 weeks) prior to the addition of the second agent. Five of the 7 patients who received a biologic as their initial drug had monitoring of serum drug levels; the remaining 2 patients were receiving ustekinumab and vedolizumab which were increased to maximal dosing after partial response on standard dosing. Prior to the addition of the second advanced therapy, 6/14 patients were steroid-dependent with a median prednisone dose of 20 mg/day and a median time on steroids of 5 months (IQR 3–13 months); additionally, 2/14 patients were on immunomodulators. Patients had a median CRP of 8 mg/L (IQR <5–27 mg/L, n = 14) and a median FC of 326 µg/g (IQR 130 to >1000 µg/g, n = 11) prior to the addition of a second advanced therapy (Table 3).

In 10/14 patients, the second advanced therapy was added after a partial, but not complete, clinical response to the first drug

Table 2. Patient characteristics and clinical courses on a combination of advanced therapies

Patient	Age	IBD Type	Montreal class	Prior therapies	First drug	Second drug	Reason for adding second drug	Baseline				On combination therapy					
								CRP (mg/L)	FC (µg/g)	Colonoscopy	Clinical score	CRP (mg/L)	FC (µg/g)	Colonoscopy	Clinical score	Infection	Surgery
1*†	21	CD	A1L (3 + 4) B2	IFX	USK	VDZ	Partial clinical response, endoscopic disease	7	—	TI with apthae, moderate left-sided colitis	8	<5	—	—	1	No	No
2*†	24	CD	A1L3B2p	IFX, ADA, CTZ, NTZ	USK	VDZ	Small bowel inflammation on CT enterography	7	—	Normal ileoscopy	—	<5	15	—	1	Rotavirus, sinus	No
3	25	CD	A1L2B3p	IFX, ADA, VDZ, USK	TOF	VDZ	Partial clinical response, endoscopic disease	49	893	Left-sided colitis, anal stricture, perianal fistula	1	24	>1000	Left-sided colitis, anal stricture.	—	Pneumonia	Colectomy
4	31	IC	A2L2B1	IFX, VDZ, TOF	ADA	VDZ	Partial clinical response, endoscopic disease	14	193	Normal TI, pancolitis	3	<5	23	—	0	No	No
5	38	UC	Extensive	IFX	VDZ	ADA	Enteropathic arthritis, Erythema nodosum	45	67	—	10	15	388	Left-sided colitis, Mayo 2	1	No	No
6†	43	UC	Extensive	IFX, ADA, TOF	VDZ	USK	Enteropathic arthritis, endoscopic disease	28	>1000	Pancolitis, Mayo 2	9	—	131	—	1	No	No
7†	57	UC	Extensive	IFX	VDZ	TOF	ASUC started on VDZ + cyclosporine. Flare after stopping cyclosporine	29	>1000	Left-sided colitis, Mayo 3	6	<5	38	Right-sided colitis, Mayo 1	3	No	No
8	60	UC	Extensive	IFX, ADA	TOF	VDZ	Partial clinical response, endoscopic disease	<5	>1000	Pancolitis, Mayo 2	3	6	490	—	2	No	No
9†	27	UC	Extensive	ADA, GOL	TOF	VDZ	Partial clinical response, endoscopic disease	<5	48	Left-sided colitis, Mayo 2	6	<5	95	Left-sided colitis, Mayo 1	3	No	No
10†	36	UC	Extensive	IFX, VDZ	TOF	VDZ	Partial clinical response, endoscopic disease	26	—	Left-sided colitis, Mayo 3	15	<5	—	Left-sided colitis, Mayo 2	6	No	No
11	56	UC	Extensive	IFX	VDZ	TOF	Partial clinical response, elevated FC	9	>1000	—	5	—	—	—	—	*C. difficile*	No
12	31	UC	Extensive	ADA	TOF	VDZ	Partial clinical response, endoscopic disease	<5	<16	Left—sided colitis, Mayo 2	—	—	—	—	—	No	No
13	63	UC	Left-sided	ADA, VDZ	TOF	VDZ	Partial clinical response, endoscopic disease	<5	294	Left-sided colitis, Mayo 2	5	—	14	—	—	No	No
14	44	UC	Extensive	ADA, IFX, VDZ	TOF	VDZ	Partial clinical response, endoscopic disease	7	326	Left-sided colitis, Mayo 3	13	—	—	—	4	No	No

*Patient continued immunomodulator during the combination of advanced therapies (methotrexate for patient 1, mercaptopurine for patient 2).
†Active prednisone use at the initiation of combination therapy.
ADA, adalimumab; ASUC, acute severe ulcerative colitis; CTZ, certolizumab pegol; GOL, golimumab; IFX, infliximab; NTZ, natalizumab; TI, terminal ileum; TOF, tofacitinib; USK, ustekinumab; VDZ, vedolizumab.

with active endoscopic disease confirmed in all 10 of these patients prior to the addition of the second drug. Of the remaining 4 patients, 1 had ongoing small bowel inflammation on CT (computed tomography) enterography; 1 had FC >1000 µg/g; 1 had uncontrolled enteropathic arthritis and erythema nodosum; and 1 had been receiving vedolizumab and cyclosporine following a hospitalization but lost response after stopping cyclosporine.

In 8/14 of cases, the added advanced therapy was a drug to which the patient had been previously exposed. Vedolizumab was reutilized in 7 patients and adalimumab in 1 patient. In their first experience with vedolizumab, 3 patients had a partial response, 4 had primary nonresponse, and 1 had secondary nonresponse. Adalimumab was reutilized in 1 patient who had previously received it for enteropathic arthritis but had discontinued it after 2 months due to lack of improvement in arthritis. On second use, when adalimumab was added to vedolizumab, the patient developed anti-adalimumab antibodies; these were overcome by intensifying adalimumab dosing to 40 mg weekly (preintensification: adalimumab level undetectable, anti-adalimumab antibody >160 ng/mL, Miraca Life Sciences; postintensification: adalimumab level 10.67 µg/mL, anti-adalimumab antibody not tested, ARUP Laboratories). Anti-vedolizumab antibody titers were measured in 3 of the 6 patients who had been previously exposed to vedolizumab and were undetectable in each case.

Outcomes

In patients with elevated CRP or FC prior to the addition of the second drug and who underwent repeat testing while on combination therapy, normalization of CRP or FC was achieved in 56% (5/9) and 50% (4/8) of patients, respectively (Table 3). Among patients with available CRP, FC, or clinical scores both before and after the addition of a second advanced therapy, each measure showed improvement. For these paired comparisons, median CRP decreased from 14 mg/L (IQR 7–28) prior to combination therapy to <5 mg/L (IQR <5–6) on combination therapy (n = 9, $P = 0.02$); median calprotectin from 594 µg/g to 113 µg/g (n = 8, $P = 0.12$); and median Lichtiger score decreased from 9 (IQR 6–12) prior to combination therapy to 3 (IQR 2–4) on combination therapy (n = 7, $P = 0.02$). Two patients had paired HBI clinical scores and both of these improved: 1 patient from a score of 8 to 1, the other from 3 to 0.

Of patients on prednisone prior to combination therapy, 67% (4/6) were able to completely discontinue prednisone while on combination therapy. All patients who had a Mayo endoscopic subscore recorded both before and while on combination therapy had an improvement in this score (n = 3).

Patients received combination therapy for a median time of 31 weeks (IQR 13–47 weeks). Five of the 14 patients discontinued combination therapy during the follow-up period (2 for nonresponse; 1 had improvement and subsequent de-escalation; 1 had a noninfectious adverse effect; 1 had loss of insurance coverage), whereas 64% of patients (9/14) remained on combination therapy. One of the patients who discontinued combination therapy due to nonresponse was a 25-year-old man with Crohn colitis treated with tofacitinib and vedolizumab for 36 weeks; due to persistent severe disease, he underwent elective total proctocolectomy. The second patient who discontinued due to nonresponse was a 60-year-old man with extensive UC who despite treatment with tofacitinib and vedolizumab for 25 weeks had ongoing symptoms and elevated FC; both agents were stopped and the patient was started on ustekinumab. The patient who discontinued combination therapy due to improvement and de-escalation was a 31-year-old man with extensive UC on tofacitinib who, after completing vedolizumab induction doses, had symptomatic response. Given this improvement, the patient and physician agreed to proceed with vedolizumab monotherapy. Only 1 patient discontinued combination therapy due to an adverse effect: a 56-year-old woman with extensive UC who received vedolizumab and tofacitinib; she developed paresthesias in her hands and opted to proceed with vedolizumab monotherapy with resolution of her paresthesia. She subsequently had persistent endoscopic disease activity and *Clostridium difficile* infection on vedolizumab monotherapy and ultimately transitioned to ustekinumab monotherapy. One patient discontinued combination therapy due to loss of insurance coverage; this was a 44-year-old woman with extensive UC on tofacitinib who, after completing vedolizumab induction doses, lost insurance coverage for vedolizumab. She initially resumed tofacitinib monotherapy and ultimately underwent elective colectomy due to refractory inflammation.

While on combination therapy, 29% of patients (4/14) developed an infection (Table 4). Two of these infections required hospitalization; one was a recurrence of *C. difficile* infection and another a rotavirus infection that required admission for intravenous fluid administration. The other 2 infections were

Table 3. Outcomes

Median time on combination in weeks (IQR)	31 (13–47)
Median CRP (mg/L)	
Precombination (n = 14) (IQR)	8 (<5–27)
On combination (n = 9) (IQR)	<5 (<5 to <5)
Normalization* of CRP (<5 mg/L)	56% (5/9)
Median calprotectin (µg/g)	
Precombination (n = 11) (IQR)	326 (130 to >1000)
On combination (n = 9) (IQR)	95 (23–388)
Normalization* of calprotectin (<150 µg/g)	50% (4/8)
Normalization* of HBI (≤4) or Lichtiger (≤3)	56% (5/9)
Improvement in Mayo endoscopic subscore	100% (3/3)
Stopped prednisone on combination therapy	67% (4/6)
Discontinuation of combination therapy	36% (5/14)
Reason for discontinuation	
De-escalation of therapy	1
Nonresponse	2
Noninfectious adverse effect	1
Loss of insurance coverage	1

*Normalization only calculated for patients who had paired samples before and on combination therapy.

Table 4. Adverse events on combination advanced therapy

Surgery	7% (1/14)
Infection	
Requiring hospitalization (*C. difficile*, rotavirus)	14% (2/14)
Not requiring hospitalization (pneumonia, sinus)	14% (2/14)
Flare requiring hospitalization (with small bowel obstruction)	7% (1/14)
Medication side effect (rash, paresthesia, elevated low-density lipoprotein)	21% (3/14)

a mild pneumonia and a sinus infection that were treated with outpatient antibiotics. There were 2 hospitalizations for noninfectious events: 1 patient required hospitalization due to worsening symptoms but continued on combination therapy and another patient had nonresponse to combination therapy and required total abdominal colectomy for Crohn colitis, as described above. No patients with UC underwent colectomy while on combination therapy. 21% of patients (3/14) developed symptoms thought to represent medication side effects while on combination therapy. One developed an acneiform rash, one had an elevation in LDL (low-density lipoprotein) cholesterol, and another developed paresthesia; all three were on a combination of vedolizumab and tofacitinib.

The 2 patients who utilized immunomodulators at the time of initiation of combination therapy continued these immunomodulators (Table 2). Of these, the first patient had refractory perineal and vulvar CD despite prior colectomy with end ileostomy and subsequent completion proctectomy; at the time of this report, she had received a combination of vedolizumab, ustekinumab, and 6-mercaptopurine for 4 years with dermatologic CD as her only remaining manifestation. During the time on combination therapy, this patient had 2 infections: a rotavirus infection requiring hospitalization for intravenous fluids, and a mild sinus infection that was treated with oral antibiotics as an outpatient. The second patient had refractory jejunal and ileocolonic CD and had undergone multiple bowel resections and stricturoplasties; at the time of this report, she had received a combination of vedolizumab, ustekinumab, and oral methotrexate for 9 months. This patient did not have any infections.

Discussion

Despite the development of several new medical therapies in the past 20 years, it remains difficult to induce remission, maintain remission and prevent the need for surgery in patients with IBD. The practice of combining biologic therapies with immunomodulators has been widely adopted in an effort to improve outcomes. However, combining advanced therapies, such as concomitant administration of 2 biologics or a biologic and a JAK inhibitor, remains rare.

We report one of the largest retrospective case series to date of IBD patients treated with combined advanced therapies. All 14 patients in this cohort had objective evidence of inflammation despite active treatment with 1 advanced therapy, and 13/14 patients were receiving maximal dosing of the first agent. All had previously failed anti-TNF therapy and, of the patients with CD, all had previously required bowel resections. Despite the severity of disease in this cohort, combining vedolizumab with another advanced therapy appeared to be effective, with statistically significant reduction in median CRP and clinical scores. In addition, most patients also had improvement in FC, endoscopic scores and were able to discontinue prednisone. Patients infrequently discontinued combination therapy, with 9/14 patients remaining on combination therapy for the duration of the median 31-week follow-up period. Only 2/5 patients who discontinued combination therapy did so due to lack of improvement on the medications. Notably, 8/14 patients in this cohort had been previously exposed to one of the two drugs in their combination therapy regimen, suggesting that patients who had previously been considered to have failed an advanced therapy may still be able to benefit from that drug as part of a combination approach; this is an important consideration given the limited number of drugs currently available.

Our study adds to the limited but recently growing literature on combining advanced therapies in IBD. The first study evaluating the combination of advanced therapies was published in 2007 and examined concurrent administration of infliximab and natalizumab in 52 patients with CD; it found similar rates of adverse events in the combination therapy and infliximab monotherapy groups.[14] More recently, several retrospective case series detailing various combinations of dual biologic therapy have been published. In one, outcomes for 22 patients with refractory CD treated with dual biologic therapy were examined and the authors found that 41% and 26% of these patients achieved clinical and endoscopic remission, respectively.[19] That study described 3 combinations—vedolizumab and anti-TNF, ustekinumab and anti-TNF, or vedolizumab and ustekinumab—and reported that only 2 patients experienced infections requiring antibiotics. In another study that examined a cohort using the same drug combinations, dual biologic therapy in 15 patients (14 CD, 1 UC) resulted in 73% (n = 11) attaining symptomatic improvement, 67% reducing corticosteroids (n = 10), and 44% having endoscopic or radiographic improvement (n = 4).[20] Four patients (27%) had infections requiring antibiotics. Prior to these 2 recently published cohorts, a meta-analysis examined 7 studies with a total of 18 IBD patients treated with dual biologic therapy and described clinical improvement in all patients without any adverse effects.[21] In addition to dual biologic combinations, biologics have been reported to be used in combination with tofacitinib in small case series. One recent abstract reported on 5 patients with IBD (2 CD, 3 UC) complicated by arthritis who were treated with a combination of vedolizumab and tofacitinib. This study reported improvement in symptoms, clinical scores, inflammatory markers and did not report any serious adverse events.[22] Another case series described 5 UC patients who received tofacitinib in combination with infliximab for a median of 9 months, with the only adverse event being one case of varicella-zoster that was treated with oral valacyclovir and a 2-week pause of tofacitinib therapy.[23] However, a response to that letter reported a case of a CD patient who developed Legionella meningitis and suffered permanent neurologic deficits while on combination therapy with infliximab and tofacitinib.[24] Another report included 4 children with IBD who received tofacitinib in combination with vedolizumab for at least 9 weeks and had no adverse effects.[25]

Particular contributions from our cohort to this body of literature include that 7/14 patients were treated with a combination of vedolizumab and tofacitinib, the largest published series of patients treated with a combination of JAK inhibitor and biologic. In addition, most prior studies of combined advanced therapies have focused on refractory CD rather than UC; in our cohort, 11/14 patients had UC, making our series the largest examining UC patients. Our cohort also includes 2 patients who tolerated long-term dual biologic therapy in combination with immunomodulators for refractory CD.

One of the primary concerns when considering combining advanced therapies is whether doing so would unacceptably raise the risk of infection or other adverse effects in comparison to monotherapy. In our cohort, no patients discontinued combination therapy due to infec-

tion. Only 1 patient elected to discontinue combination therapy due to a potential adverse effect, development of paresthesia after adding tofacitinib to vedolizumab, though paresthesia is not one of the commonly reported adverse effects of tofacitinib.[26,27] Acknowledging the limitation of our cohort's size, the overall rate of adverse effects including infection was not substantially different than those previously reported for infliximab or tofacitinib monotherapy.[28,29]

Although limited by the duration of the follow-up period, it seems combining vedolizumab with other advanced therapies is generally safe. This observation may differ based on the specific combination of therapies utilized. For instance, it is possible that combining an anti-TNF and a JAK inhibitor, which have higher rates of adverse events individually, may lead to a less acceptable rate of adverse events than combinations that include ustekinumab or vedolizumab, which have more favorable safety profiles. In addition, it will be important to clarify the role of immunomodulators in patients receiving combined advanced therapies; for example, it is possible that there could be altered pharmacokinetics in patients on dual biologics or on a biologic combined with a JAK inhibitor, potentially rendering immunomodulators less beneficial. Furthermore, it may be that the risk of infection or malignancy associated with immunomodulators is augmented in patients receiving combined advanced therapies.

Another concern with utilizing a combination of advanced therapies is cost. The high costs associated with IBD care are problematic for patients, providers, and health systems, and a large proportion of these expenditures come from the use of advanced therapies.[30–32] Therefore, the expense of combining advanced therapies may be a significant obstacle to widespread adoption. Still, the costs of medications must be balanced against a potential reduction in nonpharmaceutical healthcare spending related to uncontrolled disease, need for surgery and its associated costs and potential complications, as well as associated declines in quality of life and work productivity. In addition, the optimal strategies for the use of combination advanced therapy still need to be determined, in part because the choice of strategy may greatly influence the cost of a patient's therapy. For example, whether a second advanced therapy should be used as a "bridge therapy" with future de-escalation to a single advanced therapy or whether some patients may require long-term maintenance combination therapy that utilizes inhibition of multiple inflammatory pathways is not known. Strategies for patient selection also require delineation. In this cohort, most patients had partial but inadequate response to the first drug used in their combination, but there may be additional reasons to use a second therapy, such as ongoing extraintestinal manifestations despite luminal inflammatory control. These points emphasize the need for further studies to better determine the effectiveness and outcomes of combining advanced therapies for refractory IBD.

To our knowledge, our study reports one of the largest cohorts of patients treated with a combination of 2 advanced therapies, the largest cohort of patients with UC treated with combination advanced therapy, and the largest cohort treated with a combination of tofacitinib and a biologic. However, it has important limitations, including the inherent drawbacks and biases of its retrospective design. As such, patient selection bias may be present, follow-up was not protocolized, and biochemical and endoscopic assessments differed among patients. The follow-up period, at a median of 31 weeks, is likely sufficient to judge the initial effectiveness of therapy, but may not be long enough to be informative regarding long-term outcomes or the cumulative risk of adverse effects over time. In addition, this follow-up period precludes evaluation of the outcomes of treatment de-escalation to a single advanced therapy, which, for example, might be attempted after deep remission is documented.

In summary, treatment with vedolizumab in combination with other biologics or tofacitinib was generally well tolerated and appeared effective in reducing disease activity as measured by inflammatory markers, endoscopic scores, and steroid use in a cohort of patients with refractory IBD. This therapeutic strategy merits further study with larger cohorts and more rigorous assessments of effectiveness and safety.

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Conflict of Interest Statement

Dr. Fudman has served on an advisory board for Pfizer.

Author Contributions

Dr. Llano and Dr. Fudman had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Llano, Boktor, and Fudman. Acquisition of data: Llano, Shrestha, Boktor, and Fudman. Analysis and interpretation of data: Llano, Boktor, and Fudman. Drafting of the manuscript: Llano, Burstein, Boktor, and Fudman. Critical revision of the manuscript for important intellectual content: Burstein, Boktor, and Fudman. Statistical analysis: Llano and Fudman. Study supervision: Fudman. No writing assistance was used in developing this manuscript. All authors approved the final version of the manuscript.

Data Availability

De-identified clinical data will be provided upon request to the corresponding author.

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