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Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease

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Summary

Background: Biologic therapies in patients with Crohn's disease often yield low clinical and endoscopic remission rates. After multiple failed therapies, combining two biologic therapies is possibly the sole medical alternative to recurrent surgery. However, data on this approach are limited.

Aims: To assess the efficacy and safety of concomitant use of two biologic therapies in the largest cohort to date of refractory Crohn's disease patients.

Methods: Data were extracted from Crohn's disease patients started on dual biologic therapy at two referral centres. Biologics utilised include infliximab, adalimumab, vedolizumab, ustekinumab, certolizumab and golimumab. The primary outcome was endoscopic improvement (>50% reduction in Simplified Endoscopic Score-Crohn's disease [SES-CD] or explicitly stated). Endoscopic remission (SES-CD < 3 or stated), clinical response (Crohn's disease–patient-reported outcome-2 score [PRO2] reduced by 8), clinical remission (PRO2 < 8), and C-reactive protein (CRP) were also assessed.

Results: A total of 22 patients with 24 therapeutic trials of dual biologic therapy were identified. The majority of patients had prior surgical resections (91%), stricturing (59%) or penetrating (36%) phenotype, and perianal fistulas (50%). Median number of prior failed biologics was 4. Endoscopic improvement occurred in 43% of trials and 26% achieved endoscopic remission. Fifty per cent had clinical response and 41% achieved clinical remission. There were significant post-treatment reductions in median SES-CD (14.0 [12.0-17.5] to 6.0 [2.5-8.0], $P = 0.0005$], PRO-2 (24.1 [20.3-27.0] to 13.4 [4.6-21.8], $P = 0.002$] and CRP (17.0 [11.0-24.0] to 9.0 [4.0-14.0], $P = 0.02$). Presence of perianal fistulas decreased from 50% to 33%. Adverse events occurred in 13% of trials.

Conclusion: Dual biologic therapy was associated with clinical, biomarker and endoscopic improvements in selected patients with refractory Crohn's disease who failed multiple biologics. Further studies are needed to validate this approach.

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Edward Yang and Nicola Panaccione contributed equally.

1 | INTRODUCTION

Crohn's disease is a progressive immune-mediated disorder that can involve the entire gastrointestinal tract and presents with an inflammatory, stricturing, or penetrating phenotype.[1] Complications of Crohn's disease—including strictures, fistulas and abscesses—occur in 50% of patients.[2] Additionally, 50% of patients require surgery within 10 years of diagnosis.[3,4] Biologic medications have significantly advanced the management of inflammatory bowel disease and have become the cornerstone in the management of moderate-to-severe Crohn's disease.[1] Effective biologic agents for treating Crohn's disease include tumour necrosis factor-α (TNF)-antagonists (infliximab, adalimumab and certolizumab pegol), and more recently, antibodies inhibiting the p40 subunit of interleukins (IL)-12 and −23 (ustekinumab) and $\alpha_4\beta_7$ integrins on leukocytes (vedolizumab).[5] Randomised controlled trials demonstrate that combination therapy with infliximab and azathioprine is more effective than either treatment alone.[6] However, few patients achieve prolonged clinical remission and significant risk for subsequent surgical resections exists despite biologic therapies.[1] In refractory Crohn's disease patients who have failed multiple biologics, therapeutic options are limited. Inability to achieve clinical remission or response deceases quality of life, and recurrent bowel resections can lead to complications such as short bowel syndrome with dependence on parenteral support, bile acid diarrhoea and nutritional deficiencies.[1,7,8] Thus, just as combination therapy with a biologic and immunomodulator is more effective than either alone,[6] the concomitant use of dual biologics that target different inflammatory pathways is a potential therapeutic approach in patients with severe and treatment refractory disease.[9] In all Crohn's disease patients, the simultaneous use of two biologic therapies can potentially lead to improved clinical and endoscopic outcomes.

Biologic agents are effective in treating immune-mediated diseases, but concerns remain regarding adverse events, including infection and malignancy. Data from the TREAT registry demonstrated that while infliximab was associated with an increase in serious infections, stronger associations were shown with corticosteroids, Crohn's disease severity and narcotic use.[10] Large nationwide cohort studies have demonstrated that both thiopurine and TNF-antagonist monotherapy was associated with an increased risk of lymphoma, and combination therapy further increased this risk.[11] While thiopurines are associated with infection and malignancy, their combination with TNF-antagonists is commonplace. Conversely, newer approved biologic agents for Crohn's disease such as vedolizumab and ustekinumab have not yet demonstrated these risks. Vedolizumab targets the α4β7 integrin receptor to block lymphocyte homing to the intestinal mucosa, and has demonstrated a favourable safety profile in clinical trial[12] and real-world[13] settings. Ustekinumab inhibits the common p40 subunit of IL-12 and −23 and is safe and effective in Crohn's disease. Additionally, randomised controlled trials as well as real world data demonstrate a favourable safety profile across multiple diseases.[14,15]

Previous randomised controlled trial data analysing the combination of natalizumab and infliximab in patients with refractory Crohn's disease did not demonstrate increased adverse events over infliximab monotherapy.[16] Although the trial was not designed to analyse efficacy and endoscopic endpoints were not assessed, a trend existed towards symptom-based clinical improvement. Currently, natalizumab is rarely used due to the risk of progressive multifocal leukoencephalopathy and availability of safer and more selectively targeted anti-integrin therapies such as vedolizumab.[1] Additional data on dual therapy with conventional biologics remain limited to case reports and series.[17-20] Thus, a major knowledge gap exists on the safety and efficacy of combining contemporary biologic therapies in Crohn's disease.

Despite the safety of newer biologics, simultaneous treatment with two (dual) biologic medications (DBT) is rarely utilised. It remains unknown if concomitant use of these newer biologics with one another or with a TNF-antagonist would increase the overall risk for infectious complications compared with current standard of care. We hypothesise that vedolizumab may be an optimal therapeutic anchor to dual biologic therapy due to its favourable safety profile, which is attributed to its gut-specific mechanism. For similar safety considerations, ustekinumab may be a reasonable alternative anchor.[12,13,21,22] We report the largest cohort to date on the preliminary evidence of efficacy and tolerability of DBT in a high-risk group of patients with refractory Crohn's disease.

2 | MATERIALS AND METHODS

2.1 | Patient population

Data were reviewed from patient records at the University of California, San Diego (La Jolla, California) and University of Calgary (Calgary, Alberta). Data were extracted from patients with Crohn's disease who had started a combination of two different biologics between January 1, 2007 and December 31, 2018. At the University of California, San Diego, we utilised a program, "SlicerDicer", in the electronic medical record (Epic Systems Corporation), that permits identification of all patients with overlapping dates of biologic prescriptions or medication documentation, regardless of duration. Subsequently, individual chart review was performed to confirm patients received dual biologic therapy. At the University of Calgary, all patients starting dual biologic therapy for any duration were identified prospectively and the data were extracted retrospectively. No patient was started on dual biologic therapy for an indication other than Crohn's disease, such as rheumatologic or dermatologic diseases. Biologics searched include permutations for combinations of adalimumab, infliximab, certolizumab, golimumab, vedolizumab, natalizumab and ustekinumab. Chart review and data extraction were performed on each potential combination (EY and NP).

Data regarding demographics, disease phenotype, prior biologic therapies (prior response, dosing and failures), prior medications (corticosteroids, immunomodulators and antibiotics), prior surgeries,

presence of fistulas, laboratory data and adverse events were obtained thorough chart review. Endpoints were assessed at the time of endoscopic evaluation closest to 1 year of treatment with DBT or at the time of treatment failure.

2.2 | Approach to combining biologics

All therapeutic trials consisted of two biologic medications which included vedolizumab, ustekinumab or a TNF-antagonist paired with each other. In all therapeutic trials, patients were receiving therapy with a single biologic agent, and the second biologic was added on. Documented infusion of the second concomitant biologic medication was considered the start dates for DBT. Therapeutic drug monitoring was utilised in the majority of cases as standard of care at our institutions—this includes reasons for biologic failure (such as primary nonresponse, secondary nonresponse, immunogenicity and pharmacokinetic or mechanistic failure) and dose-escalated regimens.

2.3 | Outcomes

The primary outcome was endoscopic improvement during maintenance therapy, defined as either > 50% reduction in Simplified Endoscopic Score-Crohn's disease (SES-CD) or explicitly stated on the endoscopy report by an inflammatory bowel disease specialist. Other outcomes included endoscopic remission (SES-CD < 3 or clear stated), clinical response (Crohn's disease–patient-reported outcome-2 score [PRO-2] reduced by 8), clinical remission (PRO2 < 8) and adverse events.[23,24] Need for surgery was considered treatment failure for all endoscopic and clinical outcomes. Per-patient analysis was repeated using the most recent therapeutic trials. PRO-2 scores were calculated using standardised forms routinely given to patients, or from records if clearly stated.[23,24]

2.4 | Statistical analysis

Data analysis included descriptive statistics computed for continuous variables (means and SD). Percentages were used for categorical variables. Between-groups comparisons were performed using chi-squared, Fishers exact test, t test or Wilcoxon rank testing, as appropriate. *P*-values ≤ 0.05 were considered significant. All analyses were done using STATA SE 15.1 (StataCorp).

2.5 | Ethics

All authors had access to study data, reviewed and approved the final manuscript. Study protocol and materials were approved by the institutional review boards at University of California, San Diego and the University of Calgary.

TABLE 1 Baseline characteristics

Characteristics	
Median age	35
Age at diagnosis < 16 y old	32% (7/22)
Female gender	55% (12/22)
Crohn's disease location	
Ileal	18% (4/22)
Colonic	27% (6/22)
Ileocolonic	55% (12/22)
Proximal involvement	5% (1/22)
Crohn's disease phenotype	
Inflammatory	5% (1/22)
Stricturing	59% (13/22)
Penetrating	36% (8/22)
Any history of perianal fistulas	55% (12/22)
Mean number of failed biologics	4
Immunomodulator	79% (19/24)
Steroid	33% (8/24)
Antibiotic	33% (8/24)
Prior surgery	91% (20/22)

3 | RESULTS

3.1 | Baseline characteristics

A total of 24 therapeutic trials of DBT among 22 patients with Crohn's disease were identified. The median age was 35 (IQR 31-43), 95% of patients were diagnosed before the age of 40 and 32% were diagnosed before the age of 16 (Table 1). The majority of patients had either a stricturing (59%, n = 13) or penetrating (36%, n = 8) phenotype. Fifty-five per cent (n = 12) of the total patients had any prior history of perianal fistulas (Table 1). The median number of prior failed biologics was 4. Of the 94 total failed single biologic trials among 22 patients, the most common reasons for failure were secondary nonresponse without immunogenicity (47%, n = 44), followed by primary nonresponse (43%, n = 40), immunogenicity (7%, n = 7) and adverse drug event (3%, n = 3; Table 2).

Prior to initiating DBT, 79% (n = 19) of trials were receiving immunomodulators, 33% (n = 8) receiving corticosteroids and 33% (n = 8) receiving antibiotics. Additionally, 91% (n = 20) of patients had undergone prior inflammatory bowel disease-related surgery, and 50% of trials had ongoing perianal fistulas prior to initiating DBT (Table 1). Prior to initiating DBT, all patients were receiving biologic therapy with vedolizumab (n = 15), ustekinumab (n = 8) or infliximab (n = 1; Table 2). No patients were in clinical remission; the median PRO-2 score prior to DBT was 24.1 (IQR 20.0-27.0), with 91% (n = 20) having at least moderate disease activity. PRO-2 scores could not be calculated in two patients due to the presence of an ostomy. No patients were in endoscopic remission at baseline. At baseline, median SES-CD was 14.0 (IQR 12.0-17.5) and all patients had at least moderate disease activity on endoscopy. Baseline C-reactive protein (CRP)

TABLE 2 Description of prior biologic agents and dual biologic therapy (DBT) regimens: the median number of prior failed biologics was four

Reasons for prior biologic failure		Biologic at baseline prior to DBT initiation		Combinations of DBT	
Primary non-response	43% (40/96)	Vedolizumab	63% (15/24)	Vedolizumab/ustekinumab	33% (8/24)
Secondary non-response[a]	47% (44/96)	Ustekinumab	33% (8/24)	Vedolizumab/infliximab	25% (6/24)
Immunogenicity	7% (7/96)	Infliximab	4% (1/24)	Vedolizumab/adalimumab	17% (4/24)
Adverse event	3% (3/96)			Ustekinumab/adalimumab	8% (2/24)
				Vedolizumab/certolizumab	8% (2/24)
				Ustekinumab/infliximab	4% (1/24)
				Vedolizumab/golimumab	4% (1/24)

[a]Without immunogenicity.

was elevated in 79% (n = 19), with a median CRP of 17.0 mg/L (IQR 11.0-24.0 mg/L; Table 3).

The most common combinations of individual biologics were vedolizumab and ustekinumab (33%, n = 8). Vedolizumab was combined with a TNF-antagonist in 13 trials (54%) and ustekinumab was combined with a TNF-antagonist in 3 trials (12.5%, Table 2). A total of 79% of all DBT regimens included at least one biologic that had induced a prior initial response with subsequent loss of response (secondary nonresponse) and 29% of DBT trials utilised a biologic that had not been previously used. In therapeutic trials achieving an endoscopic response (n = 10), seven trials utilised at least one biologic that demonstrated prior secondary nonresponse and two trials utilised a biologic that had not been previously used. All baseline biologics and 63% (n = 15) of the second biologic agents in each therapeutic trial were administered as a dose-escalated regimen.

TABLE 3 Patient parameters and disease activity before and after treatment

	Baseline	Post treatment
PRO-2 score (median)[a]	24.1	13.4
Clinical remission	0/22 (0%)	9/22 (41%)
Mild	2/22 (9%)	2/22 (9%)
Moderate	20/22 (91%)	9/22 (41%)
Severe	0/22 (0%)	2/22 (9%)
Clinical response	n/a	11/22 (50%)
Endoscopic[b]		
Remission	0/23 (0%)	6/23 (26%)
Improvement	n/a	10/23 (43%)
C-reactive protein (median)	17 mg/L	9 mg/L
Albumin (median)	36 g/L	37 g/L
Perianal fistula present	12/24 (50%)	8/24 (33%)
Required surgery	n/a	8/24 (33%)
Adverse event	n/a	3/24 (13%)
Serious adverse event	n/a	2/24 (8%)

[a]PRO-2 (Crohn's disease-patient reported outcome-2 score) unable to be calculated in two trials due to presence of an ostomy.

[b]Endoscopic endpoint data not yet available in four trials; three were considered failure of DBT due to surgery or entering a clinical trial—one was awaiting follow-up but achieved clinical response.

3.2 | Efficacy of dual biologics

Endoscopic improvement occurred in 43% of therapeutic trials, and endoscopic remission was achieved in 26% of trials. The median SES-CD significantly reduced from 14.0 (IQR 12.0-17.5) to 6.0 (IQR 2.5-8.0; P = 0.0005; Figure 1). The median time to endoscopic assessment was 225 days from initiation of DBT.

Clinical response occurred in 50% of therapeutic trials, clinical remission was achieved in 41% and steroid-free clinical remission was achieved in 36%. The median PRO-2 score significantly reduced from 24.1 (IQR 20.3-27.0) at baseline to 13.4 (IQR 4.6-21.8) after treatment (P = 0.002; Figure 1), and the median CRP concentration declined from 17.0 mg/L (IQR 11.0-24.0) to 9.0 mg/L (IQR 4.0-14.0; P = 0.02; Table 3). Presence of perianal fistulas declined from 50% at baseline to 33% post-treatment (Table 3). Surgery was required after 33% (n = 8) of therapeutic trials and these were considered treatment failures. At the patient level, endoscopic improvement, endoscopic remission, clinical response and clinical remission rates were 43%, 29%, 50% and 40% respectively.

Patients were treated with DBT for a median of 274 days (IQR 191-365) and followed for up to 1 year. At 1 year, the proportion of patients remaining on DBT was 38%, all of which were successful and ongoing trials of DBT (Figure S1). The most common reasons for ending a trial of DBT were nonresponse or worsening of disease activity requiring surgery. At the end of DBT, 75% (n = 18) of trials were additionally receiving immunomodulators, 17% (n = 4) receiving corticosteroids and 25% (n = 6) receiving antibiotics.

The most commonly utilised drug class in DBT was TNF antagonists, which is also the only drug class for Crohn's disease with multiple approved medications. Reasons for prior TNF-antagonist failure that were assessed in this study included mechanistic failure (primary nonresponse and secondary nonresponse despite adequate drug concentrations), secondary nonresponse due to immunogenicity and adverse event (Figure 2). In both trials of DBT

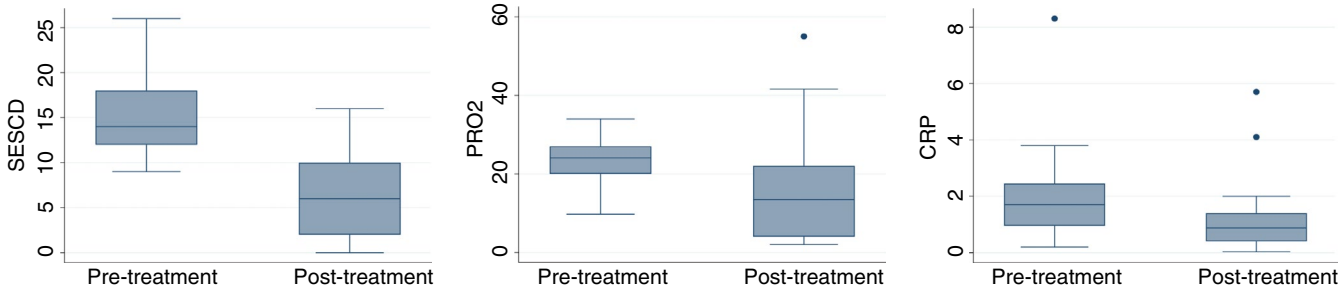

FIGURE 1 Endpoints of dual biologic therapy (DBT). A, SES-CD, simplified endoscopic score—Crohn's disease. B, PRO-2, Crohn's disease—patient reported outcome-2 score. C, CRP, C-reactive protein

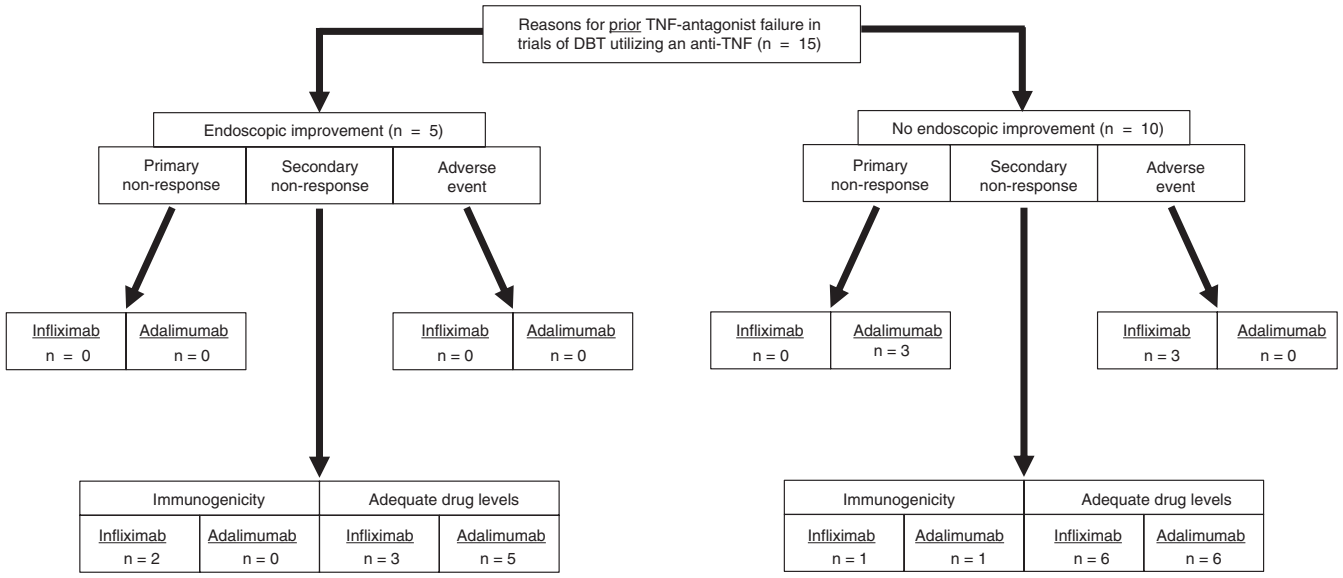

FIGURE 2 Flowchart of reasons for prior TNF-antagonist failure in dual biologic therapy regimens that utilized a TNF-antagonist. TNF, tumor necrosis factor-α antagonist

that achieved or did not achieve endoscopic improvement utilising a TNF-antagonists (n = 15), all patients had prior failure to both infliximab and adalimumab as separate treatment regimens—five achieved the primary endpoint of endoscopic improvement and 10 did not. The most common reason for prior failure of either infliximab or adalimumab was secondary nonresponse despite adequate drug concentrations, and there was no signal for differences between those with and without improvement. Although specific drug concentration measurements were not available, documentation by expert inflammatory bowel disease specialists that drug concentrations were adequate at the time of treatment failure was utilised.

Reasons for prior biologic failure for the entire cohort were assessed (Table S1). Among all therapeutic trials that achieved endoscopic response (n = 10), nine trials utilised at least one biologic in the regimen that either had demonstrated a prior response (secondary nonresponse) or had never been exposed to (naive) (Table S1). Among therapeutic trials that did not achieve an endoscopic response (n = 13), 10 trials utilised at least one biologic in the regimen that either had prior secondary nonresponse or the patient was naïve to (Table S1).

3.3 | Adverse events

Adverse events occurred in three trials (13%). One trial ended due to drug-induced lupus attributed to adalimumab. One patient developed pneumonia and another had reported basal cell skin cancer, recurrent Clostridium Difficile infection and Acinetobacter bacteremia in a patient with a recurrent history of all three diseases prior to initiation of DBT.

Among the combinations used as DBT, vedolizumab combined with ustekinumab had numerically higher rates of endoscopic improvement, but similar endoscopic remission and adverse event rates (Table 4).

4 | DISCUSSION

Patients with longstanding Crohn's disease often fail multiple biologic therapies and require surgical resections. As remission rates of individual biologics are low and limited further options exist, combining biologics may be a reasonable alternative to avoid disease progression and recurrent surgery. However, limited evidence

TABLE 4 Endpoints for combinations of dual biologic therapy (DBT)

	Endoscopic improvement	Endoscopic remission	Clinical response	Clinical remission	Adverse events
Vedolizumab/ustekinumab	63% (5/8)	25% (2/8)	71% (5/7)[b]	57% (4/7)[b]	13% (1/8)
Vedolizumab/TNF-antagonist	33% (4/12)[a]	25% (3/12)[b]	42% (5/12)[b]	33% (4/12)[b]	15% (2/13)
Ustekinumab/TNF-antagonist	33% (1/3)[a]	33% (1/3)[b]	33% (1/3)	33% (1/3)	0% (0/3)
All DBT trials	43% (10/23)[a]	26% (6/23)[b]	50% (11/22)[b]	41% (9/22)[b]	13% (3/24)

[a]Endoscopic endpoint data not yet available in four trials; three were considered failure of DBT due to surgery or entering a clinical trial (two vedolizumab/TNF-antagonist, one ustekinumab/TNF-antagonist)—one was awaiting follow-up but achieved clinical response (vedolizumab/TNF-antagonist).

[b]PRO-2 unable to be calculated in two trials due to presence of an ostomy (one in vedolizumab/ustekinumab and one in vedolizumab/TNF-antagonist).

on this approach exists. We report the largest study to date assessing the efficacy and safety of concomitant use of two (dual) biologic therapies in refractory Crohn's disease. This study reflects a high-risk population, with a large majority having a stricturing or penetrating phenotype and a high prevalence of perianal disease. Objective endoscopic outcomes were achieved in significant proportions of patients and endoscopic scores decreased significantly. Furthermore, objective documentation of fistula resolution existed in many patients. This is consistent with clinical remission rates, PRO-2 reductions and objective reductions in CRP. Three adverse events (13%) were recorded.

Overall, the preliminary evidence on the efficacy of DBT in this study appears promising. This is particularly evident when considering the limited available therapeutic options in this cohort of refractory Crohn's disease patients. In these patients, 91% had undergone prior surgical resections and the median number of previously failed biologics was 4. In addition, the severe and treatment-refractory disease phenotype described in our cohort is not uncommon in other tertiary academic medical centres. Thus, when considering the range of previously failed medical and surgical therapies in patients with refractory and high-risk Crohn's disease, an endoscopic improvement rate of 43% may imply a significant beneficial effect of this regimen. Additionally, the proportion of patients remaining on dual biologic therapy at 1 year was similar to the endoscopic response rate. Although there was no preliminary signal, adverse event rates were comparable to previous TNF-antagonist data.[25-27]

Previously, pooled data using small case series and case reports in inflammatory bowel disease patients treated with DBT included 10 Crohn's disease patients, with a majority having received vedolizumab and a TNF antagonist.[20] Although prior small case series had similar adverse event rates to this study, endoscopic data were generally lacking.[18,19] In contrast, this study significantly increase available data on this topic in patients with severe- and high-risk Crohn's disease phenotypes.

Although a study limitation was its retrospective design, objective endoscopic and biomarker endpoints were evaluated and patient reported outcomes were assessed. Adverse events were documented for a long duration, and the therapeutic impact of a diverse range of biologic combinations and dosing was assessed. While a possibility exists that patients started on dual biologic therapy for very short durations were not captured in this study, all patients receiving DBT were identified using either software from electronic medical records or prospective identification of patients, to permit identification of all patients with overlapping dates of biologic prescriptions or medication documentation, regardless of duration. Additionally, chart review was performed to confirm patients received dual biologic therapy. Lastly, data were not collected for patients in whom DBT was recommended, but not initiated.

The ideal approach to selecting dual biologic regimens remains to be determined. Vedolizumab or ustekinumab may be ideal adjunct therapies in DBT regimens due to their favourable safety profile.[12,13,21,22] For this reason, most patients in our study received vedolizumab, and the most frequently used pairing was with ustekinumab. One consideration is an individualised approach that incorporates reasons for prior biologic failures, such as utilising biologics with prior response (secondary nonresponse without immunogenicity) in addition to targeting an alternative untreated inflammatory pathway while avoiding biologics that have previously caused immunogenicity. While we did not find a significant difference in endoscopic response rates in this study when comparing prior reasons for biologic failure or alternate inflammatory targets, this study was not designed to detect this difference. Another consideration may be that the patients in our cohort had a high median number of previously failed biologic agents, which limits therapeutic choices from a mechanistic standpoint.

In summary, DBT was associated with clinical, biomarker and endoscopic improvements in a highly selective cohort with refractory Crohn's disease who have failed multiple biologics. While our findings appear promising, additional real world reports and randomised controlled trial data will assist in determining the efficacy and safety of DBT in refractory Crohn's disease.

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AUTHORSHIP

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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