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Comparative Effectiveness of Dual Biologic Therapy and Biologic Small-Molecule Therapy for Refractory Inflammatory Bowel Disease: A Retrospective Single-Center Study

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ABSTRACT

Patients with refractory inflammatory bowel disease (IBD) face difficulty in the treatment strategy. Combined advanced targeted therapies may obtain higher therapeutic efficacy. However, few studies compare the efficacy and safety of dual biologic therapy (DBT) with biologic small-molecule therapy (BMT) for refractory IBD. We aimed to compare the effectiveness of DBT with BMT. We retrospectively analyzed the data of patients with refractory IBD treated with DBT ($n = 22$) or BMT ($n = 21$). The primary outcome was the clinical remission rate at week 12. Secondary outcomes included the clinical response rate, endoscopic response rate, endoscopic remission rate, colectomy rate, and rate of adverse events (AEs) at week 12. At week 12, the clinical remission rates in the DBT group and BMT group were 22.7% and 28.6%, respectively. No statistically significant difference was observed between the two groups ($p = 0.661$). There were also no statistically significant differences between the DBT group and BMT group in the clinical response rate (68.2% vs. 71.4%, $p = 0.817$), endoscopic response rate (66.7% vs. 68.8%, $p = 1.000$), endoscopic remission rate (4.8% vs. 18.8%, $p = 0.296$) and colectomy rate (4.5% vs. 23.8%, $p = 0.167$). Two patients (9.5%) in the BMT group and no patients in the DBT group experienced AEs. However, the difference was not statistically significant ($p = 0.233$). In conclusion, this study revealed that there may be similar effectiveness and safety of DBT and BMT for patients with refractory IBD. Further multi-center, prospective randomized controlled trials are necessary to confirm this conclusion.

1 | Introduction

Although there have been more new medication options for patients with inflammatory bowel disease (IBD) than ever before, a "therapeutic ceiling" has emerged in which no single treatment seems to be effective in any more than 20%–30% of the patients [1]. Combined treatment strategies have revolutionized management across the IBD area of medicine, especially for refractory IBD. In recent years, combined advanced targeted therapies (CATT), which means simultaneously using at least two advanced therapies

Fan Yin and Xiaolei Liu contributed equally to this work.

Yongquan Shi and Min Chen were co-correspondence authors.

Summary

- What is the current knowledge on the topic?
  - Combined advanced targeted therapies may obtain higher therapeutic efficacy for patients with refractory inflammatory bowel disease (IBD). However, few studies compare the efficacy and safety of dual biologic therapy (DBT) with biologic small-molecule therapy (BMT) for refractory IBD.
- What question did this study address?
  - This study compares the efficacy and safety of DBT with BMT for refractory IBD patients.
- What does this study add to our knowledge?
  - We found that the clinical remission/response rate, endoscopic response/remission rate, colectomy rate, and rate of adverse events at week 12 in the DBT group were numerically lower than those in the BMT group, but the differences were not statistically significant.
- How might this change clinical pharmacology or translational science?
  - Our study provides some data for the selection of dual-targeted treatment options.

(i.e., biologic agents and/or advanced small-molecule therapies) to obtain higher therapeutic efficacy [2], have been applied in clinical practice increasingly. Recently, a phase 2, randomized controlled trial (RCT) suggested that combination therapy with guselkumab and golimumab might be more effective for ulcerative colitis (UC) than therapy with either drug alone [3]. Other observational data or meta-analyses also explored and confirmed the effectiveness of CATT for IBD, especially for refractory IBD [4–11]. However, few studies compared the effectiveness of dual biologic therapy (DBT, defined as the combination of two advanced biologic agents) with biologic small-molecule therapy (BMT, defined as the combination of an advanced biologic agent with a small-molecule agent) in the area of IBD.

In this study, we aimed to conduct a retrospective study to compare the effectiveness of DBT and BMT for patients with refractory IBD.

2 | Methods

2.1 | Study Design

We performed a retrospective chart review of patients with refractory IBD treated with CATT from November 2021 to August 2024 at Xijing Hospital of Air Force Military Medical University, a large IBD tertiary medical center in China. The study was approved by the institutional research ethics committee of Xijing Hospital, the Air Force Military Medical University, and had been conducted in accordance with the Declaration of Helsinki.

2.2 | Patient Selection

Refractory IBD patients treated with CATT between November 2021 and August 2024 were included in this study. Patients with refractory IBD were defined according to the international expert consensus published by the International Organization for the Study of IBD (IOIBD), which was defined by the failure of biologics and advanced small molecules with at least two different mechanisms of action, or postoperative recurrence of Crohn's disease (CD) after two surgical resections in adults or one in children, or chronic antibiotic-refractory pouchitis, complex perianal disease, or comorbid psychosocial complications that impair disease management. The eligible patients' data were collected, including demographics (age at diagnosis, body mass index [BMI], gender), previous medications, clinical information (disease duration, extraintestinal manifestations (EIM), complex perianal fistulas, disease activity, and laboratory findings) and regimens of CATT. Patients with inadequate clinical information were excluded. According to the type of treatment regimens, the patients were classified as DBT group and BMT group. Biologic agents used before DBT and BMT included infliximab, adalimumab, ustekinumab, and vedolizumab. IBD patients included in this study had used one to three types of these biologics alone before dual-targeted therapies.

2.3 | Outcomes

The primary outcome was the clinical remission rate at week 12. Secondary outcomes included the clinical response rate, endoscopic response/remission rate, colectomy rate, and rate of adverse events (AEs) at week 12. For UC patients, clinical response was defined as a decrease of total Mayo score ≥ 3 or a decrease of baseline $\geq 25\%$, with bleeding stool subscore reduction ≥ 1 or bleeding stool subscore of 0 or 1. Clinical remission was defined as a total Mayo score ≤ 2 with no subscore > 1. Endoscopic response was defined as a decrease of Mayo endoscopic score (MES). Endoscopic remission was defined as MES $= 0$. For CD patients, clinical response was defined as a decrease of Crohn's Disease Activity Index (CDAI) ≥ 100. Clinical remission was defined as CDAI < 150. Endoscopic response was defined as a decrease of SES-CD $\geq 50\%$ or at least a 2-point reduction for patients with a baseline SES-CD of 4 or Rutgeerts score improvement ≥ 1. Endoscopic remission was defined as SES-CD < 3 or Rutgeerts score i0–i1.

2.4 | Statistical Analysis

Continuous variables were presented as median and interquartile range (IQR) and compared using the Mann–Whitney test. Categorical variables were presented as frequency with percentage and compared using Fisher's exact test or Pearson's chi-squared test. It was considered statistically significant when a two-sided p-value was < 0.05. For data analysis, the Statistical Package for Social Sciences (SPSS 26.0 Package Facility; SPSS Inc., Chicago, IL, USA) software was used.

3 | Results

3.1 | Clinical Characteristics of Patients

The study finally included 43 patients with refractory IBD treated with CATT (DBT group = 22; BMT group = 21). Baseline characteristics such as age at diagnosis, BMI, gender, disease

TABLE 1 | Baseline characteristics of patients with refractory IBD prior to dual therapy.

Characteristics	DBT ($n=22$)	BMT ($n=21$)	p
Age at diagnosis, y	25.0 (18.3)	35.0 (18.5)	0.53
BMI, kg/m^2	19.4 (4.7)	18.6 (2.1)	0.362
Male	14 (63.6%)	10 (47.6%)	0.290
Disease duration, m	52.5 (68.8)	47.0 (45.5)	0.349
EIM	4 (18.2%)	7 (33.3%)	0.255
Complex perianal fistulas	5 (22.7%)	2 (9.5%)	0.448
Disease activity			0.438
Moderate	5 (22.7%)	7 (33.3%)	
Severe	17 (77.3%)	14 (66.7%)	
Prior medication exposures			
Corticosteroids	15 (68.2%)	18 (85.7%)	0.318
Immunomodulators	12 (54.5%)	6 (28.6%)	0.084
Number of biologic agents			
1	3 (13.6%)	6 (28.6%)	0.407
2	16 (72.7%)	12 (57.1%)	0.284
3	3 (13.6%)	3 (14.3%)	1.000
JAKi	1 (4.5%)	4 (19.0%)	0.314
Steroid-dependence	4 (18.2%)	4 (19.0%)	1.000
Steroid-resistance	8 (36.4%)	13 (61.9%)	0.094
CRP, mg/L	14.2 (52.2)	30.5 (79.7)	0.618
ALB, g/L	33.6 (16.7)	35.2 (9.7)	0.535

Note: Complex perianal fistulas: simple fistula is defined as a lower tract lesion (superficial, low intersphincteric, or low trans-sphincteric) with a single external opening but no rectovaginal fistulas, anorectal strictures or abscesses. All other fistulas are classified as complex.
Abbreviations: ALB, albumin; BMI, body mass index; BMT, biologic small-molecule therapy; CRP, C-reactive protein; DBT, dual biologic therapy; EIM, extraintestinal manifestations; IBD, inflammatory bowel disease; JAKi, JAK inhibitor.

duration, EIM, complex perianal fistulas, disease activity, prior medication exposures, steroid dependence, steroid resistance, serum levels of C-reactive protein (CRP) and albumin (ALB) were similar between the DBT group and the BMT group ($p>0.05$) (Table 1).

Therapies in the DBT group included infliximab + ustekinumab (5/22, 22.7%), infliximab + vedolizumab (2/22, 9.1%), adalimumab + ustekinumab (8/22, 36.4%) and ustekinumab + vedolizumab (7/22, 31.8%). Therapies in the BMT group included infliximab + upadacitinib (6/21, 28.6%), adalimumab + upadacitinib (1/21, 4.8%), vedolizumab + upadacitinib (5/21, 23.8%), infliximab + tofacitinib (3/21, 14.3%), ustekinumab + tofacitinib (1/21, 4.8%) and vedolizumab + tofacitinib (5/21, 23.8%). The patient therapy options in each group are shown in Table 2.

TABLE 2 | Dual therapies of patients with refractory IBD.

Therapy options	DBT ($n=22$)	BMT ($n=21$)
DBT		
IFX + UST	5 (22.7%)	—
IFX + VDZ	2 (9.1%)	—
ADA + UST	8 (36.4%)	—
UST + VDZ	7 (31.8%)	—
BMT		
IFX + UPA	—	6 (28.6%)
ADA + UPA	—	1 (4.8%)
VDZ + UPA	—	5 (23.8%)
IFX + TOFA	—	3 (14.3%)
UST + TOFA	—	1 (4.8%)
VDZ + TOFA	—	5 (23.8%)

Abbreviations: ADA, adalimumab; BMT, biologic small-molecule therapy; DBT, dual biologic therapy; IBD, inflammatory bowel disease; IFX, infliximab; TOFA, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

3.2 | Primary and Secondary Outcomes

At week 12, 22.7% (5/22) of the patients in the DBT group and 28.6% (6/21) in the BMT group achieved clinical remission. There was no significant difference between them ($p=0.661$). There were 68.2% (15/22) of DBT group and 71.4% (15/21) of BMT group patients in clinical response at week 12 ($p=0.817$). 4.5% (1/22) and 23.8% (5/21) of patients required colectomy within 12 weeks in the DBT and BMT groups, respectively ($p=0.167$).

For endoscopic evaluation, 66.7% (14/21) and 4.8% (1/21) of patients in the DBT group, 68.8% (11/16) and 18.8% (3/16) of patients in the BMT group, achieved endoscopic response and endoscopic remission at week 12, respectively. There were no significant differences in the endoscopic response rate ($p=1.000$) and endoscopic remission rate ($p=0.296$) between the two groups.

Two patients in the BMT group (9.5%, 2/21) experienced AEs, including leukopenia ($n=1$) and herpes zoster ($n=1$). The AEs were mild, and the patients recovered after symptomatic treatment. No significant AEs were observed in the DBT group. The difference in AEs was not statistically significant between the two groups ($p=0.233$). The primary and secondary outcomes are shown in Figure 1.

4 | Discussion

To the best of our knowledge, this is the first study to compare the effectiveness and safety of DBT and BMT for refractory IBD patients in a real-world setting.

We reported comparable efficacy data for DBT and BMT over a 12-week period of follow-up. The clinical remission rate (22.7% vs. 28.6%), clinical response rate (68.2% vs. 71.4%) and colectomy rate (4.5% vs. 23.8%) between the DBT and BMT groups were not statistically significantly different ($p>0.05$). The results were

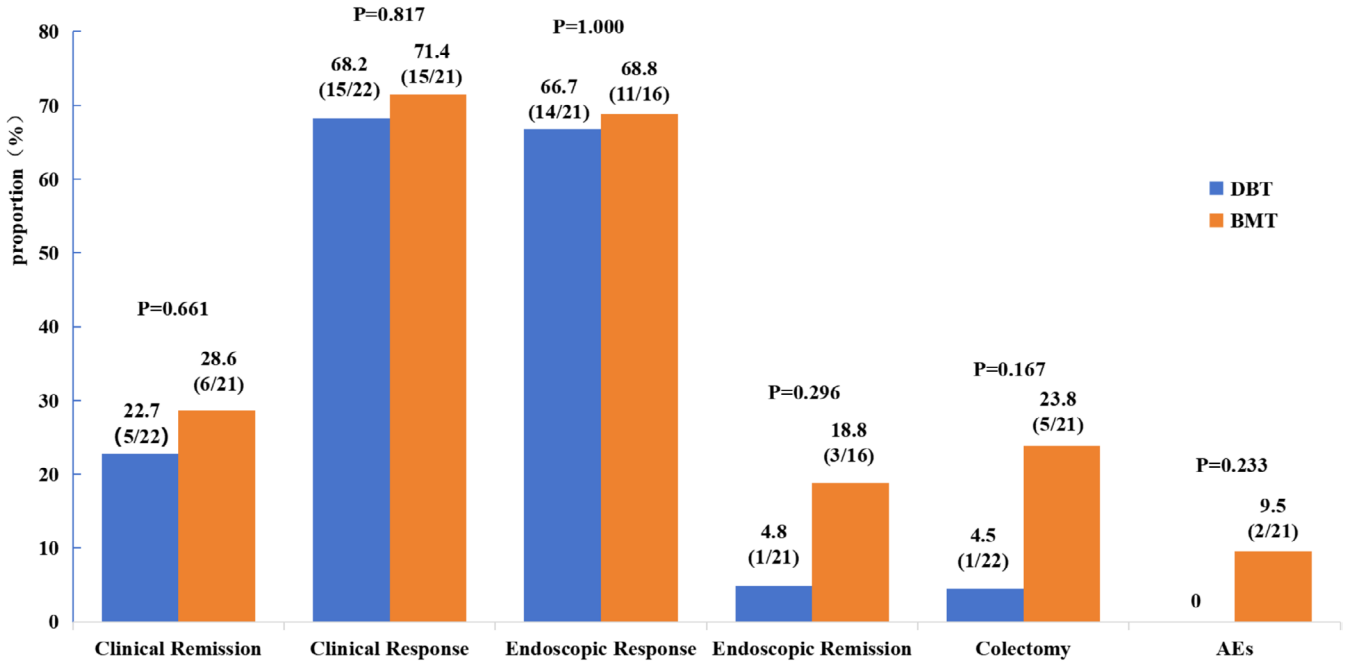

FIGURE 1 | The clinical remission/response rate, endoscopic response/remission rate, colectomy rate, and rate of AEs of DBT and BMT at week 12. AEs, adverse events; BMT, biologic small-molecule therapy; DBT, dual biologic therapy.

consistent with previous studies. A retrospective study including 16 refractory IBD patients treated with DBT reported a clinical remission and response rate of 25% and 68.8% at month 6, respectively [6]. Limited data on upadacitinib combined with biologics in refractory IBD patients were reported. However, Kwapisz et al. [8] reported a 20% colectomy rate of IBD patients treated with DBT after a median follow-up period of 6 months, which was higher than 4.5% of our study. This difference in colectomy rate may be related to the different follow-up periods and treatment regimens.

For endoscopic outcomes, there were 21 patients in the DBT group and 16 patients in the BMT group evaluated at week 12. Our results showed that the endoscopic response and remission rates in the DBT group were numerically lower than those in the BMT group (66.7% vs. 68.8%, 4.8% vs. 18.8%), but the differences were not significant. A previous cohort study assessed the efficacy of DBT in refractory CD patients and showed an endoscopic remission rate of 26% at a median follow-up of 225 days [5]. The result was higher than 4.8% in our study, which may be due to their longer follow-up period. Another systematic review reported an endoscopic response of 93% in IBD patients who received DBT [12]. The higher response rate than ours may be related to the fact that half of their patients were treated with an immunomodulator or steroid at the same time, while the patients in our study had no other concomitant medications. However, one retrospective study reported an endoscopic response rate of 54.5% in patients with refractory CD who received BMT and an endoscopic remission rate of 18.2% [13]. The results were similar to ours.

Although CATT is quite promising for patients with refractory IBD, the biggest concern is safety. A review of the literature including 16 studies on the use of dual biologics in IBD reported that AEs were seen in 19%–26% of patients with dual biologic therapy, and infection was the most common reported adverse event [10]. In our study, we compared the differences in AEs between the DBT and BMT groups. All AEs occurred in the BMT group, which were mild. However, no statistically significant differences were observed between the two groups.

There were several limitations in our study. Firstly, it was a retrospective study with a relatively small sample size, which reduced the statistical power to a certain extent and made it hard to draw definitive conclusions. In fact, we tried to perform a post hoc power estimate and found it to be relatively low (0.08). If we need to conclude the stated conclusion, 250 patients (power: 0.8, type of equivalent study) in each group are needed. Secondly, the data of the study was derived from a single large tertiary IBD center, which leads to our study findings not being generalizable to other centers. Thirdly, the follow-up period of our study was relatively short.

Although its limitations, our study first compared the effectiveness and safety of DBT with BMT in refractory IBD patients and found that there may be similar efficacy and safety between them. Further multi-center, prospective RCTs with a long-term follow-up period are necessary to confirm this conclusion.

Author Contributions

F.Y., X.L., and M.C. analyzed the data and wrote the manuscript. D.H., S.L., and X.F. performed the research. Y.S. and M.C. designed the research.

Conflicts of Interest

The authors declare no conflicts of interest.

Disclaimer

All the combination therapies in this study were not experimental and it was not approved by the regulatory agencies.

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