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Real-World Effectiveness and Safety of Dual Targeted Therapy in Refractory Inflammatory Bowel Disease: A Retrospective Cohort Study from the Middle East

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Abstract

Background: Inflammatory bowel disease is a chronic immune-mediated disorder where a subset of patients develops refractory disease despite treatment with advanced therapies. Dual targeted therapy (DTT), the concurrent use of two targeted agents with different mechanisms of action, has emerged as a potential strategy for this highly challenging patient population. However, real-world data on the effectiveness and safety of DTT, particularly from the Middle East, remain scarce.

Aims: This study aimed to evaluate the real-world outcomes of DTT in adult patients with refractory Inflammatory bowel disease in Qatar.

Methods: We conducted a retrospective, observational study of adult patients with refractory Crohn's disease (CD) or Ulcerative colitis (UC) who received DTT for at least eight weeks between January 2020 and May 2025 at two IBD referral center in Qatar. Data on patient demographics, disease characteristics, treatment history, and clinical, endoscopic, and safety outcomes were extracted from electronic medical records. Clinical remission was defined as a Harvey-Bradshaw Index (HBI) ≤4 for CD and a Mayo Clinic Score ≤2 for UC. Endoscopic remission was defined as a Simple Endoscopic Score for Crohn's Disease (SES-CD) ≤2 or a Mayo endoscopic sub-score of 0–1.

Results: A total of 24 patients (14 CD, 10 UC) were included, with a median age of 46.0 years and a median of three prior failed biologic therapies. The median duration of DTT was 47.0 weeks. In the overall cohort, 45.8% of patients achieved clinical remission, with a statistically significant association observed between the specific DTT combination and remission rates (p=0.027); the combination of infliximab plus ustekinumab was most effective, achieving remission in 80% of patients. Endoscopic remission was observed in 39.1% of patients. Adverse events were uncommon, occurring in only three patients (12.5%): two cases of anemia and one fungal infection, all of which were managed conservatively.

Conclusions: In this real-world cohort of highly refractory Inflammatory bowel disease patients in the Middle East, dual targeted therapy was associated with substantial rates of clinical and endoscopic remission. The safety profile was favorable, with adverse events occurring in only 12.5% of patients. In this cohort, DTT appeared to be an effective and safe rescue strategy for patients with refractory Inflammatory bowel disease in this region, warranting further prospective evaluation to confirm long-term outcomes.

Background

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic relapsing immune-mediated disorder associated with substantial morbidity and progressive bowel damage in a subset of patients. Despite the widespread use of biologic therapies, treatment failure remains common. With anti-Tumor Necrosis Factor (TNF) agents, primary non-response occurs in approximately 10–30% of patients, while secondary loss of response develops in 23–46% over time, often necessitating dose escalation, switching, corticosteroid exposure, hospitalization, or surgery [1, 2]. These limitations are likely to reflect the complex and redundant inflammatory pathways involved in IBD pathogenesis, which may not be adequately controlled by single-target therapy.

As the therapeutic armamentarium expanded to include agents with distinct mechanisms of action—such as vedolizumab (anti-integrin α4β7), ustekinumab (anti-IL-12/23), and Janus kinase (JAK) inhibitors—many patients with refractory disease still fail to achieve sustained remission [3, 4]. Dual targeted therapy (DTT) has therefore emerged as a potential strategy for highly refractory IBD; DTT refers to the concomitant use of two advanced targeted agents,

most commonly dual biologic therapy (two biologics with different mechanisms) or a biologic combined with a small molecule agent, aiming to modulate complementary inflammatory pathways and improve steroid-free disease control in patients who have failed sequential monotherapies [3, 4]. A systematic review and meta-analysis reported pooled clinical remission rates of 59% and endoscopic remission rates of 34%, with any adverse events occurring in 31% and serious adverse events in 6.5% of patients receiving combination advanced therapies [3]. Similarly, observational data in refractory CD demonstrated that dual biologic therapy may induce clinical response in ~50%, clinical remission in ~41%, and endoscopic remission in ~26%, with an overall adverse event rate of ~13% across therapeutic trials [5]. Multicenter real-world studies have further suggested that DTT can provide meaningful steroid-sparing benefits with an acceptable safety profile under careful monitoring [6, 7].

However, evidence from Middle Eastern populations remains scarce. Regional differences in disease phenotype, comorbidity patterns, infection epidemiology, and healthcare delivery may influence both effectiveness and safety outcomes. Therefore, this retrospective study aims to evaluate the real-world effectiveness, safety, and steroid-free outcomes of DTT in adult patients with refractory IBD treated at two centers in Qatar between 2020 and 2025. The findings from this study will provide valuable insights into the real-world effectiveness and safety of DTT in a Middle Eastern population with refractory IBD, potentially informing clinical practice and future research directions in this challenging patient population.

Materials and Methods

This retrospective, observational study was conducted at two IBD referral centers in Qatar: Al Khor Hospital (AKH), and the Ambulatory Care Center (ACC), both within Hamad Medical Corporation. We evaluated consecutive adult patients treated between January 2020 and May 2025 who received DTT for refractory IBD. The primary objective was to assess the real-world effectiveness, safety, and steroid-free outcomes associated with DTT in routine clinical practice.

Eligible patients were aged ≥18 years at the time of DTT initiation and had an established diagnosis of CD or UC, confirmed through standard clinical, endoscopic, histologic, and/or radiologic criteria. While no single consensus definition exists, refractory was defined for this study in line with current European Crohn's and Colitis Organization (ECCO) concepts as active disease despite failure of, or intolerance to, at least two advanced therapies from different classes (e.g., anti-TNF, anti-integrin, anti-IL-12/23) [8]. Treatment failure was defined as primary non-response (lack of clinical improvement after an adequate induction period), secondary loss of response (recurrence of symptoms after an initial response), or intolerance necessitating discontinuation [9]. DTT was defined as the concurrent use of two biologic agents or one biologic and one JAK inhibitor for a minimum duration of eight weeks. Patients were excluded if they were younger than 18 years, had IBD-unclassified, received DTT for less than eight weeks, had insufficient data for outcome assessments, or received combination therapy exclusively within a clinical trial with restricted data access.

Clinical and laboratory data were extracted from electronic medical records using a standardized data collection form. Variables included demographics (age, sex, nationality), body mass index, smoking status, disease duration, and phenotype. For CD, disease location and behavior were documented according to the Montreal classification [10]. The presence of perianal disease and extra-intestinal manifestations was recorded. Prior treatment exposures, reasons for discontinuation, and corticosteroid use were documented. For DTT, the biologic combinations, duration of therapy, and clinical rationale for initiation were collected. Concomitant medications, including systemic corticosteroids, immunomodulators, and antibiotics, were also recorded.

Clinical effectiveness outcomes were assessed using validated disease activity indices. For CD, disease activity was evaluated using the Harvey-Bradshaw Index (HBI), with clinical remission defined as HBI ≤4 and clinical response defined as a reduction of ≥3 points from baseline [11]. For UC, disease activity was assessed using the Mayo Clinic Score, with clinical remission defined as a total Mayo score ≤2 with no individual sub-score >1, consistent with established clinical trial endpoints [12]. Since partial Mayo scores were used in outpatient follow-up, remission required a partial Mayo score ≤2. Biochemical remission was defined as CRP normalization and/or FCP reduction to <250 µg/g, in alignment with treat-to-target recommendations [13].

Endoscopic outcomes were evaluated using validated scoring systems when available. For CD, endoscopic activity was measured using the Simple Endoscopic Score for Crohn's Disease (SES-CD), with endoscopic remission defined as SES-CD ≤2 [10]. For UC, mucosal activity was graded using the Mayo endoscopic sub-score, with endoscopic remission defined as a sub-score of 0–1 and complete mucosal healing defined as a sub-score of 0 [12, 13]. Because endoscopic reassessment was performed according to clinical indications rather than standardized intervals, analyses were conducted based on available clinical examinations.

Steroid-related outcomes were re-specified. Steroid-free time was defined as the duration from systemic corticosteroid discontinuation to steroid re-initiation, or end of follow-up. Steroid-free clinical remission required fulfillment of clinical remission criteria in the absence of systemic corticosteroids.

Safety outcomes included all adverse events (AEs) documented during DTT exposure. Serious adverse events (SAEs) were defined according to International Council for Harmonization (ICH) Good Clinical Practice criteria as events resulting in hospitalization, life-threatening complications, disability, or death [14]. Definitions were applied to clinical and laboratory data. Healthcare utilization outcomes included IBD-related hospitalizations, emergency department visits, and surgeries.

To ensure data quality, extraction was performed by trained research personnel. A random 20% sample of records underwent independent secondary review for accuracy and consistency. Discrepancies were resolved by consensus. Data were de-identified prior to analysis and stored in a secure database.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics and outcomes. Continuous variables were reported as medians with interquartile ranges (IQR), and categorical variables as frequencies and percentages. For comparative analyses between CD and UC subgroups, the Mann-Whitney U test was used for continuous variables, while Fisher's exact test was used for categorical variables due to the small sample sizes. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. Institutional Review Board approval was obtained from the Hamad Medical Corporation Medical Research Center (MRC-01-25-1395), and the requirement for informed consent was waived due to the retrospective design and use of de-identified data.

Results

Study Population and Baseline Characteristics

A total of 24 adult patients with refractory IBD treated with DTT were included in the analysis. The cohort comprised 14 patients with CD (58.3%) and 10 patients with UC (41.7%). All patients had active diseases at the time of DTT initiation.

The overall median age was 46.0 years (IQR 22.5–54.5). As shown in Table 1, patients with CD were highly significantly younger than those with UC (median 24.5 [IQR 20.0–42.2] vs 52.0 [IQR 49.0–57.5]; p = 0.005). Body mass index (BMI) also differed significantly between subgroups, with the CD cohort having a lower BMI compared with the UC cohort (median 18.2 [IQR 16.4–20.8] vs 25.1 kg/m² [IQR 21.8–28.0]; p = 0.001). Median disease duration for the entire cohort was 9.5 years (IQR 5.8–19.2), with CD patients having a significantly shorter disease duration relative to UC patients (6.5 [IQR 4.2–8.0] vs 20.0 [IQR 15.0–25.0] years; p = 0.002).

Males represented 58.3% (14/24) of the study population, with no significant sex distribution difference between CD and UC (57.1% vs 60.0%; p = 1.000). The median number of prior biologic failures was three (IQR 2.0–3.5), similar across CD and UC subgroups (p = 0.356).

Most patients were never-smokers (79.2%, 19/24), while 16.7% (4/24) were ex-smokers and 4.2% (1/24) were current smokers. The frequency of ever-smoking did not differ significantly between CD and UC patients (21.4% vs 20.0%; p = 1.000; Table 1).

Primary Outcomes

Clinical remission was achieved in 45.8% (11/24) of patients overall. Remission rates were numerically higher in CD compared with UC (57.1% [8/14] vs 30.0% [3/10]), although the difference did not reach statistical significance (p = 0.240). The odds of achieving clinical remission were higher in CD (OR 3.11; 95% CI 0.56–17.33). Clinical response, including remission, was observed in 62.5% (15/24) of patients, with comparable rates between CD and UC (64.3% vs 60.0%; p = 1.000; Table 2).

Secondary Outcomes

Corticosteroid-free remission (CSFR) was documented in 70.8% (17/24) of patients. CSFR occurred more frequently in CD (78.6%, 11/14) than UC (60.0%, 6/10), without statistical significance (p = 0.393; OR 2.44; 95% CI 0.41–14.75). Biochemical remission was achieved in 54.2% (13/24) of the cohort, with similar proportions in CD and UC (57.1% vs 50.0%; p = 1.000). Endoscopic remission was observed in 39.1% (9/23) of patients with available endoscopic reassessment (median time from DTT initiation to follow-up endoscopy: 42 weeks [IQR 28–60]). Rates were numerically higher in UC patients (50.0%, 5/10) than in CD (30.8%, 4/13), though not statistically significant (p = 0.417; OR 0.44; 95% CI 0.08–2.46). (Table 2)

Subgroup Analyses (CD vs UC)

Comparative analyses between disease subtypes demonstrated differences in clinical outcomes and healthcare utilization. Hospitalization during dual targeted therapy occurred in 20.8% (5/24) of the overall cohort. While hospitalization was numerically more frequent among patients with Crohn's disease compared with ulcerative colitis (28.6% [4/14] vs 10.0% [1/10]; p=0.36), this difference did not reach statistical significance. The estimated odds of hospitalization were higher in CD (OR 3.60), although the confidence interval was wide and crossed one, given the limited power of the analysis (Table 3).

Dual targeted therapy discontinuation was observed in 16.7% (4/24) of patients. Discontinuation occurred more commonly in CD than UC (21.4% [3/14] vs 10.0% [1/10]), but this difference was not statistically significant (p = 0.63).

Importantly, treatment discontinuation was not attributable to adverse events or unsatisfactory clinical response. In two cases, discontinuation was based on patient preference driven by concerns regarding the perceived safety of combination biologic therapy. In the remaining two patients, discontinuation was based on a physician decision due to achievement of deep, individualized remission, independent of disease course and therapeutic strategy. No discontinuations were mandated by serious adverse events. (Table 3)

Surgery during DTT was recorded exclusively among CD patients (28.6%, 4/14), whereas no UC patients required surgery. Although this suggests a clinically notable difference, statistical significance was not reached ($p = 0.114$), likely to reflect sample size limitations. Overall, while several outcomes numerically differed between CD and UC, no statistically significant differences were observed for treatment response, biochemical outcomes, adverse events, hospitalization, or treatment discontinuation. (Table 3)

Smoking Status

When stratified by smoking history, surgery during DTT was significantly more frequent among ever-smokers compared with never-smokers (60.0% [3/5] vs 5.3% [1/19]; $p = 0.018$). Ever-smoking was associated with a substantially increased odds of surgery (OR 27.00; 95% CI 1.83–399.23). However, this finding should be interpreted with caution due to the small number of smokers in the cohort (n=5). No statistically significant associations were observed between smoking status and clinical remission, response, hospitalization, or discontinuation, although CSFR was numerically lower among ever-smokers. (Table 1)

DTT Combinations

Four DTT combinations met the threshold for descriptive subgroup evaluation ($n \geq 3$). Clinical remission rates varied across regimens, with the highest remission observed in patients receiving infliximab plus ustekinumab (80.0%, 4/5), followed by ustekinumab plus vedolizumab (62.5%, 5/8). In contrast, no clinical remission occurred with Risankizumab plus vedolizumab (0/4) or tofacitinib plus vedolizumab (0/3). An exploratory omnibus comparison demonstrated a statistically significant association between the chosen regimen and clinical remission ($p = 0.027$) and with CSFR ($p = 0.041$). This finding should be interpreted cautiously, given small subgroup sizes. (Table 4)

Safety and Adverse Events

Adverse events were reported in 12.5% of patients (3/24) during exposure to DTT. All events were non-serious and were managed conservatively without requiring treatment discontinuation. Two cases of anemia (8.3%) and one fungal infection (4.2%) were observed. One anemia case occurred in a 58-year-old female with ulcerative colitis receiving Risankizumab plus upadacitinib who subsequently achieved clinical remission. The second occurred in a Crohn's disease patient treated with Risankizumab plus vedolizumab and was associated with treatment failure. The fungal infection was documented in a Crohn's disease patient receiving infliximab in combination with ustekinumab, who nevertheless achieved clinical remission.

Overall, the adverse events were mild and distributed across different DTT combinations without clustering to a specific regimen. Notably, two of the three patients experiencing AEs ultimately achieved clinical remission. No serious adverse events, opportunistic infections requiring hospitalization, thromboembolic events, malignancies, or deaths were observed during follow-up, supporting a favorable safety profile of DTT in this cohort. (Table 3)

Treatment Discontinuation and Follow-up

The median duration of dual targeted therapy (DTT) exposure was 47.0 weeks (IQR 22.0–78.0). DTT discontinuation occurred in 16.7% (4/24) of patients. Discontinuation was numerically more frequent among patients with Crohn's disease than among those with ulcerative colitis (21.4% [3/14] vs 10.0% [1/10]); however, this difference did not reach statistical significance (p = 0.63). The estimated odds of treatment discontinuation were higher in CD (OR 2.45), with a wide confidence interval reflecting the small number of events. As stated previously, treatment discontinuation was not attributable to medication-related adverse events. (Table 3)

Table 1. Baseline Characteristics of Inflammatory Bowel Disease Patients Treated with Dual Targeted Therapy (Number 24)

Variable	Overall (n=24)	CD (n=14)	UC (n=10)	p-value
Age (years), median (IQR)	46.0 (22.5–54.5)	24.5 (20.0–42.2)	52.0 (49.0–57.5)	0.005
Male sex, n (%)	14 (58.3%)	8 (57.1%)	6 (60.0%)	1.000
BMI (kg/m²), median (IQR)	21.3 (17.8–25.1)	18.2 (16.4–20.8)	25.1 (21.8–28.0)	0.001
Ethnicity, n (%)				
Arab	19 (79.2%)	10 (71.4%)	9 (90.0%)	0.358
Southeast Asian	2 (8.3%)	2 (14.3%)	0 (0.0%)	0.493
Western	2 (8.3%)	1 (7.1%)	1 (10.0%)	1.000
South Asian	1 (4.2%)	1 (7.1%)	0 (0.0%)	1.000
Smoking Status, n (%)				
Never smoker	19 (79.2%)	11 (78.6%)	8 (80.0%)	1.000
Ever smoker (ex/current)	5 (20.8%)	3 (21.4%)	2 (20.0%)	1.000
Disease duration (years), median (IQR)	9.5 (5.8–19.2)	6.5 (4.2–8.0)	20.0 (15.0–25.0)	0.002
Perianal Disease, n (%)	3 (12.5%)	3 (21.4%)	0 (0.0%)	0.239
Extra-intestinal Manifestations (EIM), n (%)	9 (37.5%)	6 (42.9%)	3 (30.0%)	0.678
Prior biologic failures (n), median (IQR)	3.0 (2.0–3.0)	3.0 (2.0–3.8)	3.0 (2.0–3.0)	0.356
Names of Prior Biologics Failed, n (%)				
Ustekinumab	21 (87.5%)	13 (92.9%)	8 (80.0%)	0.550
Infliximab	19 (79.2%)	12 (85.7%)	7 (70.0%)	0.615
Vedolizumab	14 (58.3%)	7 (50.0%)	7 (70.0%)	0.421
Adalimumab	13 (54.2%)	9 (64.3%)	4 (40.0%)	0.408
Reason for Prior Biologic Discontinuation, n (%)				
Primary non-response	15 (62.5%)	9 (64.3%)	6 (60.0%)	1.000
Secondary loss of response	9 (37.5%)	5 (35.7%)	4 (40.0%)	1.000

Legend: CD = Crohn's disease; UC = ulcerative colitis; BMI = body mass index; IQR = interquartile range; n = Number. Continuous variables are presented as median (IQR) and compared using the Mann-Whitney U test. Categorical variables are presented as frequencies (percentages) and compared using Fisher's exact test. Patients may have failed multiple prior biologics, hence the percentages for individual biologics sum to more than 100%.

Table 2. Comparison of Clinical, Biochemical, and Endoscopic Effectiveness Outcomes Between Crohn's Disease and Ulcerative Colitis Patients Receiving Dual Targeted Therapy for Refractory Inflammatory Bowel Disease(N=24)

Outcome	Overall (n=24)	CD (n=14)	UC (n=10)	p-value
Clinical remission	11 (45.8%)	8 (57.1%)	3 (30.0%)	0.240
Clinical response (incl. remission)	15 (62.5%)	9 (64.3%)	6 (60.0%)	1.000
Corticosteroid-free remission (CSFR)	17 (70.8%)	11 (78.6%)	6 (60.0%)	0.393
Biochemical remission	13 (54.2%)	8 (57.1%)	5 (50.0%)	1.000
Endoscopic remission*	9 (39.1%)	4 (30.8%)	5 (50.0%)	0.417
Treatment failure	9 (37.5%)	5 (35.7%)	4 (40.0%)	1.000

Legend: CD = Crohn's disease; UC = ulcerative colitis; CSFR = corticosteroid-free remission. Data are presented as frequencies and percentages, n (%). Comparisons between the CD (n=14) and UC (n=10) subgroups were performed using Fisher's exact test. Clinical remission was defined as a Harvey-Bradshaw Index ≤4 for CD and a partial Mayo Clinic Score ≤2 for UC. Biochemical remission was defined as normalization of C-reactive protein (<5 mg/L) and/or fecal calprotectin (<250 µg/g). Endoscopic remission was defined as a Simple Endoscopic Score for Crohn's Disease (SES-CD) ≤2 or a Mayo endoscopic sub-score of 0–1. Endoscopic remission rates were calculated based on the subset of patients with available endoscopic reassessment data (overall n=23; CD n=13; UC n=10).

Table 3. Safety Profile, Healthcare Utilization, and Treatment Discontinuation During Dual Targeted Therapy (N=24)

Outcome	Overall (n=24)	CD (n=14)	UC (n=10)	p-value
Any adverse event (AE)	3 (12.5%)	2 (14.3%)	1 (10.0%)	1.000
Anemia	2 (8.3%)	2 (14.3%)	0 (0.0%)	0.500
Fungal infection	1 (4.2%)	0 (0.0%)	1 (10.0%)	0.417
Hospitalization during DBT	5 (20.8%)	4 (28.6%)	1 (10.0%)	0.36
Surgery during DBT	4 (16.7%)	4 (28.6%)	0 (0.0%)	0.114
DBT discontinuation	4 (16.7%)	3 (21.4%)	1 (10.0%)	0.63

Legend: CD = Crohn's disease; UC = ulcerative colitis; AE = adverse event; DTT = dual targeted therapy. Data are presented as frequencies and percentages, n (%). Comparisons between the CD (n=14) and UC (n=10) subgroups were performed using Fisher's exact test. Adverse events represent any documented side effect during the therapy period. Hospitalization and surgery refer specifically to IBD-related events occurring after the initiation of dual targeted therapy. Treatment discontinuation includes cessation of therapy for any reason, including patient preference, physician decision, or persistent disease activity.

Table 4. Clinical Outcomes and Safety Events Stratified by Specific Dual Targeted Therapy Combinations (N=24)

Combination	n	Clinical Remission	CSFR	Biochemical Remission	Endoscopic Remission	Hospitalization	Discontinuation
Ustekinumab + Vedolizumab	8	5 (62.5%)	7 (87.5%)	6 (75.0%)	3/8 (37.5%)	3 (37.5%)	2 (25.0%)
Infliximab + Ustekinumab	5	3 (60.0%)	4 (80.0%)	4 (80.0%)	3/4 (75.0%)	2 (40.0%)	2 (40.0%)
Risankizumab + Vedolizumab	4	0 (0.0%)	2 (50.0%)	1 (25.0%)	0/4 (0.0%)	4 (100.0%)	2 (50.0%)
Tofacitinib + Vedolizumab	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0/3 (0.0%)	0 (0.0%)	0 (0.0%)
Other Combinations	4	2 (50.0%)	4 (100.0%)	2 (50.0%)	3/4 (75.0%)	1 (25.0%)	3 (75.0%)

Legend: CSFR = corticosteroid-free remission. Data are presented as frequencies and percentages, n (%). This table details the outcomes for the specific dual targeted therapy combinations administered to the cohort. Combinations administered to fewer than three patients (Adalimumab & Ustekinumab [n=2], Risankizumab & Upadacitinib [n=1], and Adalimumab & Upadacitinib [n=1]) are grouped under "Other Combinations". Endoscopic remission rates were calculated based on the subset of patients within each specific combination group who underwent endoscopic reassessment (n=23 total). An exploratory omnibus comparison demonstrated a statistically significant association between the chosen regimen and clinical remission ($p = 0.027$) as well as CSFR ($p = 0.041$).

Discussion

Dual targeted therapy is an emerging strategy for managing highly refractory IBD, yet its application, particularly in Middle Eastern populations, remains largely uninvestigated. In this retrospective study of 24 patients with refractory IBD from Qatar, we found a clinical remission rate of 45.8% and a clinical response rate of 62.5% after a median follow-up of 47 weeks. These findings contribute valuable real-world evidence on the effectiveness and safety of DTT in a unique and challenging patient cohort.

Our overall clinical remission rate of 45.8% aligns with the existing body of literature, which reports remission rates ranging from 41% to 59% in similarly refractory populations [3, 5]. For instance, a retrospective cohort of 22 Crohn's disease (CD) patients reported a clinical remission rate of 41% [5], while a systematic review and meta-analysis of 30 studies reported a pooled remission rate of 59% [3]. The slightly lower rate in our study compared to the meta-analysis may be attributable to the highly refractory nature of our cohort, who had failed a median of three prior biologic therapies. When examining disease subtypes, our study found a numerically higher clinical remission rate in our CD cohort (57.1%) compared to UC patients (30.0%). The remission rate in our CD cohort is notably higher than the 41% reported by Yang et al. in a comparable CD-only cohort [5], suggesting that DTT may be particularly beneficial in this subgroup. Conversely, the 30.0% remission rate in our UC patients is slightly lower than the 37% rate reported in the VEGA trial combining Guselkumab and Golimumab [15], this difference may be partly explained by the effectiveness of the specific therapeutic combination used in that trial.

Endoscopic outcomes in our study also showed promise, with an overall endoscopic remission rate of 39.1%. This is consistent with the 34% pooled rate reported by Ahmed et al. [3] and the 36% rate from the meta-analysis by Glassner et al. [16]. The 50% rate of mucosal healing in UC patients (50.0%), which surpasses the rates typically seen with

monotherapy and approaches the efficacy observed in some prospective DTT studies like the 50% rate reported by Buer et al. [17], suggests that DTT can induce significant mucosal healing even in patients who have failed multiple previous therapies.

One of the most significant findings from our study was the exploratory analysis of specific DTT combinations. We observed a statistically significant association between the chosen regimen and clinical remission ($p = 0.027$), though this finding is exploratory and must be interpreted with caution given the small subgroup sizes (range n=3–8 per regimen). Notably, the combination of infliximab plus ustekinumab achieved an 80% remission rate (4/5), and ustekinumab plus vedolizumab achieved a 62.5% remission rate (5/8). This aligns with emerging mechanistic rationale suggesting that combining anti-TNF-α with anti-IL-12/23 inhibition or combining non-selective anti-integrin therapy with systemic IL-12/23 inhibition, can be highly effective [18]. In contrast, the combination of risankizumab plus vedolizumab resulted in 0% clinical remission (0/4), a finding that warrants further investigation to understand potential negative interactions or the unsuitability of this combination for this specific patient profile.

The safety profile of DTT in our cohort was excellent and highly encouraging. The overall AE rate was only 12.5%, consisting of two cases of anemia and one fungal infection, with no SAEs and no AEs leading to treatment discontinuation. This is substantially lower than the 31% pooled AE rate and 6.5% serious AE rate reported in the meta-analysis by Ahmed et al. [3] and is comparable to the 13% AE rate observed by Yang et al. [5]. This low AE rate, particularly in this highly refractory disease population, supports the growing consensus that combining biologics, especially those with different mechanisms of action, does not significantly increase safety risks beyond those of monotherapy [18, 19].

Our study also identified smoking as a significant risk factor for requiring surgery during DTT ($p = 0.018$), with ever-smokers having a markedly increased odds of surgery (OR 27.00). This underscores the critical importance of smoking cessation counseling as an integral part of IBD management, even in patients on advanced therapies. Furthermore, while not statistically significant, we observed a higher rate of surgery exclusively in the CD cohort (28.6% vs 0% in UC), which is consistent with the more complicated and penetrating phenotype often seen in refractory CD [10]. The baseline differences in our cohort, with CD patients being significantly younger and having a lower BMI, may also suggest a more aggressive disease phenotype in this subgroup, potentially contributing to the observed trends in outcomes and healthcare utilization.

This study has limitations, primarily its retrospective design and small sample size, which limit the statistical power to detect significant differences in some subgroup analyses and prevent definitive conclusions about the superiority of specific combinations. The heterogeneity of DTT regimens used also makes direct comparisons challenging. The small sample size particularly impacts the reliability of subgroup analyses, such as the smoking and surgery association, and explains why some clinically meaningful trends (e.g., higher remission in CD) did not reach statistical significance. However, as one of the first studies to evaluate DTT in a Middle Eastern population, it provides crucial real-world data that can inform clinical practice in the region. Notably, this cohort size is consistent with other early real-world DTT studies, such as Yang et al. (n=22) and Eronen et al. reflecting the strict criteria for refractory disease and the inherent novelty of this therapeutic approach in routine clinical practice.

Conclusions

Our findings suggest that dual targeted therapy is an effective and safe rescue strategy for patients with highly refractory IBD who have failed multiple lines of therapy. We observed high rates of clinical remission, particularly in patients with Crohn's disease, and an excellent safety profile with minimal adverse events. The significant

association between specific DTT combinations and clinical outcomes highlights the need for further research to identify optimal pairing strategies. Future prospective multicenter studies with larger cohorts are needed to confirm our findings, validate the efficacy of specific combinations, and establish the long-term durability and safety of this promising therapeutic approach.

Abbreviations

AE: Adverse event; AKH: AlKhor Hospital; ACC: Ambulatory Care Center; BMI: Body mass index; CD: Crohn's disease; CI: Confidence interval; CRP: C-reactive protein; CSFR: Corticosteroid-free remission; DTT: Dual targeted therapy; ECCO: European Crohn's and Colitis Organisation; FCP: Fecal calprotectin; HBI: Harvey-Bradshaw Index; IBD: Inflammatory bowel disease; ICH: International Council for Harmonisation; IQR: Interquartile range; IRB: Institutional Review Board; JAK: Janus kinase; OR: Odds ratio; SAE: Serious adverse event; SES-CD: Simple Endoscopic Score for Crohn's Disease; TNF: Tumor necrosis factor; UC: Ulcerative colitis

Declarations

Human Ethics and Consent to Participate declarations

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. Ethics approval was obtained from the Medical Research Committee of Hamad Medical Corporation, Doha, Qatar (Approval No. MRC-01-25-1395). The requirement for individual informed consent was waived by the ethics committee due to the retrospective design of the study and the use of de-identified patient data.

Clinical Trial Number

not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AH: Substantial contributions to concept or design, acquisition, analysis, or interpretation of data, drafting of the manuscript, critical review of the manuscript for important intellectual content, agreed to be accountable for all aspects of the work, will review the final version to be published, supervised the work. AK: Substantial contributions to concept or design, drafting of the manuscript, critical review of the manuscript for important intellectual content,

agreed to be accountable for all aspects of the work, will review the final version to be published. KAE: Substantial contributions to concept or design, drafting of the manuscript, agreed to be accountable for all aspects of the work, will review the final version to be published. AB: Acquisition, analysis, or interpretation of data, critical review of the manuscript for important intellectual content, agreed to be accountable for all aspects of the work, will review the final version to be published. FA: Acquisition, analysis, or interpretation of data, critical review of the manuscript for important intellectual content, agreed to be accountable for all aspects of the work, will review the final version to be published. MN: Substantial contributions to concept or design, critical review of the manuscript for important intellectual content, agreed to be accountable for all aspects of the work, will review the final version to be published. MA: Acquisition, analysis, or interpretation of data, critical review of the manuscript for important intellectual content, agreed to be accountable for all aspects of the work, will review the final version to be published. All authors read and approved of the final manuscript.

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