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ORIGINAL RESEARCH

Advanced Combination Therapy with Biologics and Upadacitinib in Refractory Inflammatory Bowel Disease: A Retrospective Study from Taiwan

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Background: Refractory inflammatory bowel disease (IBD) remains challenging despite the availability of various biologics. Advanced combination therapy (ACT) with biologics and Upadacitinib (UPA), a rapid-onset oral selective Janus kinase inhibitor, has shown promise in managing refractory IBD. However, its use in Asia has not been explored. This study aims to fill that gap by providing data from Taiwan.

Materials and Methods: This retrospective study included refractory IBD patients who received ACT with biologics and UPA, followed up at the Chang Gung Inflammatory Bowel Disease Center from July 2020 to August 2024. Patients were assessed for clinical response and remission at weeks 4, 12, and 24. Safety profiles were monitored throughout the follow-up period to evaluate the risk of adverse events.

Results: Sixteen refractory IBD patients were enrolled. The median disease duration was 4.5 years [IQR 2.25–9.50]. The most common regimen was Ustekinumab plus UPA (63%). Clinical response rates at weeks 4, 12, and 24 were 88%, 83%, and 100%, respectively, while remission rates were 31%, 50%, and 80%. One patient (6.25%) experienced a minor adverse event (acne), with no major events like herpes zoster reactivation or major cardiac complications.

Conclusion: This is the first study in Asia to demonstrate that UPA-based ACT is both effective and safe in treating refractory IBD. However, the limitations of this retrospective, single-center study with a relatively small sample size highlight the need for future larger-scale, multi-center prospective studies to confirm these findings, identify predictors of treatment response, and evaluate long-term outcomes.

Keywords: inflammatory bowel disease, advanced combination therapy, dual advanced therapy, biologics, upadacitinib

Introduction

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, relapsing, and remitting condition that can significantly impair patients' quality of life and impose a considerable burden on healthcare systems.[1] The etiology of IBD is multifactorial, influenced by genetic predisposition, immune dysregulation, environmental factors, and gut microbiota. Treatment strategies aim to target multiple pathways within the immune system, categorized into innate and adaptive immunity.[2–5]

Conventional therapies for IBD, such as corticosteroids, 5-aminosalicylic acid (5-ASA), and thiopurines, primarily function by non-specifically suppressing inflammation. While effective in controlling inflammation, these treatments

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often fail to achieve sustained remission in patients with moderate-to-severe disease. Many patients, especially those with CD, face a progressive disease course and over half may require surgical resection with a significant proportion experiencing postoperative recurrence. Similarly, in UC, approximately 25% of patients encounter episodes of acute severe disease requiring hospitalization, and colectomy remains a potential outcome despite aggressive medical therapy.[6,7]

The advent of advanced therapies has significantly transformed IBD management by targeting specific mechanisms involved in the inflammatory process. One major class of these therapies is anti-tumor necrosis factor (TNF) agents, which neutralize TNF-alpha, a cytokine crucial for driving tissue destruction and promoting inflammatory cytokine production in IBD's inflamed mucosa. Examples include infliximab, adalimumab, golimumab, and certolizumab. Another important category includes anti-interleukin (IL)-12/23 agents, such as ustekinumab (UST), which targets the p40 subunit of IL-12 and IL-23 to neutralize both cytokines while risankizumab, guselkumab, and mirikizumab selectively target the p19 subunit of IL-23. A second group of advanced therapies focuses on inhibiting lymphocyte migration to the intestinal mucosa. Anti-integrin therapies, such as vedolizumab (VDZ), block lymphocyte adhesion and migration, while sphingosine-1-phosphate receptor modulators, like ozanimod, regulate lymphocyte trafficking by restricting their egress from lymph nodes. The third category targets multiple cytokine-signaling pathways by blocking Janus kinases (JAKs). Tofacitinib primarily targets JAK3 and JAK1, affecting gamma-chain cytokines, gp130 family cytokines, interferons, and IL-10 family cytokines. In contrast, filgotinib and upadacitinib (UPA) are more selective for JAK1.Together, these advanced therapies have revolutionized the treatment landscape for IBD, offering hope for improved disease control and long-term outcomes.

However, despite their promise, most biologics have achieved a clinical remission rate of only approximately 40% at 52 weeks in patients with IBD, leaving a significant proportion of patients without long-term remission.[8–11] The possible mechanisms of treatment failure including primary non-response, secondary loss of response, immunogenicity and patient-related factors (eg Non-adherence to treatment regimens, psychological issues and coexisting condition which can adversely impact treatment outcomes).[12,13] The emerging concept of "difficult-to-treat IBD" further highlighted a subset of patients who present unique therapeutic challenges.[14]

To break through the therapeutic ceiling effects, various strategies, including therapeutic drug monitoring (TDM), intensified treatment guided by inflammatory markers, optimizing drug sequencing (ascending or descending ladder approaches), switching or sequential therapy, and advanced combination therapy (ACT) have been implemented in clinical practice to enhance treatment outcomes.[15,16]

Historically, combining immunomodulators with biological agents has proven more effective than monotherapy. The SONIC trial showed that moderate-to-severe CD patients treated with infliximab and azathioprine achieved higher corticosteroid-free clinical remission rates than monotherapy. Similarly, the UC-SUCCESS trial demonstrated that combination therapy in moderate-to-severe UC patients improved remission and mucosal healing rates compared to monotherapy.[17,18] However, the combination of traditional immunomodulators with newer biological agents has yielded mixed results, reflecting the need for further exploration.[19]

With the development of novel biologics in IBD, the concept of ACT has gained increasing attention. ACT involves the simultaneous use of two biologics or targeted therapies with complementary mechanisms of action to address the multifactorial immune dysregulation in IBD. Early evidence for ACT emerged from randomized-controlled trials (RCTs) evaluating dual biologic combinations revealed promising results in managing refractory IBD. Sands et al investigated natalizumab plus infliximab versus infliximab monotherapy in CD patients refractory to anti-TNF therapy, finding higher remission rates in the combination group, though not statistically significant, with no increase in serious adverse events.[20] The VEGA trial showed higher clinical response and remission rates, as well as significantly better endoscopic outcomes in moderate-to-severe UC patients, with guselkumab plus golimumab compared to monotherapy.[21]

Acknowledging the potential of ACT, the 2024 European Crohn's and Colitis Organization (ECCO) guidelines suggest that ACT could be essential in cases of uncontrolled extraintestinal manifestations or symptomatic immune-mediated disorders that require more than one therapeutic agent to achieve remission. Additionally, ACT may also be a viable option for managing refractory CD.[22]

In addition to dual biologic combination therapy, recent evidence highlights the potential of integrating small molecule therapies, particularly JAK inhibitors (JAKis), with biologics for managing refractory IBD. JAKis, such as tofacitinib and UPA, have been proven effective in managing IBD in previous studies.[23–25] A recent study conducted by Alayo et al evaluating the efficacy of combining tofacitinib with biologics, most commonly vedolizumab (VDZ) or infliximab, revealed a clinical response rate of 50%, with corticosteroid-free response and remission rates of 35.7% and 10.7% at week 8. By week 26, clinical response increased to 90%, and remission was achieved in 70% of patients.[26] Two studies assessed UPA combined with biologics for refractory IBD. Yusuke et al reported an 83.3% clinical remission rate for UPA with UST in refractory CD while another case series of 12 refractory IBD patients showed improvements in partial Mayo scores for UC and Harvey-Bradshaw index (HBI) for CD, though the latter was not statistically significant.[27,28]

Although ACT combining UPA with biologics shows promise in managing refractory IBD, its application comes with several challenges, particular regarding safety issues. A major concern involves the potential adverse events of JAKis, including infections, hypercholesterolemia, thromboembolism events, major adverse cardiovascular events (MACEs), and malignancy. Post-marketing trials of tofacitinib have indicated an increased risk of thromboembolic diseases and MACEs. However, novel selective JAK-1 inhibitors, such as UPA, appear to offer a safer profile compared to tofacitinib, although long-term safety data remain limited.[29] Moreover, ACT for refractory IBD involving biologics and small molecule therapies like JAKis, poses significant cost and accessibility challenges, particularly in resource-constrained settings or for patients without comprehensive insurance coverage in some regions. As for the optimal timing and sequencing of combination therapies—whether initiated simultaneously or as add-on therapy following failure of a single agent—remain areas of active investigation. Given that few studies have specifically addressed the efficacy and safety of UPA in combination with biologics, and the majority of these studies have been conducted in Western populations, with minimal data available on Asian IBD populations. This study presents the first preliminary investigation of the efficacy and safety of ACT with UPA and biologics in refractory IBD patients in Taiwan.

Materials and Methods

Patient Cohort and Data Collection

This study was conducted at Chang Gung Memorial Hospital, Linkou branch, a tertiary referral medical center in Northern Taiwan. Sixteen refractory IBD patients received UPA-based advanced combination therapy (UPA-based ACT) between July 2020 and August 2024. Medical records were reviewed to gather baseline characteristics, including age, gender, body mass index (BMI), smoking habits, IBD type, disease extent, phenotype, disease activity, extraintestinal manifestations, complications (eg, fistulas, abscesses, IBD-related surgeries), previous biologic exposure, and the regimens and durations of combination therapy. Patients were selected for ACT based on the presence of refractory symptoms (eg, abdominal pain, diarrhea, bloody stool) and/or complications despite receiving optimal conventional therapy and at least one biologic agent. All participants were screened for latent TB infection, hepatitis B and C, and other potential risk factors prior to initiating therapy and all patients in this study received herpes zoster vaccination prior to initiating UPA therapy according to ECCO guideline's recommendations.[30]

Clinical Outcomes

The primary outcome of the study was the clinical response and remission rates at week 4. Secondary outcomes included clinical response and remission rates at weeks 12 and 24, as well as safety profiles throughout the follow-up period. Clinical response for CD was defined as a reduction of at least 100 points from the baseline Crohn's Disease Activity Index (CDAI), while for UC, it was defined as a reduction in Mayo score of at least 30% from baseline, with a decrease of at least 1 point in the rectal bleeding sub-score. Clinical remission was defined as a CDAI score below 150 for CD and a Mayo score of 2 or less, with no sub-score greater than 1 for UC. Endoscopic response was defined as at least a 50% reduction in the Simple Endoscopic Score for Crohn's Disease (SES-CD) in CD and a reduction of 1 point or more in the

Mayo endoscopic sub-score for UC. Endoscopic remission was defined as an SES-CD score of 0–2 for CD and a Mayo endoscopic sub-score of 0 for UC. If patients were intolerant or refractory to UPA-based ACT, other biologic agents or alternative treatments were applied as appropriate.

Statistical Analysis

Continuous variables were expressed as median values with interquartile ranges (IQR), and categorical variables were expressed as frequencies and percentages. The Wilcoxon signed-rank test was used to analyze changes in laboratory parameters before and after UPA-based ACT. Statistical significance was set at $P < 0.05$. All analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patients Characteristics

Sixteen patients with refractory IBD (8 males and 8 females; 7 with CD and 9 with UC) who had persistent symptoms despite receiving optimal conventional therapy and at least one biologic agent were included in the study. The median age was 41.5 (IQR 30–52) year-old and the median duration since IBD diagnosis was 4.5 years (IQR 2.25–9.50). The baseline median CDAI score was 357 (IQR 234–451) while the median partial Mayo score was 8 (IQR 7.5–9.0) before ACT. Among the patients, four (25%) exhibited extraintestinal manifestations (EIMs), including peripheral arthritis, ankylosing spondylitis, erythema nodosum, and uveitis, while another four (25%) had IBD-related complications. The most common combination regimen was UST plus UPA (63%), followed by VDZ plus UPA (25%), Risankizumab plus UPA (6%), and Adalimumab plus UPA (6%). The median follow-up duration was 3 months (IQR 1.00–6.75) (Table 1).

Table 1 Demographic Characteristics

	N=16
General data	
Female, n (%)	8 (50%)
Age (years), median [IQR]	41.5 [30–52]
Body mass index, median [IQR]	24.95 [22.18–26.50]
Smoking, n (%)	3 (18.75%)
IBD types	
Crohn's disease (CD), n (%)	7 (43.75%)
Ulcerative colitis (UC), n (%)	9 (56.25%)
CD Montreal Location	
L1, ileal, n (%)	1 (14.29%)
L2, colonic, n (%)	0
L3, ileocolonic, n (%)	6 (85.71%)
L4, isolated upper disease, n (%)	0
CD Montreal phenotypes	
B1, non-stricturing, non-penetrating, n (%)	2 (28.57%)
B2, stricturing, n (%)	4 (57.14%)
B3, penetrating, n (%)	1 (14.29%)
P, perianal disease modifier, n (%)	0
UC Location	
E1 (proctitis), n (%)	0
E2 (left-sided colitis), n (%)	4 (44.44%)
E3 (pancolitis), n (%)	5 (55.56%)
Disease diagnosis duration (years), median [IQR]	4.5 [2.25–9.50]
Clinical disease activity (Baseline)	
CDAI, median [IQR]	357 [234–451]
Partial Mayo score, median [IQR]	8 [7.5–9.0]

(*Continued*)

Table 1 (Continued).

	N=16
Extraintestinal manifestation, n (%)	4 (25%)
Complications fistula/abscess/IBD-related surgery, n (%)	4 (25%)
Previous biologics exposure before UPA-based ACT, n (%)	
1	6 (37.5%)
2	5 (31.25%)
>/= 3	5 (31.25%)
Biologics combined with Upadacitinib, n (%)	
Vedolizumab	4 (25%)
Ustekinumab	10 (62.5%)
Risankizumab	1 (6.25%)
Adalimumab	1 (6.25%)
Adverse events, n (%)	1/16 (6.25%)
Follow-up duration (months), median [IQR]	3 [1–6.75]

Abbreviations: N, number; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; CDAI, Crohn's disease activity index; UPA, Upadacitinib; ACT, advanced combination therapy.

Clinical Outcomes

The clinical response rates at weeks 4, 12, and 24 were 88%, 83%, and 100%, respectively (Figure 1a), while the clinical remission rates were 31%, 50%, and 80%. (Figure 1b) Overall, 15 of 16 patients (93.75%) achieved a clinical response, and 9 of 16 (56.25%) achieved clinical remission. Among 6 patients with available endoscopic data, 5 (83.33%) achieved an endoscopic response, and 2 (33.33%) achieved endoscopic remission during the follow-up period. (Figure 1c) Only one patient (6.25%) experienced a minor adverse event (acne), with no reports of major adverse events such as herpes zoster reactivation or major cardiac events. Regarding laboratory parameters, the C-reactive protein (CRP) level significantly decreased after UPA-based ACT (p = 0.007), while no significant changes were observed in hemoglobin or albumin levels (Table 2).

Discussion

Although biological therapies are central to managing moderate-to-severe IBD, long-term response rates remain suboptimal. This has led to increasing interest in ACT, particularly in patients who do not respond adequately to standard biologic or targeted therapies. The rationale for combination therapy lies in the complex immune dysregulation underlying IBD, which involves cytokines, immune cells, and gut barrier dysfunction. Traditional single-agent therapies, such as anti-TNF agents, have shown efficacy but are often insufficient in refractory cases. With the emerging positive

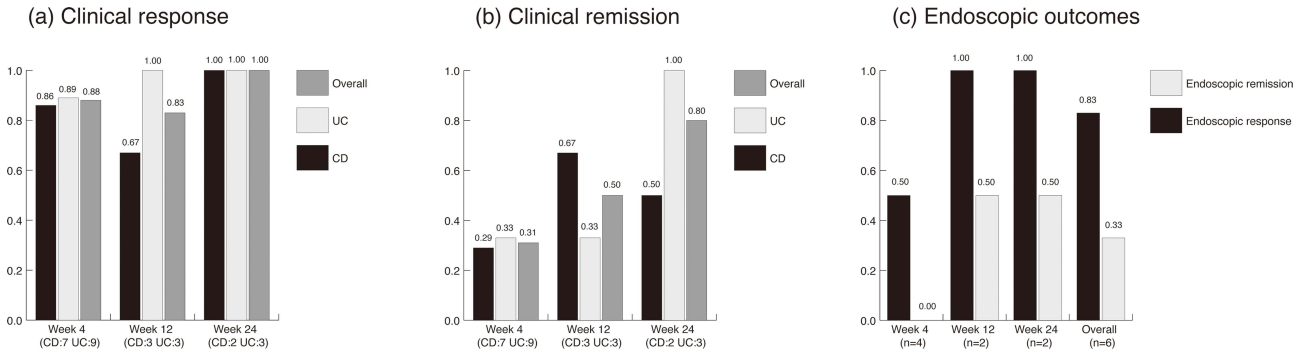

Figure 1 (**a**) Outcomes of Advanced Combination TherapyClinical response at week 4, 12, 24 post advanced combination therapy in Crohn's disease (CD), ulcerative colitis (UC) and overall population. (**b**) Clinical remission at week 4, 12, 24 post advanced combination therapy in CD, UC and overall population. (**c**) Endoscopic outcomes at week 4, 12, 24 post advanced combination therapy in CD and ulcerative colitis (UC).

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Table 2 Laboratory Parameters Pre- and Post-Advanced Combined Therapy

	Pre-Treatment	Post-Treatment	*p* Value
Hemoglobin (mg/dL), median [IQR]	11.95 [10.53–12.90]	12 [10.75–13.10]	0.65
C-reactive protein (mg/L), median [IQR]	4.76 [1.96–52.05]	2.34 [0.64–5.81]	0.007*
Albumin (g/dL), median [IQR]	3.95 [3.74–4.23]	4.11 [4.00–4.20]	0.059

Note: *$P<0.05$.

outcomes of ACT in refractory IBD, studies have increasingly focused on identifying optimal regimens, assessing efficacy, safety profiles, and evaluating the pharmacokinetics and temporality of combination therapies.[16,31,32]

ACT can be conceptualized through pharmacokinetic and temporal perspectives. From a pharmacodynamic perspective, combining drugs with distinct mechanisms of action (MOAs) can result in sub-additive, additive, or synergistic effects. For instance, if drug A alone achieves a 30% remission rate and drug B achieves a 40% remission rate, the combined use of both drugs might be considered sub-additive if it results in a remission rate lower than 70%, additive if it produces a 70% remission rate, or synergistic if it leads to a remission rate higher than 70%. Similarly, the impact of combination therapies on safety and adverse events warrants careful evaluation. Drugs with overlapping MOAs that target the same immune pathway may offer limited additional therapeutic benefits while increasing the risk of adverse events, such as infections, due to excessive and redundant suppression of critical immune functions. Conversely, therapies that address complementary components of the immune response could potentially enhance therapeutic outcomes without significantly elevating the risk of adverse events. However, the safety and efficacy of drug combinations cannot be fully inferred from the individual safety profiles or MOAs of the agents, nor can the risk-benefit profile be reliably predicted solely from mechanistic or preclinical studies. The goal of ACT is to enhance clinical response by leveraging complementary or synergistic mechanisms while minimizing side effects.[31]

The largest meta-analysis to date, conducted by Waseem et al, which included 30 studies with 279 patients highlighted the most commonly used combination regimens, with anti-TNF agents combined with VDZ being the most frequent. This was followed by UST combined with VDZ, and anti-TNF agents combined with UST. The three combination regimens described above demonstrated either complementary or synergistic effects. Clinical remission rates across these regimens were 58.8%, while endoscopic remission rates were 34.3%, and serious adverse events occurred at a rate of 6.5%. These findings underscore the potential of ACT to improve outcomes in refractory cases, although the risk of adverse events remains a concern.[33] Another meta-analysis by Alayo et al supported these findings, reporting clinical response rates ranging from 40% to 80% and remission rates between 20% and 40%. Adverse event rates were relatively low, ranging from 0% to 12%. These data further reinforce the idea that combination therapies may enhance clinical outcomes without substantially increasing adverse event rates.[34]

JAKis, such as tofacitinib and UPA, represent a novel class of drugs that target intracellular signaling pathways critical to the inflammatory cascade. Combining JAKis with other biologics has demonstrated promising results in previous studies, with no major adverse events reported. However, several post-marketing studies have highlighted potential adverse effects associated with JAKis, raising significant safety concerns regarding the use of ACT combining JAKis and biologics in clinical practice. A global post-marketing surveillance database for tofacitinib analyzed 4,426 UC case reports, documenting 12,103 adverse events, of which 1,839 were classified as serious adverse events. The most commonly reported adverse events were infections (3.28 per 100 patient-years), vascular disorders (1.26 per 100 patient-years), and respiratory disorders (0.74 per 100 patient-years). The most frequently reported infections were nasopharyngitis (14.3%) and herpes zoster (13.5%).[35] In the OCTAVE trials and the open-label extension, there was a notable indication of an increased risk of herpes zoster infection, observed in 5.6% of the study population, with a dose-dependent relationship. Across all Phase 2, Phase 3, and open-label extension studies involving UC patients receiving tofacitinib, 65 patients (5.6%) developed herpes zoster infections. Identified risk factors for herpes zoster infections included age $\geq$ 60 years, lower body weight, and prior exposure to TNF inhibitors.[36] As for UPA, CELEST trial revealed that approximately 4.7% of patients with CD receiving UPA developed herpes zoster but most cases were non-serious and resolved with appropriate anti-viral treatments.[37] In U-EXCEED and U-ENDURE trials, herpes zoster infections

were generally reported in 2~5% of patients.[38] As for the vascular disorders, the thromboembolism rate for tofacitinib was increased in high risk population such as age >/= 50 years, history of cardiovascular diseases, thromboembolism events, and malignancy or with long-term use of higher dose.[39] The thromboembolism risk associated with UPA is low and comparable to, or even lower than, that observed with tofacitinib. Other side effects, including hypercholesterolemia, malignancies, and MACEs, though uncommon, have been reported in previous trials. Further long-term studies with larger populations are warranted to better evaluate these risks.[29] In studies combining UPA with biologics, only mild side effects were reported, including respiratory discomfort, acne, nausea, and fungal or influenza infections, all of which resolved with appropriate treatment.[27,28]

In our study, the overall clinical response and remission rates were 93.75% and 56.25%, respectively, aligning well with previous findings. We evaluated both short-term (4 weeks) and long-term (12 and 24 weeks) efficacy, with promising results. Importantly, all patients in our study were thoroughly screened before initiating UPA-based ACT, and all received vaccination to prevent herpes zoster infection. The UPA-based ACT was well-tolerated, with only one minor adverse event (acne) reported. These findings suggest that UPA-based ACT is not only effective but also demonstrates a favorable short-term safety profile when implemented with careful patient selection and close monitoring during treatment.

In addition to pharmacokinetics, the timing and sequencing of combination therapies are additional factors to consider. Strategies generally fall into two categories: "simultaneous induction" and "add-on therapy." Simultaneous induction involves initiating different biologic therapies at the same time, whereas add-on therapy introduces a second biologic in patients who fail to respond to the initial biologic. During maintenance therapy, a "step-down" approach may be considered by withdrawing one of the two agents used in combination therapy. This strategy is particularly appropriate when the benefits of combination therapy persist beyond the period of concurrent drug use, or when safety concerns related to one of the agents, or the combination itself, justify de-escalation. Conversely, continuous combination maintenance therapy may be appropriate when the sustained efficacy of combination therapy is required to maintain disease control, provided no additional safety risks arise from the long-term use of both agents. Another potential approach is intermittent re-induction therapy, wherein a second agent with a distinct mechanism of action is used for a limited duration to regain disease control in cases of symptom recurrence, re-emergence of inflammatory biomarkers, or as part of a planned cycle of treatment to sustain disease remission.[31] In our study, UST plus UPA was the most common regimen, followed by VDZ plus UPA. Interestingly, clinical response and remission rates were higher in the latter combination. This may be attributed to the complementary mechanisms of VDZ and UPA, which target lymphocyte trafficking and intracellular signaling pathways, respectively. In contrast, the overlapping effects of UST and UPA, which both target the Janus kinase pathway, may limit their combined efficacy. Besides, UPA was added to other biologics in all patients in our study due to inadequate response to previous treatments. This "add-on" approach reflects real-world clinical practice, where treatment is often escalated based on disease activity and patient response. However, current evidence comparing these approaches remains limited, and further research is needed to determine the optimal strategy for various patient populations.

Although ACT has the potential to provide significant clinical benefits for refractory IBD, its high cost and accessibility challenges limit its widespread use. For examples, access to biologics and JAKis is often restricted in low- and middle-income countries and the insurance systems may not cover combination therapies, leaving the patients to bear significant out-of-pocket expenses. Future studies to reduce costs, expand insurance coverage, and introduce biosimilars are essential to ensure equitable access to these therapies.[40]

Overall, in patients with refractory IBD, a rational combination therapy approach requires a thorough understanding of prior medication outcomes, the pharmacokinetics of the combination regimens, carefully patient selection and well-discussed with the patients about the possible benefits and side effects. Key considerations include: (1) the presence of initial clinical response; (2) adverse events, especially serious ones like anaphylaxis or infections; (3) complications such as penetrating disease or perianal fistulae; (4) concurrent extra-intestinal symptoms or immune-mediated inflammatory diseases (IMIDs); (5) criteria for previous treatment failure (eg, endoscopic findings, treatment intolerance, or symptom mimics); and (6) drug pharmacokinetics, including anti-drug antibodies and attempts to address suboptimal drug levels.

There are several limitations in our study. First, it is a retrospective, single-center study with a relatively small sample size. Second, not all patients had complete endoscopic data before and after UPA-based ACT, which may have impacted the assessment of mucosal healing. Third, the six-month follow-up period may not be long enough to fully evaluate the long-term safety of UPA-based ACT.

Conclusions

In conclusion, this study is the first in Asia to evaluate the efficacy and safety of UPA-based ACT in refractory IBD. Our preliminary results indicate that UPA-based ACT is effective and safe in this patient population. However, larger prospective, multi-center studies are required to identify predictors of therapeutic response, explore the optimal sequencing and timing of combination therapies, and assess the cost-effectiveness and the accessibility of ACT across different healthcare systems. Such researches will help optimize individualized precision medicine, maximizing the efficacy of ACT while minimizing its side effects.

Data Sharing Statement

The corresponding author would share the data underlying this article upon reasonable request.

Ethics Approval and Informed Consent

This retrospective study was conducted in accordance with the ethical principles of the Declaration of Helsinki. As per the requirements of the Institutional Review Board (IRB) of Chang Gung Medical Foundation (approval No. 202400030B0), patient consent to review medical records was not required due to the retrospective nature of the study. To ensure confidentiality, all patient data were anonymized and de-identified prior to analysis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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