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ORIGINAL RESEARCH

Age-Stratified Efficacy of Upadacitinib in Refractory Pediatric Crohn's Disease and Geriatric Ulcerative Colitis: An Asian Cohort Study

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Background and Aims: Inflammatory Bowel Disease presents significant management challenges, particularly in pediatric and elderly populations with refractory conditions. Despite advances in biologic therapies, current treatments remain limited with inconsistent response rates. This study investigated Upadacitinib efficacy in Asian adolescent and elderly populations with refractory IBD.

Methods: This single-center, retrospective cohort study examined 21 patients at the Sixth Affiliated Hospital of Sun Yat-sen University: 11 pediatric refractory CD patients (aged 9–17) and 10 elderly refractory UC patients (aged 60+). Diagnoses were confirmed via comprehensive criteria including clinical symptoms, biomarkers, endoscopic findings, histological examination, and radiological results. Patients had refractory IBD, defined as failure of at least two biologic agents with distinct mechanisms or comorbid psychosocial complications impairing disease management.

Results: Pediatric CD patients showed remarkable efficacy, with 72.7% achieving steroid-free clinical remission at week 12, maintained at 57.1% by week 24, and reaching 88.9% at final follow-up. Endoscopic remission improved from 50% at week 12 to 57.1% at final follow-up. Elderly UC patients showed modest outcomes, with 20% achieving clinical remission throughout the study. Laboratory parameters demonstrated significant improvements, particularly in C-reactive protein and albumin levels. The safety profile was generally favorable with minimal adverse events. Teenage CD patients experienced minor dermatological side effects, while UC patients showed no significant adverse events. One serious pneumonia case in the elderly group highlighted potential infection risks.

Conclusion: This pioneering Asian study provides critical insights into UPA's potential as alternative treatment for challenging IBD cases in adolescent and elderly populations, demonstrating different efficacy and safety profiles across age groups and contributing evidence for personalized medicine approaches in managing refractory IBD.

Keywords: upadacitinib, inflammatory bowel disease, (IBD), pediatric crohn' s disease, geriatric ulcerative colitis, refractory IBD

Introduction

Inflammatory Bowel Disease (IBD) is a chronic, relapsing condition that significantly impacts the gastrointestinal tract, encompassing two primary subtypes: Crohn's Disease (CD) and Ulcerative Colitis (UC). Over recent decades, the global prevalence of IBD has been steadily increasing, particularly in Western and newly industrialized countries.[1,2] This rise spans various age groups, with notable increases in both adolescents and the elderly, highlighting diverse epidemiological patterns.

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Managing IBD in pediatric and elderly populations presents unique challenges. Adolescents with refractory CD experience higher disease burdens, including accelerated progression, increased complications, and greater treatment demands. Effective management during adolescence is critical, as it can significantly influence growth, development, and psychological well-being.[3] Similarly, elderly patients with refractory UC face complex therapeutic issues, such as polypharmacy, comorbidities, and reduced drug tolerability. With the global population aging, the number of elderly IBD patients is rising, requiring optimized treatment strategies to improve prognosis and quality of life.

Current IBD treatments primarily include anti-Tumor Necrosis Factor (TNF) agents, such as Infliximab (IFX), Adalimumab (ADA), Ustekinumab (UST), and Vedolizumab (VDZ). While these biologics have expanded therapeutic options, their effectiveness varies among patients, and high costs, inconsistent response rates, and potential adverse effects remain significant limitations.[4] Small molecule therapies, particularly Janus Kinase (JAK) inhibitors, have introduced a new dimension to IBD treatment. Tofacitinib and Upadacitinib (UPA) are notable JAK inhibitors that have demonstrated promising results in adult IBD populations.[5] These oral agents offer advantages like rapid onset of action and ease of administration. However, their use in pediatric populations is limited, and experience in elderly patients with refractory UC is scarce, with real-world data on safety and efficacy in these groups being insufficient. Upadacitinib, a selective JAK1 inhibitor, has shown superior efficacy in inducing and maintaining remission in adult UC and CD patients compared to placebo, leading to its approval for adult IBD treatment.[6,7] Despite these advancements, comprehensive studies evaluating Upadacitinib in Asian adolescents with refractory CD and elderly patients with refractory UC are still lacking. Unlike in the West where IBD incidence is stabilizing, many Asian countries are facing a rapid increase in new cases, with pediatric patients sometimes presenting with unique clinical features, such as a higher prevalence of perianal disease.[8] Furthermore, a significant "drug lag" can limit patient access to the latest therapies compared to Western nations.[9]

This study aims to address this specific gap by focusing on a challenging subgroup: patients with highly refractory IBD, who have typically failed multiple classes of biologic agents.[10] We conducted a retrospective analysis of Upadacitinib's effectiveness and safety in 11 adolescents with refractory Crohn's Disease and 10 elderly patients with refractory Ulcerative Colitis. We evaluated outcomes in these difficult-to-treat populations to assess Upadacitinib's role in personalized IBD management.

Methods

This retrospective cohort study examined patients treated with upadacitinib at the Sixth Affiliated Hospital of Sun Yat-sen University between January 1, 2023, and December 1, 2024. The study population comprised CD patients aged 9–17 years and UC patients aged 60 years or older. Diagnoses were established using comprehensive criteria encompassing clinical symptoms, biomarkers, endoscopic findings, histological examination, and radiological results. Refractory IBD in this study was defined as patients meeting one of the following criteria: (1) failure to respond adequately to at least two biologic agents with distinct mechanisms of action and advanced small molecule therapies, or (2) comorbid psychosocial complications that impair disease management (eg, complications that hinder treatment adherence or follow-up).[10]

The study protocol was approved by the hospital's Medical Ethics Committee (approval number: 2025ZSLYEC-149) and registered at ClinicalTrials.gov (NCT06922331). This study was conducted in accordance with the Declaration of Helsinki and adhered to all applicable ethical guidelines for medical research involving human subjects.

Given the retrospective design, informed consent was waived while maintaining patient confidentiality. Data collection was conducted through a dual-physician review system at each participating center, where one physician collected data using standardized forms while another validated the entries. Any discrepancies were resolved through consensus discussions.

For patients receiving concomitant corticosteroids at baseline, tapering was conducted at the treating physician's discretion based on individual clinical response. This adaptive approach reflects real-world clinical practice where treatment decisions are individualized according to patient needs.[11]

The collected data encompassed demographic information (sex, age at diagnosis, age at UPA initiation, BMI), disease characteristics (duration, location, behavior, perianal involvement, extraintestinal manifestations), smoking status, comorbidities, treatment history, and clinical outcomes. For UC patients, we evaluated clinical remission, endoscopic

outcomes using the Mayo endoscopic subscore and Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and histological remission. For CD patients, assessments included clinical remission, endoscopic outcomes using the Simple Endoscopic Score for Crohn's Disease (SES-CD), and radiological findings, including imaging remission and intestinal Doppler ultrasound parameters. Laboratory parameters monitored included albumin, hemoglobin, C-reactive protein, erythrocyte sedimentation rate, platelet count, liver function tests, and D-dimer levels. Fecal calprotectin was not routinely collected due to accessibility and cost considerations.

Outcome Measures

Steroid-free clinical remission was defined as achieving clinical remission while being completely off corticosteroids for at least 12 weeks prior to assessment, consistent with current IBD clinical trial standards.[12]

For pediatric CD patients, the primary endpoint was steroid-free clinical remission (SF-CR) at weeks 12 and 24, and at the final follow-up, defined as a Pediatric Crohn's Disease Activity Index (PCDAI) score ≤10. Secondary endpoints included clinical response (defined as a PCDAI reduction ≥12.5 points from baseline), endoscopic outcomes (remission defined as SES-CD ≤2; mucosal healing defined as SES-CD=0), and radiological responses. Radiological response was defined as improvement in bowel wall thickness, inflammatory fat, mural blood flow, and enhancement on CT/MR enterography, while remission was characterized by normalization of inflammatory parameters. Intestinal ultrasound response was defined as a bowel wall thickness (BWT) reduction >2mm, with remission indicated by normalization of wall thickness (≤3mm for small bowel, ≤4mm for colon).

For elderly UC patients, the primary endpoint was SF-CR at weeks 8 and 24, and at the final follow-up, defined as a modified Mayo score ≤2 with no subscore >1. Secondary endpoints encompassed clinical response (defined as ≥30% reduction in Mayo score and ≥1-point decrease in bleeding subscore), endoscopic outcomes (using Mayo endoscopic subscore and UCEIS, with endoscopic remission defined as Mayo endoscopic subscore ≤1 and mucosal healing as subscore=0), histological assessment using the Nancy scoring system, and laboratory parameters. All adverse events and serious adverse events were documented.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26. The Wilcoxon signed-rank test for paired samples was employed to evaluate improvements in clinical, endoscopic, histological, and laboratory parameters during follow-up. Continuous variables were expressed as median (interquartile range). Statistical significance was set at $P<0.05$ for both primary and secondary outcomes. All results were considered exploratory in nature.

Results

Patient Population

A total of 21 patients were enrolled in this study, comprising 11 pediatric refractory CD patients and 10 elderly refractory UC patients. The median age at diagnosis was 13 years (IQR, 11–13) for CD patients and 65.5 years (IQR, 57.25–68.0) for UC patients. Upadacitinib (UPA) therapy was initiated at a median age of 14 years (IQR, 13–16) and 67 years (IQR, 60.75–72) for CD and UC patients, respectively. Disease duration was documented as 2 years (IQR, 1–3) for CD patients and 0.75 years (IQR, 0.27–12.5) for UC patients. Baseline body mass index (BMI) was recorded at 16.8 kg/m² (IQR, 16.42–19.38) for CD patients and 19.50 kg/m² (IQR, 18.36–21.18) for UC patients. Table 1 provides the demographic details.

In the CD cohort, disease location was predominantly ileocolonic (L3) in six patients, followed by ileal (L1) and colonic (L2) in two patients each, with one case classified as not applicable (N/A). Disease behavior was categorized as non-stricturing, non-penetrating (B1) in seven patients, stricturing (B2) in three patients, and one case as N/A. None of the CD patients had undergone intestinal resection. Upper gastrointestinal involvement was observed in two patients, while perianal disease was present in eight patients. Extraintestinal manifestations, including oral ulcers and skin lesions, were documented in two CD patients.

Table 1 Patient Demographics and Disease Characteristics

Patient ID	Sex	Baseline BMI	Age and Disease Duration			Disease Manifestations		Disease Manifestations				Baseline PCDAI/ Mayo
			Age at Diagnosis (years)	Age at UPA Start (years)	Duration of disease (years)	Disease location	Disease Behavior	Previous Intestinal Resection	Upper GI Involvement	Perianal Disease	Extraintestinal Manifestation	
CD1	Male	25.62	7	9	1.5	L3	B1	No	No	Yes	No	22.5
CD2	Male	16.67	10	12	2	L3	B1	No	No	Yes	No	20
CD3	Female	13.60	13	14	1	L2	B1	No	No	Yes	No	25
CD4	Female	20.96	13	14	1	L3	B1	No	No	Yes	No	15
CD5	Male	16.80	14	15	1	L3	B2	No	No	Yes	No	12.5
CD6	Male	17.09	12	14	2	L2	B1	No	No	Yes	No	12.5
CD7	Male	16.78	11	13	0.5	L3	B1	No	No	Yes	Oral ulcers	10
CD8	Male	13.76	13	15	2	L1	B2	No	No	No	No	12.5
CD9	Male	16.42	13	16	3	N/A	N/A	No	No	No	No	17.5
CD10	Male	19.38	12	17.5	5	L1	B2	No	Yes	Yes	No	12.5
CD11	Female	17.85	14	17	3	L3	B1	No	Yes	No	Skin rash	20
UC1	Male	19.89	65	75	10	E3	N/A	N/A	No	No	No	7
UC2	Male	37.04	66	67	0.08	E3	N/A	N/A	No	No	No	6
UC3	Male	19.96	67	67	0.5	E3	N/A	N/A	No	No	Oral ulcers	9
UC4	Male	18.78	55	60	0.42	N/A	N/A	N/A	No	No	No	11
UC5	Female	22.03	74	79	5	N/A	N/A	N/A	No	No	No	9
UC6	Female	20.89	48	69	20	E3	N/A	N/A	No	No	No	9
UC7	Female	18.75	59	60	1	E2	N/A	N/A	No	Yes	Articular manifestations	7
UC8	Male	17.19	67	67	0.08	E3	N/A	N/A	No	No	No	N/A
UC9	Male	19.10	71	71	0.33	E3	N/A	N/A	No	No	No	11
UC10	Male	5.08	58	61	61	E3	N/A	N/A	No	No	No	12

Notes: Disease Location: L1 = ileal, L2 = colonic, L3 = ileocolonic; E2 = left-sided, E3 = extensive, Disease Behavior: B1 = non-stricturing non-penetrating, B2 = stricturing.
Abbreviations: CD, Crohn's Disease; UC, Ulcerative Colitis; UPA, Upadacitinib; BMI, Body Mass Index; PCDAI, Pediatric Crohn's Disease Activity Index; N/A, Not applicable.

The UC cohort predominantly consisted of extensive colitis (E3), with one case of left-sided colitis. No UC patients had undergone intestinal resection or exhibited upper gastrointestinal involvement. Perianal disease was observed in one UC patient, while extraintestinal manifestations (articular involvement and oral ulcers) were documented in two patients.

All patients demonstrated active disease at UPA initiation, with median PCDAI scores of 15 (IQR, 12.5–20.0) for CD patients and median Pediatric Ulcerative Colitis Activity Index(PUCAI) scores of 9 (IQR, 7–11) for UC patients.

Treatment history (Table 2) revealed previous biologic therapy failure in all patients, including infliximab, adalimumab, ustekinumab, and vedolizumab. Steroid-refractory disease was documented in 52.4% (11/21) of patients. One CD patient had previous tofacitinib exposure. At UPA initiation, exclusive enteral nutrition was being administered to 36.4% (4/11) of CD patients, while 27.3% (3/11) were receiving concurrent biologic therapy.

Clinical Outcomes in Pediatric Refractory CD Patients

Among the 11 pediatric refractory CD patients, steroid-free clinical remission was achieved in 72.7% (8/11) at week 12, maintained in 57.1% (4/7) at week 24, and sustained in 88.9% (8/9) at final follow-up. Clinical response was observed in 27.3% (3/11) at week 12.

Endoscopic remission was achieved in 50% (3/6) at week 12, decreased to 33.3% (2/6) at week 24, and improved to 57.1% (4/7) at final follow-up. Mucosal healing remained consistent at 50% across all time points. Radiological remission rates demonstrated progressive improvement, increasing from 11.1% (1/9) at week 12 to 55.6% (5/9) at week 24, and reaching 63.6% (7/11) at final follow-up. Intestinal ultrasound (IUS) remission was documented in 9.1% (1/11) at weeks 12 and 24, with no remission observed at final follow-up. The details are listed in Table 3. Figure 1 shows the clinical, endoscopic, radiological, and intestinal ultrasound outcomes for CD patients. The clinical and endoscopic scores for CD patients (CDAI and SES-CD) are shown in Figure 2.

A significant reduction in PCDAI was observed, decreasing from a median of 15.0 (IQR, 12.5–20.0) at baseline to 6.25 (4.4–8.75) at week 12 (P=0.005), and further to 5.0 (1.25–8.75) at final follow-up (P=0.011). Serum C-reactive protein (CRP) levels demonstrated significant improvement, declining from 39.6 mg/L at baseline to 2.2 mg/L at week 12 (P=0.013), with sustained improvement at week 24 (4.9 mg/L, P=0.017) and final follow-up (9.6 mg/L, P=0.128). Albumin levels increased significantly from 35.2 g/L to 40.6 g/L at week 12 (P=0.05), with continued improvement at subsequent time points. Detailed information is shown in Supplementary Figure 1–2.

Clinical Outcomes in UC Patients

Among the 10 elderly refractory UC patients, clinical response was achieved in 20% (2/10) at week 8, with steroid-free clinical remission observed in 20% (2/10) of patients. The steroid-free clinical remission rate was maintained at 10% (1/10) at week 24 and remained stable through the final follow-up.

Endoscopic outcomes demonstrated progressive improvement, with endoscopic remission achieved in 20% (2/10) of patients at week 8, increasing to 30% (3/10) at week 24, before returning to 20% (2/10) at final follow-up. Mucosal healing was observed in 10% (1/10) at week 8, improved to 30% (3/10) at week 24, and stabilized at 10% (1/10) at final follow-up. Histological remission, defined as a Nancy index ≤1, was achieved in 10% (1/10) of patients at final follow-up. The detailed outcomes for these patients are listed in Table 4. The clinical and endoscopic outcomes for UC patients are shown in Figure 3.

Modified Mayo scores demonstrated improvement from baseline median of 9.0 (IQR, 7.0–10.3) to 6.0 (3.0–9.0) at week 8 (P=0.109), with further reduction to 3.5 (3.0–7.8) at final follow-up (P=0.144). Endoscopic assessment revealed improvement in Mayo endoscopic subscores from baseline 3.0 to 1.0 at week 8 (P=0.157), maintained at 1.0 (1.0–2.75) at final follow-up (P=0.102). The UCEIS decreased from baseline 5.0 (4.75–6.25) to 1.0 (0.0) at week 8 (P=0.18), with final follow-up values of 1.5 (0.25–4.25) (P=0.109). The Nancy histological index improved from baseline 4.0 (2.5–4.0) to 2.5 (2.0) at week 8 (P=0.18), further decreasing to 1.5 (1.0) at final follow-up (P=0.18). Figure 4 presents the UC clinical and endoscopic scores (Mayo and UCEIS), along with histological scores (Nancy index).

Laboratory parameters showed trending improvements, though not reaching statistical significance. Median CRP levels decreased from baseline 23.0 mg/L to 11.0 mg/L at week 8 (P=0.249), further declining to 2.55 mg/L at week 24 (P=0.593) and 5.9 mg/L at final follow-up (P=0.18). Hemoglobin levels increased from baseline 101 g/L to 108 g/L at

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Table 2 Patient Previous Treatment History and Upadacitinib Treatment Details

Patient ID	Previous Treatment History				Upadacitinib Treatment Details			
	Previous Therapies	Biologic Failures (n)	Failed Biologics	Tofacitinib Exposed	Duration (weeks)	Monotherapy or Combination therapy	Induction Dose (mg/day)	Maintenance Dose
CD1	GlucocorticoidsEEN	2	IFXADA	No	77	Combo with ADA	45	Decreased to 15 mg after 12 weeks
CD2	No	2	USTADA	No	33	Mono	15	Increased to 30 mg after 12 weeks
CD3	AZAMTXCsGlucocorticoidsEEN	3	IFXADAUST	No	12	Mono	45	Dropouts After Induction Phase
CD4	No	1	ADA	No	49	Mono	45	Decreased to 30 mg after 12 weeks
CD5	MTXGlucocorticoidsEEN	2	USTADA	No	45	Combo with UST	45	Decreased to 30 mg after 12 weeks
CD6	AZAGlucocorticoidsEEN	2	IFXUST	No	43	Mono	45	Decreased to 30 mg after 12 weeks
CD7	EEN	1	ADA	No	47	Combo with EEN	45	Decreased to 30 mg after 12 weeks
CD8	GlucocorticoidsEEN	2	IFXADA	Yes	41	Combo with EEN	45	Decreased to 30 mg after 12 weeks
CD9	EEN	1	IFX	No	12	Combo with EEN	45	—
CD10	EEN	1	UST	No	12	Combo with EEN	45	—
CD11	EEN	2	IFXADA	No	12	Mono	45	—
UC1	5-ASAAZAGlucocorticoids	1	IFX	No	8	Mono	45	Dropouts After Induction Phase
UC2	5-ASA	1	VDZ	No	1	Mono	45	Dropouts After Initiating Medication
UC3	5-ASAGlucocorticoids	1	VDZ	No	8	Mono	45	Dropouts After Induction Phase
UC4	5-ASAGlucocorticoids	0	IFX	No	1	Mono	45	ASUC patient with poor initial response to steroids + upadacitinib.
UC5	5-ASAGlucocorticoids	2	USTVDZ	No	4	Mono	45	Died of severe pneumonia infection at week 4
UC6	5-ASA	1	IFX	No	22	Mono	45	Decreased to 15 mg after 8 weeks
UC7	5-ASAGlucocorticoids	1	VDZ	No	8	Mono	45	Dropouts After Induction Phase
UC8	5-ASAGlucocorticoids	1	VDZ	No	17	Mono	45	Decreased to 15 mg after 8 weeks
UC9	5-ASA	1	VDZ	No	8	Combo with VDZ	45	Dropouts After Induction Phase
UC10	5-ASAMTXEEN	2	IFXVDZ	No	20	Mono	45	Decreased to 15 mg after 8 weeks

Abbreviations: EEN, Exclusive Enteral Nutrition; AZA, Azathioprine; MTX, Methotrexate; Cs, Cyclosporine; IFX, Infliximab; ADA, Adalimumab; UST, Ustekinumab; VDZ, Vedolizumab; 5-ASA, 5-Aminosalicylic acid; ASUC, Acute Severe Ulcerative Colitis; N/A, Not applicable.

Table 3 Clinical, Endoscopic, Radiological, and Intestinal Ultrasound Outcomes in Adolescent Patients with Refractory CD Patients

Patient ID	Clinical Outcomes					Endoscopic Outcomes							Radiological Outcomes					Intestinal Ultrasound Outcomes				
	Baseline Clinical Remission	Steroid-free Clinical Remission/Response				Baseline Endoscopic Remission	Endoscopic Remission			Mucosal Healing			Baseline Radiological Remission	Radiological Remission/Response				Baseline IUS Remission	IUS Remission/Response			
		12w Response	12w Remission	24w Remission	Last F/U		12w	24w	Last F/U	12w	24w	Last F/U		12w Response	12w Remission	24w Remission	Last F/U		12w Response	12w Remission	24w Remission	Last F/U
CD1	No	No	No	No	No	No	No	No	No	No	No	No	No	N/A	No	No	No	No	No	No	No	No
CD2	No	Yes	Yes	No	Yes		No	No	No	No	No	No		No	No	No	No		No	No	No	No
CD3	No	No	No	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A
CD4	No	Yes	Yes	No	Yes	N/A	N/A	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes	Yes		N/A	N/A	No	No
CD5	No	No	Yes	Yes	Yes	No	N/A	N/A	Yes	Yes	Yes	Yes	No	N/A	N/A	Yes	No		N/A	N/A	Yes	Yes
CD6	No	No	Yes	Yes	Yes		No	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		No	No	N/A	No
CD7	No	No	Yes	Yes	Yes	N/A	Yes	Yes	N/A	N/A	Yes	Yes	No	Yes	Yes	N/A	Yes		Yes	No	N/A	No
CD8	No	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	No	No		N/A	N/A	N/A	Yes		Yes	Yes	Yes	No
CD9	No	Yes	Yes	N/A	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A		Yes	No	N/A	N/A
CD10	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		No	No	N/A	N/A
CD11	No	No	No	N/A	Yes		N/A	N/A	N/A	N/A	N/A	N/A		N/A	Yes	N/A	Yes		No	No	N/A	N/A

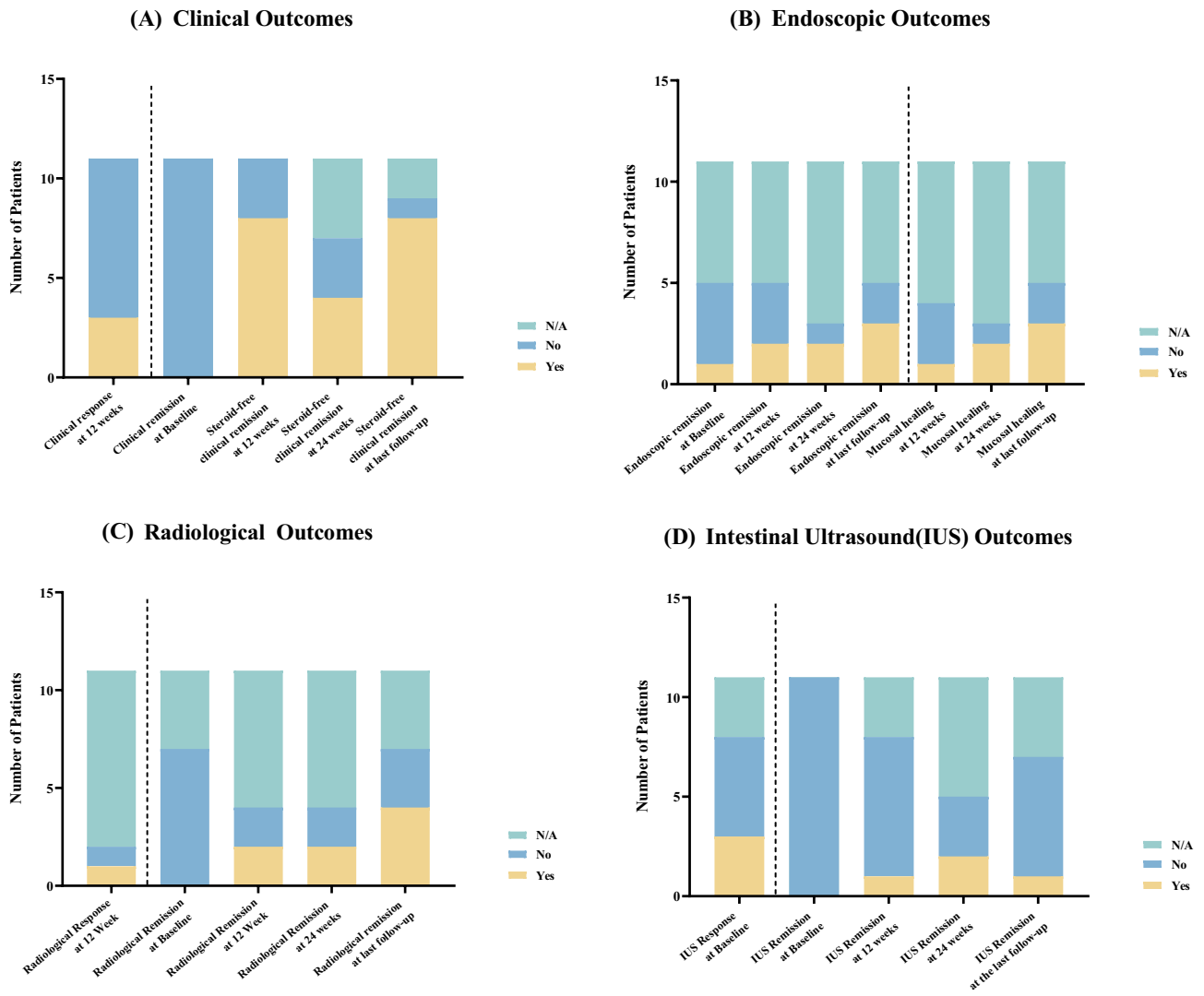

Figure 1 (**A**) Clinical Outcomes in Pediatric Refractory CD Patients. (**B**) Endoscopic Outcomes in Pediatric Refractory CD Patients. (**C**) Radiological Outcomes in Pediatric Refractory CD Patients. (**D**) Intestinal Ultrasound (IUS) Outcomes in Pediatric Refractory CD Patients.

week 8 (P=0.893), reaching 119 g/L at week 24 (P=0.109) and 114.5 g/L at final follow-up (P=0.655). Albumin levels improved from baseline 34.8 g/L to 37.9 g/L at week 8 (P=1.00), with further increases to 43.5 g/L at week 24 (P=0.109) and 42.4 g/L at final follow-up (P=0.18). Erythrocyte sedimentation rate showed minimal change from baseline 24.0 mm/h to 24.5 mm/h at week 8 (P=0.655). Baseline D-dimer levels were recorded at 0.96 μg/L (IQR 0.73–1.42), with no subsequent measurements obtained. Detailed information is shown in Supplementary Figure 3–4.

Safety Profile

The safety profile of UPA was generally favorable. In the CD cohort, two patients developed dermatological adverse events within the first 12 weeks of treatment: one case of folliculitis and one case of acne. No adverse events were reported in the UC cohort during the study period. These findings suggest that UPA demonstrated an acceptable safety profile in both pediatric CD and elderly UC populations, though longer-term safety data collection is warranted.

Discussion

Our study is the first in Asia to examine the effectiveness of upadacitinib (UPA) in two challenging patient populations with inflammatory bowel disease (IBD): adolescents with Crohn's disease (CD) and older adults with ulcerative colitis

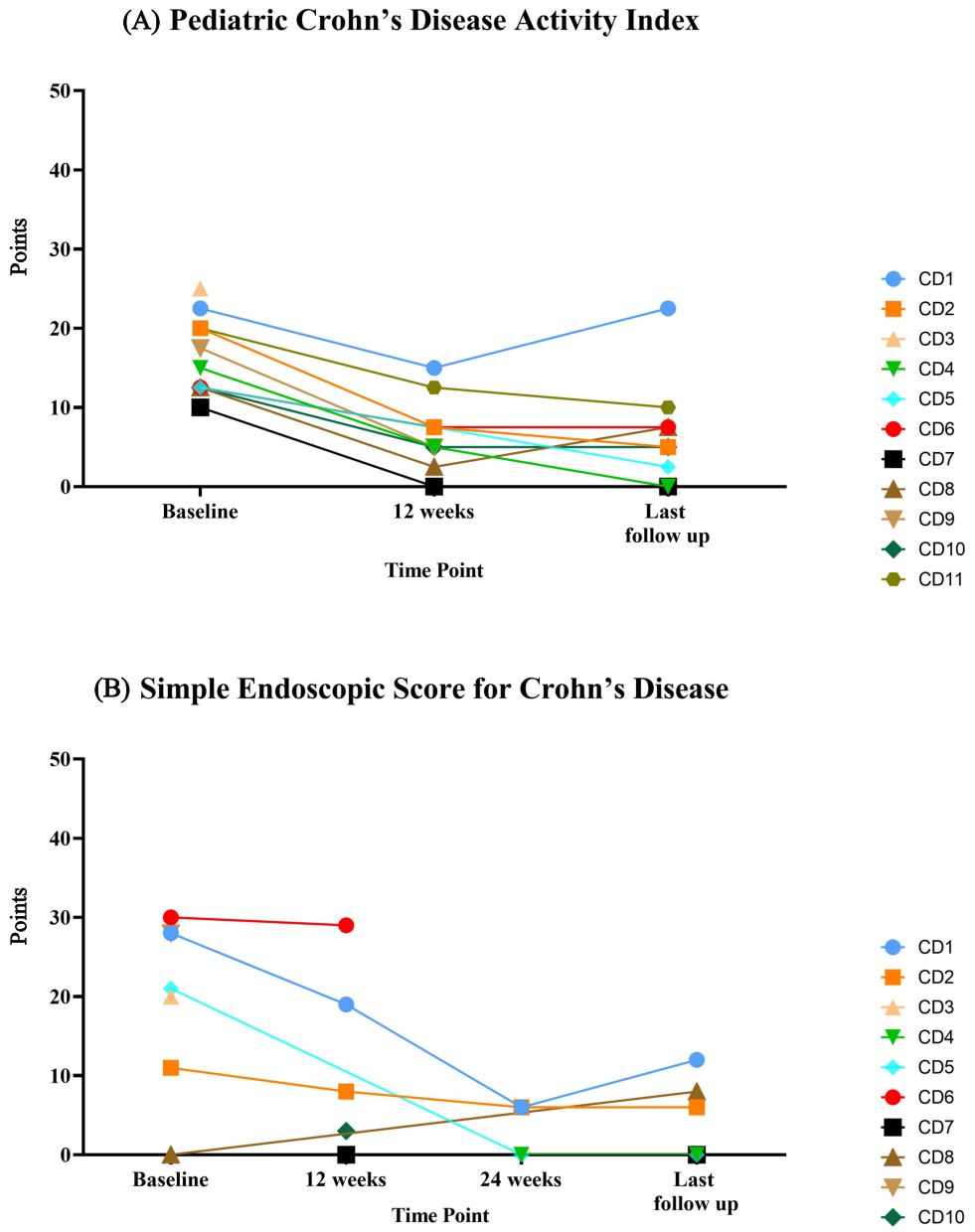

Figure 2 (**A**) Clinical Activity in Pediatric Refractory CD Patients: CDAI Scores. (**B**) Endoscopic Activity in Pediatric Refractory CD Patients: SES-CD Scores.

(UC). The results show that UPA is a highly effective agent for inducing and maintaining steroid-free remission in adolescents with CD. In our cohort, 72.7% of adolescent patients achieved remission during induction, 57.1% maintained it at 24 weeks, and 88.9% were in remission by the end of the study. For older adults with UC, 20% achieved remission during both induction and follow-up.

Our findings of high efficacy in adolescent CD are consistent with and expand upon existing literature. While adult Phase 3 trials of UPA for CD reported clinical remission rates of approximately 40–50%,[13] our observed rate of 72.7% suggests a potentially superior response in adolescents. This is supported by other real-world pediatric cohorts, where steroid-free clinical remission rates of 75% have been reported in similarly refractory adolescent IBD populations.[14] This pronounced efficacy in adolescents likely stems from a combination of factors, including the distinct disease phenotype of pediatric-onset IBD and the specific pharmacological properties of UPA. It is noteworthy that pharmacokinetic differences do not appear to be a primary driver, as population pharmacokinetic modeling has shown that adolescents and adults have comparable UPA exposure at similar doses.[15]

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Table 4 Clinical, Endoscopic, Histologic Outcomes in Elderly Patients with Refractory UC Patients

Patient ID	Clinical Outcomes				Endoscopic Outcomes					Histologic Outcomes		
	Baseline Clinical Remission	Steroid-free Clinical Remission/Response			Baseline Endoscopic Remission	Endoscopic Remission		Mucosal Healing		Nancy Index at Baseline	Nancy Index	
		8w Response	8w Remission	Last F/U		8w	Last F/U	8w	Last F/U		8w Remission	Last F/U
UC1	No	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	Grade 4 (GVE 8–9)	N/A	N/A
UC2	No	N/A	N/A	No	No	N/A	N/A	N/A	No	Grade 4 (GVE 9)	N/A	N/A
UC3	No	N/A	N/A	Yes	No	N/A	N/A	N/A	No	Grade 4 (GVE 8)	N/A	Grade 1 (GVE 1–2)
UC4	No	No	N/A	N/A	No	No	N/A	N/A	N/A	Grade 4 (GVE 8)	Grade 3 (GVE 5)	Grade 3 (GVE 5)
UC5	No	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	Grade 3 (GVE 5)	N/A	N/A
UC6	No	N/A	N/A	No	No	N/A	N/A	N/A	No	Grade 4 (GVE 8)	N/A	N/A
UC7	No	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	Grade 1 (GVE 1)	N/A	N/A
UC8	No	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	Grade 1 (GVE 1)	N/A	N/A
UC9	No	Yes	Yes	N/A	No	Yes	N/A	N/A	N/A	Grade 3 (GVE 5)	N/A	N/A
UC10	No	Yes	Yes	Yes	No	Yes	N/A	N/A	No	Grade 4 (GVE 8)	Grade 2 (GVE 3–4)	Grade 2 (GVE 3–4)

Abbreviations: 12w, 12 weeks; 24w, 24 weeks; F/U, Follow-up; IUS, Intestinal Ultrasound; N/A, Assessment not performed or data not available due to early discontinuation/dropout Clinical Definitions: Clinical remission defined as PCDAI <10 for CD patients, Mayo score <2 for UC patients; Clinical response defined as decrease in PCDAI ≥12.5 points for CD patients, decrease in Mayo score ≥3 points for UC patients Endoscopic Definitions: Endoscopic remission defined as SES-CD <3 for CD patients, Mayo endoscopic subscore 0–1 for UC patients; Mucosal healing defined as absence of ulceration.

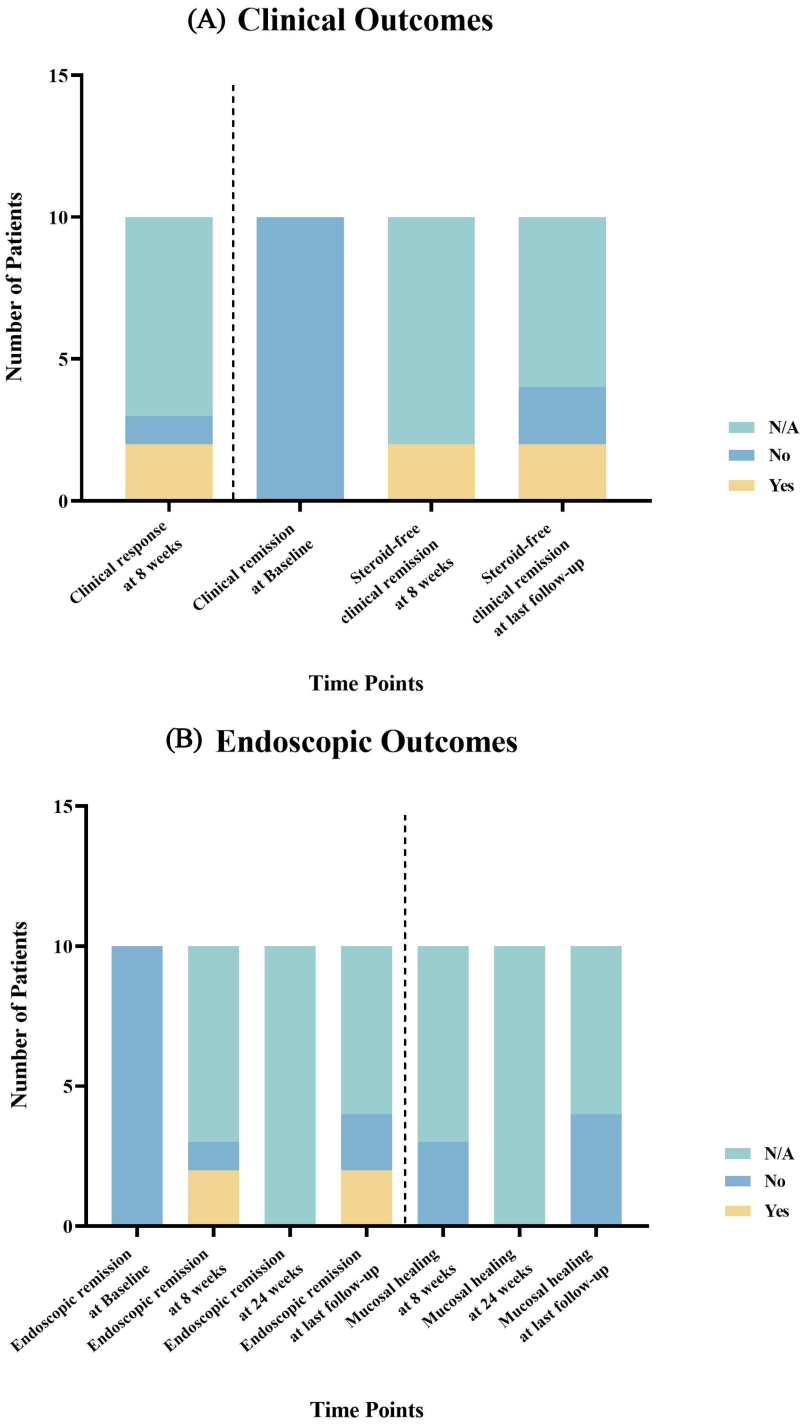

Figure 3 (**A**) Clinical Outcomes in Elderly Refractory UC Patients. (**B**) Endoscopic Outcomes in Elderly Refractory UC Patients.

This enhanced response may be explained by the unique nature of pediatric-onset IBD. Large cohort studies have established that pediatric IBD presents with a more extensive and aggressive phenotype, including higher rates of ileocolonic and perianal CD, which necessitates earlier and more intensive therapies compared to adult-onset disease.[16,17] Furthermore, the gut-associated lymphoid tissue, including Peyer's patches, is most prominent and active during adolescence before declining with age.[18,19] This heightened yet developing immune environment may be particularly responsive to potent immunomodulation. From a pharmacological standpoint, UPA's high selectivity for JAK1 may offer a distinct advantage. UPA has demonstrated superior efficacy over less selective JAK inhibitors like tofacitinib in both

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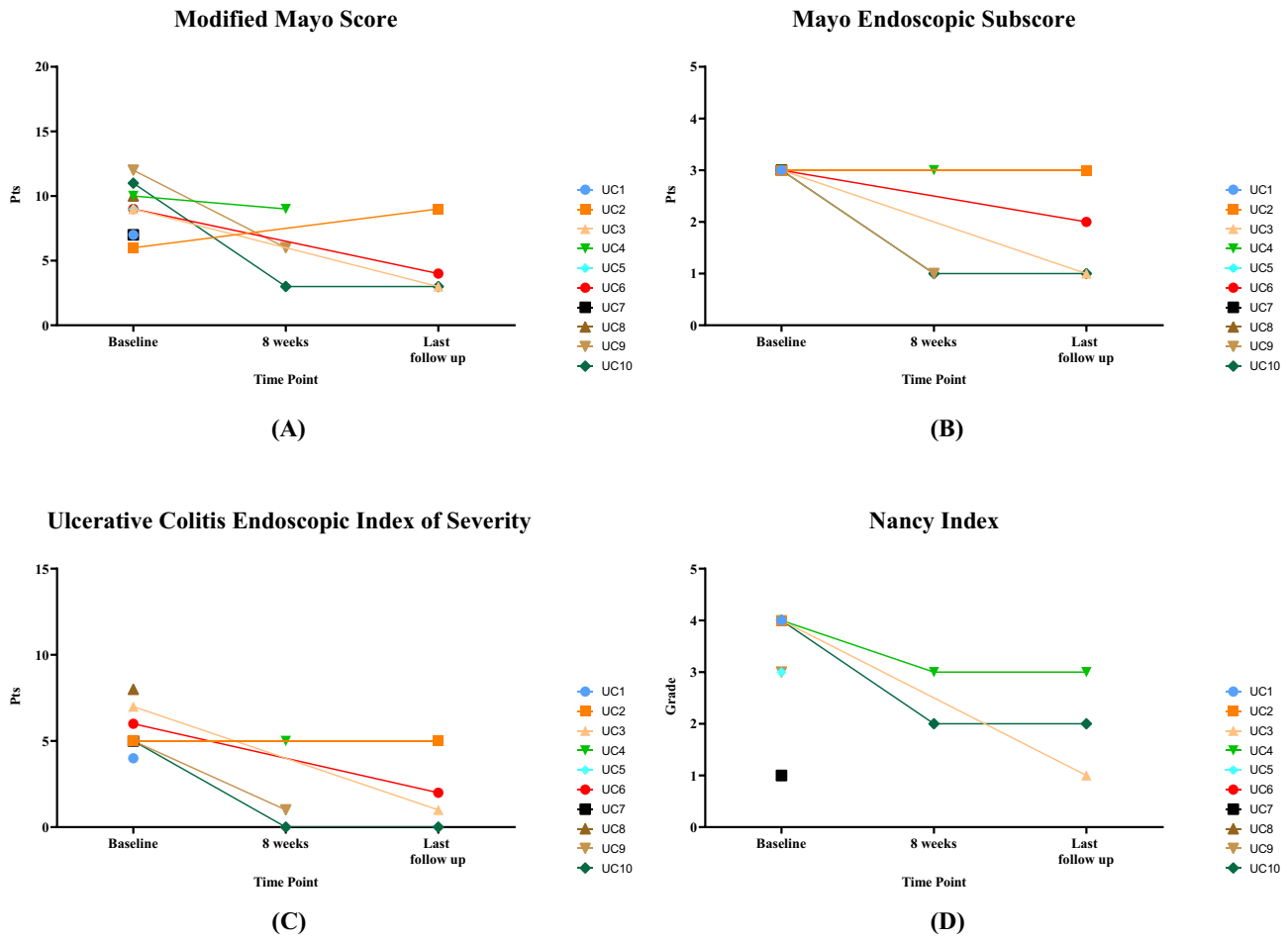

Figure 4 (**A**) Clinical Activity in Elderly Refractory UC Patients: Mayo Scores (**B**) Endoscopic Activity in Elderly Refractory UC Patients: Mayo Endoscopic Subscores (**C**) Endoscopic Activity in Elderly Refractory UC Patients: UCEIS Scores. (**D**) Histological Outcomes in Elderly Refractory UC Patients: Nancy Index.

adult and pediatric IBD populations.[20,21] This suggests that targeted JAK1 inhibition may provide an optimal balance of robust anti-inflammatory effects while potentially sparing other pathways, yielding a superior therapeutic window in this younger population.[22]

In contrast, the modest 20% remission rate in our older adult UC cohort, while lower than some Western studies,[23–25] reflects the complex challenges in managing this population. The management of older adults with IBD is often complicated by a phenomenon of "therapeutic inertia" or undertreatment, where clinicians may be hesitant to use advanced therapies due to safety concerns, even in the face of active disease.[25] This hesitation is often justified by the high burden of comorbidities, such as cardiovascular and pulmonary diseases, which are significantly more prevalent in this age group and can directly influence both drug efficacy and the risk of adverse events.[26] This is compounded by the concepts of frailty and immunosenescence. Frailty, a state of decreased physiological reserve, is an independent predictor of poor outcomes in elderly IBD and creates a vicious cycle: active disease worsens frailty, and frailty leads to undertreatment, which in turn results in worse outcomes, including higher rates of emergency surgery and mortality.[26,27] Furthermore, immunosenescence in older adults is not a simple decline but a complex immune dysregulation, characterized by a chronic, low-grade pro-inflammatory state known as "inflammaging".[28] Paradoxically, this dysregulated state may lead to a higher risk of developing anti-drug antibodies to biologics, further complicating treatment.[29] The combination of undertreatment, frailty, and immune dysregulation likely contributes to the lower treatment responses in our elderly cohort.

The side effects we observed are consistent with the known safety profile of UPA. Teenage CD patients experienced dermatological issues like folliculitis and acne, which are frequently reported with UPA, especially in younger

populations.[30] Notably, while JAK inhibitors can be associated with metabolic changes such as weight gain in pediatric rheumatic diseases,[30] this was not a prominent feature in our cohort, but warrants long-term monitoring. Reassuringly, large pharmacovigilance database analyses suggest the risk of "black box" warning events, such as MACE or thrombosis, is lower in pediatric patients compared to adults.[31] In the older adult group, the single serious case of fatal pneumonia underscores the heightened risk of infection in this vulnerable population, a primary concern highlighted in clinical practice guidelines for JAK inhibitors.[28,32] This emphasizes the need for careful risk assessment when treating older adults with potent immunomodulators.

Our research has several limitations. As a retrospective study with a small number of patients and no control group, our findings may not apply to all patients. We also could not study teenage UC patients or older CD patients, and our follow-up time was relatively short. Larger studies with more diverse patients and longer follow-up periods, ideally head-to-head randomized controlled trials comparing UPA to other advanced therapies, would help confirm our findings.

Conclusion

This first Asian study of UPA in teenagers with CD and older adults with UC shows promising results for adolescent patients while highlighting important safety considerations in the elderly population. The medication worked particularly well for teenagers with CD, achieving high rates of steroid-free clinical remission with an acceptable safety profile. In older adults with UC, while UPA demonstrated limited efficacy, the study revealed significant safety concerns, particularly increased infection risk, including one fatal pneumonia case, underscoring the need for careful risk-benefit assessment in this vulnerable population. While these findings provide initial evidence supporting UPA use in adolescent refractory CD, the conclusions must be interpreted in light of the study's limitations, including the small sample size and the comparison across different disease categories.larger, prospective, controlled studies are essential to confirm these preliminary observations, establish optimal dosing strategies, and evaluate long-term safety and efficacy profiles in both age groups.

Data Sharing Statement

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

Ethics Approval Statement

This study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (Ethics Approval Number: 2025ZSLYEC-149).

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. Hongzhen Wu, Yi Lu and Yun Su contributed equally and share senior authorship.

Clinical Trial Registration

This study is registered at ClinicalTrials.gov, identifier NCT06922331.

Patient Consent Statement

As a retrospective study, patient confidentiality was maintained, and informed consent was waived.

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Disclosure

All authors declare that they have no conflict of interest.

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