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Real-World Effectiveness and Safety of Upadacitinib in Crohn's Disease: Insights From the Eneida Registry

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ABSTRACT

Background: Upadacitinib (UPA) is the first oral Janus kinase (JAK) inhibitor approved for the treatment of Crohn's disease (CD). Real-world data, particularly from large nationwide cohorts, remain limited. This study aimed to evaluate the real-world effectiveness, safety, and treatment persistence of UPA in patients with CD.

Methods: Multicenter observational study including patients with CD who received UPA, using data from a nationwide registry. Patients were classified according to active luminal disease, extraintestinal manifestations (EIMs), or combination therapy with another biological therapy. Disease activity was assessed using the Harvey–Bradshaw Index (HBI), C-reactive protein (CRP), and fecal calprotectin (FC) at baseline and weeks 12, 24, and 52. Endoscopic outcomes were evaluated when available. Adverse events (AEs), hospitalizations, and treatment discontinuations were recorded.

Results: 300 patients were included, representing a highly treatment-refractory population, with 98% previously exposed to anti-TNF agents and 59% to three or more advanced therapies. In those treated for active luminal disease, corticosteroid-free clinical remission was achieved in 60%–62% of patients at weeks 12, 24 and 52. CRP normalization increased from 64% at week 12%–74% at week 52, while FC normalization improved from 48% to 64%. Patients treated for EIMs achieved high and sustained remission rates with excellent treatment persistence. Early remission at week 12 was strongly associated with sustained remission and meaningful endoscopic improvement. UPA was discontinued in 98 patients (39%). AEs were reported in 71 patients (24%).

Conclusions: In this large real-world cohort, UPA demonstrated sustained clinical and biochemical effectiveness, meaningful endoscopic response, and a safety profile consistent with clinical trial data. Early response emerged as a key predictor of long-term outcomes, supporting the clinical utility of UPA.

1 | Introduction

The therapeutic landscape of inflammatory bowel disease (IBD) has evolved with the introduction of Janus kinase (JAK) inhibitors, such as upadacitinib (UPA), oral small molecules characterized by rapid onset of action and low immunogenicity [1, 2].

UPA was initially approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for the treatment of adults with moderate-to-severe ulcerative colitis and subsequently in April 2023 by the EMA and in May 2023 by the FDA for adults with moderately to severely active Crohn's disease (CD) who have shown an inadequate response, loss of response, or intolerance to conventional or biological therapies. This approval positioned UPA as the first oral JAK inhibitor indicated for both induction and maintenance therapy of CD.

The efficacy and safety of UPA in CD have been demonstrated in phase II and III clinical trials, including CELEST, U-EXCEL, U-EXCEED, and the U-ENDURE extension study, showing significant clinical, biomarker, and endoscopic benefits in biologic-experienced patients [3–5]. However, these trials were conducted under highly controlled conditions and included selected patient populations, which may limit their generalizability to routine clinical practice.

In this context, real-world evidence (RWE) plays a complementary role by assessing treatment effectiveness, safety, persistence and therapeutic strategies in broader and more heterogeneous populations. This includes patients with long-standing disease, extensive prior biological exposure, comorbidities, and complex clinical scenarios that are frequently under-represented in clinical trials. Although several RWEs on UPA in CD have recently been published, many remain limited by relatively small sample sizes, short follow-up periods, and limited information on early predictors of response and outcomes beyond luminal disease [6–13].

Therefore, the aim of this study was to evaluate the real-world effectiveness and safety of UPA in a nationwide cohort of patients with CD from the ENEIDA registry, focusing on clinical, biochemical and endoscopic outcomes, treatment persistence, and early predictors of response during the first year of therapy.

2 | Methods

2.1 | Study Design and Endpoints

Data were obtained from the ENEIDA registry (Estudio Nacional en Enfermedad Inflamatoria Intestinal sobre Determinantes Genéticos y Ambientales), a nationwide prospective Spanish database established in 2007 and sponsored by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU, Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa). Clinical information in the ENEIDA registry is collected prospectively during routine clinical practice. The present study represents a retrospective analysis of these prospectively collected data.

We included all patients with Crohn's disease (CD) who initiated upadacitinib (UPA) after its approval in Spain (May 2023) and had a minimum follow-up of 12 weeks at the time of data extraction.

CD diagnosis was established according to standard international criteria [14]. UPA was prescribed according to routine clinical practice at the discretion of the treating physician. Dosing during induction and maintenance was determined at the discretion of the treating physician, and was guided by clinical response, treatment indication, and patient characteristics. Maintenance dosing was individualized, with continuation of 45 mg in cases of insufficient or partial response and dose

Key Summary

- Summarise the established knowledge on this subject
  - Upadacitinib (UPA) is the first oral Janus kinase (JAK) inhibitor approved for the treatment of Crohn's disease (CD).
  - Real-world data, particularly from large nationwide cohorts, remain limited.
- What are the significant and/or new findings of this study?
  - UPA demonstrated sustained clinical and biochemical effectiveness, meaningful endoscopic response, and a safety profile consistent with clinical trial data.
  - Early response emerged as a key predictor of long-term outcomes, supporting the clinical utility of UPA.

reduction in patients with favorable response or higher risk profiles. Patients were included if UPA was initiated for: (1) active luminal CD; (2) active extraintestinal manifestations (EIMs), with or without concomitant intestinal activity; or (3) combination therapy with a biological agent for active CD. In patients treated exclusively for EIMs without baseline luminal activity, intestinal outcomes were evaluated as maintenance of clinical and biochemical remission during follow-up.

Demographic and disease characteristics, prior therapies, reasons for biological discontinuation, cardiovascular risk factors and comorbidities were recorded. Cardiovascular risk factors were defined as the presence of diabetes mellitus, hypertension, dyslipidemia, smoking status, obesity (body mass index more than 30 kg/m^2), or a history of ischemic cardiovascular disease or severe systemic disease. Clinical activity was assessed using the Harvey–Bradshaw Index (HBI), and objective inflammation by C-reactive protein (CRP) and fecal calprotectin (FC). Disease activity was evaluated at baseline and at weeks 12,24 and 52. Endoscopic activity was assessed when available.

The primary endpoint was corticosteroid-free clinical remission at weeks 12,24 and 52. Secondary endpoints included changes in CRP and FC, endoscopic improvement, adverse events (AEs), hospitalization, surgery, and predictors of clinical, biochemical and endoscopic response.

2.2 | Definitions

Patients were classified into three groups based on the primary indication for UPA: (A) The luminal disease group, comprising patients treated primarily for active intestinal inflammation; (B) the combination therapy group, including those who received UPA in conjunction with a biological agent for at least the induction period (12 weeks); and (C) the EIMs group included patients in whom UPA was initiated primarily for active EIMs, associated with CD with FC normalization (< 250 μg/g) and in clinical remission, thus considered without active luminal disease. Other IMIDs recorded in the cohort were considered comorbid conditions and were not used to define this subgroup.

Combination therapy was defined as the concomitant use of UPA with any biological agent for at least the induction period (minimum of 12 weeks), prescribed with the intention of treating active CD or refractory EIMs.

Active disease was defined as HBI > 4 and/or objective activity (endoscopic inflammation with CRP > 5 mg/L and/or FC > 250 μg/g) [5]. Clinical remission was defined as an HBI score ≤ 4 points. Corticosteroid-free remission was defined as clinical remission in the absence of systemic corticosteroid therapy at the corresponding evaluation timepoint. FC and CRP normalization were defined as < 250 μg/g and < 5 mg/L, respectively, at each evaluated timepoint (weeks 12, 24, and 52).

Primary non-response was the absence of clinical and biochemical improvement leading to drug discontinuation during induction. Secondary non-response was discontinuation after initial response. Intolerance was discontinuation due to AEs [15]. Treatment discontinuation was at the physician's discretion.

AEs were defined as any undesirable medical occurrence during UPA treatment. Serious AEs were defined according to standard pharmacovigilance criteria, including events resulting in death, life-threatening conditions, hospitalization, persistent disability, or other medically significant events. CD–related complications were recorded separately unless considered by the treating physician to be potentially treatment-related.

EIMs were defined as inflammatory conditions associated with CD affecting organs outside the gastrointestinal tract, including musculoskeletal, dermatologic, ocular, or oral manifestations, as recorded by the treating physician. Immune-mediated inflammatory diseases (IMIDs) were defined as chronic inflammatory or autoimmune disorders not directly classified as classical EIMs but potentially sharing pathogenic mechanisms with CD. In patients treated for EIMs or IMIDs, response or remission was assessed clinically based on physician-documented improvement, reflecting routine clinical practice rather than disease-specific activity indices.

Endoscopic assessment was performed locally by the treating investigators as part of routine clinical practice, without central reading. Endoscopic reassessment during follow-up was performed according to routine clinical indication at the discretion of the treating physician, rather than a predefined study protocol. Endoscopic severity was graded by local investigators as inactive (0), mild (1), moderate (2), or severe (3), based on the overall mucosal inflammatory burden. This pragmatic grading reflects routine clinical practice in the ENEIDA registry, where formal SES-CD scoring is not systematically recorded, because the SES-CD score was not used in daily practice. Based on SES-CD definitions, mild disease was defined as $< 50\%$ surface involvement with aphthous ulcers, moderate as 50%–75% involvement with large ulcers, and severe as $> 75\%$ involvement with large ulcers (> 2 cm). Endoscopic changes were classified as worsening ($+1$), no change (0), or improvement (-1 to -3 depending on decrease in grade) [16].

2.3 | Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, IQR), and categorical

variables as frequencies and percentages. Group comparisons were performed using the Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical variables. CRP and FC values were log-transformed when appropriate.

Outcomes were analyzed using an as-observed approach; therefore, only patients with available clinical or biomarker data at each timepoint were included in the corresponding analyses, and no imputation for missing data was performed.

Longitudinal outcomes were analyzed using regression models. Factors associated with endoscopic improvement were assessed using ordinal logistic regression. Treatment persistence was evaluated using Kaplan–Meier analysis and Cox proportional hazard regression.

Multivariate analyses were restricted to patients receiving UPA for active luminal CD to avoid confounding by inactive disease or concomitant biological therapy. Mixed-effects logistic regression models with random intercepts were used to identify predictors of clinical remission and biomarker normalization. Results are reported as hazard ratios (HR) or odds ratios (OR) with 95% confidence intervals (CI).

A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using R software (version 4.4.1).

2.4 | Ethical Considerations

This cohort study was based on data from the ENEIDA database [17]. The use of the database was approved by the ethics committee of each participating center in 2006, after which data were collected prospectively. All patients included in ENEIDA signed an informed consent document authorizing the use of their clinical data for research. This project was approved by the Scientific Committee of GETECCU in September 2023.

3 | Results

3.1 | Baseline Patient Characteristics

A total of 300 patients with CD were included. Of these, 250 (83%) received upadacitinib for active luminal disease, 26 (9%) were treated for isolated EIMs, and 24 (8%) received UPA in combination with another biological agent. Results are reported according to these three predefined groups, with the primary analysis focused on the luminal disease cohort.

Baseline characteristics are summarized in Table 1. Most patients had ileal or ileocolonic disease, with predominantly inflammatory behavior, and approximately one third had a history of perianal disease. Nearly half of the cohort had a history of EIMs, most commonly musculoskeletal involvement, and 11% had concomitant IMIDs (Table 2).

Among the 300 patients, 30 individuals (10%) had a history of cancer or comorbidities other than IMIDs. Regarding cardiovascular risk, 29.3% ($n = 88$) of patients had no risk factors, 40% ($n = 120$) had one, and 21% ($n = 63$) had two. Fewer patients were presented with three (6%, $n = 18$) or four (3%, $n = 9$) risk factors, while only one patient had five, and one had six risk factors (0.3% each).

The study population was highly treatment-refractory: 98% had previously received anti-TNF therapy, 71% had been exposed to ustekinumab, and 59% had received three or more prior advanced therapies.

At baseline, patients in the luminal disease and combination therapy groups had active CD, with a median HBI score of 8 (IQR 5–11), CRP of 10 mg/L (IQR 3–30), and FC of 615 μg/g (IQR 211–1229). In contrast, patients treated exclusively for EIMs showed low clinical and biochemical activity. Baseline endoscopy was available in 210 patients (70%), with moderate-to-severe activity observed in 82%.

3.2 | Treatment Exposure

Most patients received standard induction therapy with UPA 45 mg once daily (91%). During maintenance, 70% were treated with 30 mg, 12% with 15 mg, and 18% remained on 45 mg. Concomitant corticosteroids and immunosuppressants during induction were used in 21% and 6% of patients, respectively.

Among patients receiving combination therapy ($n = 24$), upadacitinib was most frequently combined with anti-TNF agents or ustekinumab ($n = 8$ each), followed by vedolizumab ($n = 4$), anti-IL-23 agents ($n = 3$), and dupilumab ($n = 1$). In the EIMs group, upadacitinib was added to ustekinumab between two patients.

Induction therapy showed relevant differences across groups ($p < 0.0001$) (see Table 1). Most patients in the combination therapy and luminal disease groups started treatment with the highest dose of UPA (45 mg), while the EIMs group had a more varied dose initiation. For maintenance therapy, in the luminal disease and combination therapy group, approximately 20% of patients maintained the highest dose of UPA (45 mg) (see Table 1).

3.3 | Assessment of the Response

Clinical remission, CRP and FC were assessed in the three distinct groups. The longitudinal evolution of HBI, FC, and CRP during follow-up is shown in Figure 1. In luminal disease ($n = 250$), median HBI decreased from 6 (IQR 5–9) at baseline to 3 (1–6) at week 12, 3 (1–7) at week 24, and 4 (1–6) at week 52, with significant early improvement ($p < 0.001$). FC declined from 540 μg/g (279–1200) at baseline to 270 (94–660) at week 12, 249 (122–588) at week 24, and 148 (92–556) at week 52 $p < 0.001$ for the earlier timepoint. CRP decreased from 6.5 mg/L (2–17) at baseline to 2 (1–8) at week 12, 2 (1–9) at week 24, and 2 (1–6) at week 52.

TABLE 1 | Clinical and demographical characteristics of the total cohort and by treatment group. Data are expressed as median (interquartile range) or number (%).

Characteristic	Total cohort (n = 300)	Luminal (n = 250)	Combo (n = 24)	EIMs (n = 26)
Female sex	140 (47%)	111 (44%)	11 (46%)	18 (69%)
Age, years,	45 (33–54)	45 (32–54)	44 (33–54)	48 (36–56)
Disease duration, years	11 (6–19)	11 (6–19)	12 (8–20)	10 (6–17)
Smoking status				
Ex	70 (23%)	57 (23%)	7 (29%)	6 (23%)
Current	53 (18%)	43 (17%)	5 (21%)	5 (19%)
Previous surgery	150 (50%)	133 (53%)	11 (46%)	6 (23%)
Age at diagnosis				
A1	44 (15%)	38 (15%)	4 (17%)	2 (8%)
A2	180 (60%)	152 (61%)	15 (63%)	13 (50%)
A3	76 (25%)	60 (24%)	5 (21%)	11 (42%)
Disease location				
L1	130 (43%)	101 (40%)	11 (46%)	18 (69%)
L2	33 (11%)	28 (11%)	2 (8%)	3 (12%)
L3	132 (44%)	116 (46%)	11 (46%)	5 (19%)
L4	33 (11%)	29 (12%)	2 (8%)	2 (8%)
Disease behavior				
B1	159 (53%)	131 (52%)	12 (50%)	16 (62%)
B2	93 (31%)	77 (31%)	10 (42%)	6 (23%)
B3	48 (16%)	42 (17%)	2 (8%)	4 (15%)
Perianal disease	90 (30%)	76 (30%)	8 (33%)	6 (23%)
Patients with EIMs	142 (47%)	97 (39%)	19 (79%)	26 (100%)
Patients with IMIDs	34 (11.3%)	25 (10%)	3 (13%)	6 (23%)
Comorbidities or risk factors				
Obesity	66 (26%)	50 (20%)	9 (37%)	7 (27%)
Hypertension	31 (10%)	24 (10%)	2 (8%)	5 (19%)
Diabetes mellitus	15 (5%)	11 (4%)	1 (4%)	3 (11%)
Dyslipidaemia	26 (9%)	18 (7%)	1 (4%)	7 (27%)
Systemic disease or cancer	30 (10%)	25 (10%)	0 (0%)	5 (19%)
Prior advanced therapy				
Anti-TNF	294 (98%)	246 (98%)	24 (100%)	24 (92%)
IL-12/23	213 (71%)	192 (77%)	11 (46%)	10 (38%)
Anti-integrin	114 (38%)	108 (43%)	5 (21%)	1 (4%)
JAK inhibitor	7 (2%)	6 (2%)	0 (0%)	1 (4%)
UPA induction dose				
45 mg	272 (91%)	241 (96%)	21 (88%)	10 (39%)
30 mg	13 (4%)	8 (3%)	1 (4%)	4 (15%)
15 mg	15 (5%)	1 (0.4%)	2 (8%)	12 (46%)
UPA maintenance dose				
45 mg	45 (18%)	41 (20%)	4 (20%)	0 (0%)
30 mg	177 (70%)	149 (71%)	13 (65%)	15 (60%)
15 mg	32 (12%)	19 (9%)	3 (15%)	10 (40%)
CS use during induction	60 (21%)	48 (19%)	7 (29%)	5 (19%)

(Continues)

TABLE 1 | (Continued)

Characteristic	Total cohort (n = 300)	Luminal (n = 250)	Combo (n = 24)	EIMs (n = 26)
IS used during induction	15 (6%)	13 (5%)	1 (4%)	1 (4%)
Combined biologic therapy	26 (9%)	0 (0%)	24 (100%)	2 (8%)
Baseline disease severity				
HBI	8 (5–11)	6 (5–9)	7 (5–9)	3 (2–4)
CRP, mg/L	10 (3–30)	6.5 (2–17)	5 (3–9)	2 (1–9)
FC, μg/g	615 (211–1229)	540 (279–1200)	538 (290–857)	57 (30–97)
Baseline endoscopic severity	210 (70%)	180 (72%)	15 (63%)	15 (58%)
Inactive	8 (4%)	0 (0%)	0 (0%)	8 (53%)
Mild	30 (14%)	19 (11%)	4 (27%)	7 (47%)
Moderate	94 (45%)	90 (50%)	4 (27%)	0 (0%)
Severe	78 (37%)	71 (39%)	7 (46%)	0 (0%)

Note: Luminal (group of patients with luminal disease); Combo (group of patients who received upadacitinib in combination with biologic therapy for active disease); EIMs (group of patients treated for extraintestinal manifestations without luminal involvement). Age at diagnosis: $A1 < 16$ years, A2 17–40 years, $A3 > 40$; Location: L1 = ileal, L2 = colonic, L3 = ileocolonic; L4 = upper gastrointestinal involvement. Behavior: B1 = non-stricturing, non-penetrating CD, B2 = stricturing CD, B3 = penetrating Crohn's disease.

Abbreviations: CRP, serum C-reactive protein; CS, corticosteroid; EIMs, extraintestinal manifestations; FC, fecal calprotectin; HBI, Harvey Bradshaw index; IMIDs, immune-mediated inflammatory diseases; IS, immunosuppressor; UPA, upadacitinib.

In combination therapy group (n = 26), baseline HBI was 7 (5–9), declining to 4 (2–7) at weeks 12, 3 (2–5) at week 24, and 4 (2–6) at week 52 (p = 0.006 at week 12). FC showed a progressive reduction from 538 μg/g (290–857) to 458 (266–920) at week 12, 130 (94–603) at week 24, and 386 (49–441) at week 52 (p = 0.041 at week 52). CRP decreased from 5 mg/L (2–9) to 4 (1–12) at week 12, 1 (1–3) at week 24, and 2 (1–11) at week 52.

In the EIMs group (n = 26), baseline HBI was lower (3 [1–4]), and decreased modestly to 2 (1–3) at week 12 (p = 0.015), remaining stable at weeks 24 and 52. FC and CRP levels were low at baseline (57 μg/g [30–97] and 2 mg/L [1–8, 17], respectively) and did not show relevant changes during follow-up.

Figure 2 summarizes clinical and biochemical outcomes across the three subgroups. The number of patients with available data at each timepoint is indicated in the figure, and percentages were calculated based on available cases. As in other real-world cohorts, the apparent improvement in biomarker normalization over time may partly reflect the decreasing number of observations during follow-up. Patients with luminal disease showed stable remission rates with gradual improvement in CRP and FC over 1 year. Combination therapy induced an early response that peaked at week 24 and declined thereafter, particularly for FC. Patients treated for EIMs achieved the highest and most sustained clinical and biochemical responses.

3.4 | Endoscopic Improvement

Baseline endoscopy was available in 210 patients (70%), with moderate-to-severe disease activity observed in 82% (Table 1). Endoscopic assessments during follow-up were available in 113 patients, including 86 with paired baseline and follow-up evaluations.

Among patients with paired endoscopies, 46% achieved endoscopic improvement, and 16% reached endoscopic remission by the end of follow-up (Figure 3). Overall, 43% of patients showed inactive or mild disease at follow-up compared with baseline, when most had moderate or severe activity (Figure 3).

3.5 | Predictive Factors Associated With Response

In the multivariate Cox regression, the number of prior advanced therapies was significantly associated with treatment persistence. Each additional prior advanced therapy reduced the likelihood of persistence, with a hazard ratio of 0.40 (95% CI: 0.17–0.95; p = 0.038). In contrast, disease location, disease behavior, number of risk factors, and corticosteroid use at baseline were not correlated with persistence.

Logistic regression analysis was performed in patients treated for active luminal disease (n = 250), see Table 3.

Regarding clinical remission, fistulizing behavior (OR 0.14; 95% CI: 0.04–0.54; p = 0.004), a higher number of risk factors (OR 0.62; 95% CI: 0.41–0.95; p = 0.028), and corticosteroid use at baseline (OR 0.23; 95% CI: 0.08–0.70; p = 0.009) were independently associated with a lower likelihood of achieving remission. In contrast, disease location, disease duration, number of previous advanced therapies, cause of discontinuation of prior biologics (primary nonresponse, loss of response, AEs), and sex were not predictive of clinical response. Importantly, none of these factors, including those associated with reduced clinical remission, showed a significant association with the normalization of FC or CRP levels or with endoscopic improvement.

Early response was strongly predictive of long-term outcomes: patients achieving clinical remission at week 12 were more likely to maintain remission at week 52 (OR 8.1; 95% CI:

TABLE 2 | Extraintestinal manifestations (EIMs) and immune-mediated inflammatory diseases (IMIDs) in the study cohort ($N = 300$).

Any EIMs	**142 (47%)**
Arthropathy	126 (89%)
Peripheral	62
Axial	80
Enthesitis	2
Dermatologic	25 (18%)
Erythema nodosum	15
Stomatitis	9
Pyoderma gangrenosum	4
Ocular	22 (15%)
Uveitis	18
Episcleritis	4
Primary sclerosing cholangitis	3 (2%)
Other	2 (1%)
Any IMIDs	**34 (11%)**
Dermatologic	20 (59%)
Psoriasis	8 (23%)
Hidradenitis suppurativa	8 (23%)
Atopic dermatitis	1 (3%)
Chronic urticaria	1 (3%)
Alopecia areata	1 (3%)
Lichen planopilaris	1 (3%)
Rheumatologic/connective tissue	7 (20%)
Rheumatoid arthritis	4 (12%)
Systemic lupus erythematosus	2 (6%)
Sjögren's syndrome	1 (3%)
Endocrine-metabolic	
Autoimmune hypothyroidism	4 (12%)
Autoimmune cytopenia	3 (9%)
Anemia	2 (6%)
Thrombocytopenia	1 (3%)
Other	3 (9%)
IgA nephropathy	1 (3%)
Celiac disease	1 (3%)
Multiple sclerosis	1 (3%)

2.15–36.45; $p = 0.0004$). Similarly, normalization of FC (OR 5.9; 95% CI: 1.26–33.78; $p = 0.011$) and CRP (OR 7.3; 95% CI: 1.16–57.24; $p = 0.016$) at week 12 was associated with sustained normalization at week 52.

Week 12 responders also had a greater probability of endoscopic improvement: clinical remission (OR 2.7; 95% CI: 1.1–6.7; $p = 0.03$), FC normalization (OR 2.6; 95% CI: 0.98–6.95; $p = 0.05$), and CRP normalization (OR 4.2; 95% CI: 1.63–11.82; $p = 0.004$) were all linked to improved endoscopic outcomes. Achieving a complete response at week 12 (clinical remission plus FC and CRP normalization) increased the likelihood of maintaining that response at week 52 (OR 9.4; 95% CI: 1.53–78.34; $p = 0.0057$), although it did not significantly predict endoscopic improvement ($p = 0.08$).

3.6 | Upadacitinib Persistence

The median follow-up duration was 29 weeks (IQR 17–50): 29 weeks (17–47) in the luminal disease group, 29 weeks (21–58) in the combination therapy group, and 39 weeks (24–69) in the EIMs group.

By the end of follow-up, 98 patients (39%) had discontinued UPA, with 89 of these discontinuations (36%) occurring within the first year. The most frequent reason for withdrawal was primary non-response ($n = 53$), reported in 48 patients from the luminal disease group, three from the combination therapy group, and two from the EIMs group. Loss of response accounted for 13 discontinuations, all within the luminal disease group. Adverse events led to treatment cessation in 29 patients, including 25 from the luminal disease group and four from the combination therapy group. Additionally, two patients discontinued due to sustained remission, and one patient withdrew voluntarily; all three were from the luminal disease group.

After the withdrawal of UPA, physicians took the following approach: 42 patients were administered risankizumab, 24 underwent surgery, 13 received anti-TNF, seven received ustekinumab, four received vedolizumab, three received corticosteroids, one received guselkumab, and four patients remained untreated.

Kaplan–Meier curves are presented for the overall cohort (Figure 4A) and for subgroups stratified by treatment strategy (Figure 4B). For the entire cohort, the probabilities of remaining on treatment at 12, 24, and 52 weeks were 93%, 81%, and 60%, respectively.

For patients treated for active luminal disease, the probabilities were 93%, 80%, and 56% at 12, 24, and 52 weeks, respectively. In the combination therapy group, the corresponding probabilities were 92%, 78%, and 64%. Among patients treated for EIMs, persistence rates were 100% in weeks 12% and 24% and 93% in week 52. Post hoc analysis revealed significant differences between the curves for the EIMs group and the luminal disease activity group ($p = 0.0093$).

3.7 | Safety Profile

Adverse events (AEs) were reported in 71 of 300 patients (24%), with similar incidence across treatment groups (Table 4): 7 patients (29.2%) in the combination therapy group, 6 (23.1%) in the

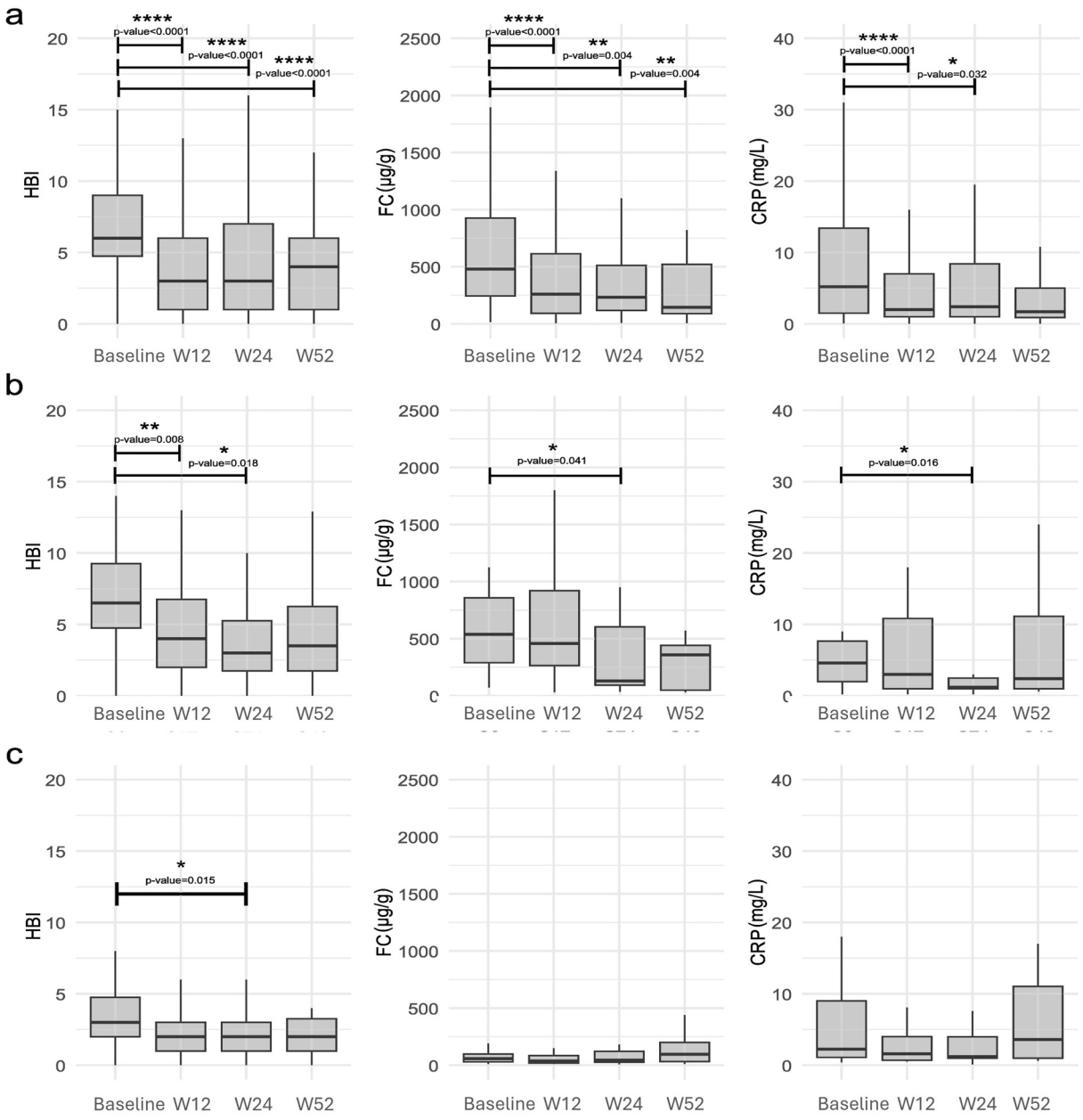

FIGURE 1 | The longitudinal evolution of clinical and inflammatory parameters. Harvey-Bradshaw Index (HBI), fecal calprotectin (FC), and C-reactive protein (CRP) over time in the cohort of patients treated for luminal disease (a), patients who received UPA in combination with biological therapy (b), and patients treated for EIMs without luminal involvement (c). Data are expressed as median and interquartile ranges.

EIMs group, and 58 (23.2%) in the luminal disease group. Treatment discontinuation due to AEs occurred in 29 patients (9.7%), including 25/250 (10%) in the luminal disease group, 4/24 (16.7%) in the combination therapy group, and none in the EIMs group. The most frequent AEs leading to discontinuation were infections, dermatologic events, and gastrointestinal complications.

Infections were the most common AEs, predominantly mild-to-moderate respiratory infections and herpes zoster. Dermatological events, mainly acne, were also observed. Serious adverse events were infrequent and included isolated cases of thrombotic events, non-melanoma skin cancer, and hemolytic uremic syndrome. No clustering of serious events was observed in patients receiving combination therapy.

During follow-up, 26 patients (8.6%) required surgery and 66 (22%) were hospitalized, mainly due to disease-related causes or surgical procedures, while a minority were related to treatment-associated adverse events.

4 | Discussion

This study demonstrates the real-world effectiveness and safety of UPA in CD, even in a cohort characterized by advanced disease and extensive prior biological exposure. Importantly, it provides novel real-world data on UPA use in patients with EIMs and IMIDs and in combination with other advanced therapies, clinical scenarios in which evidence remains limited. Overall, UPA was

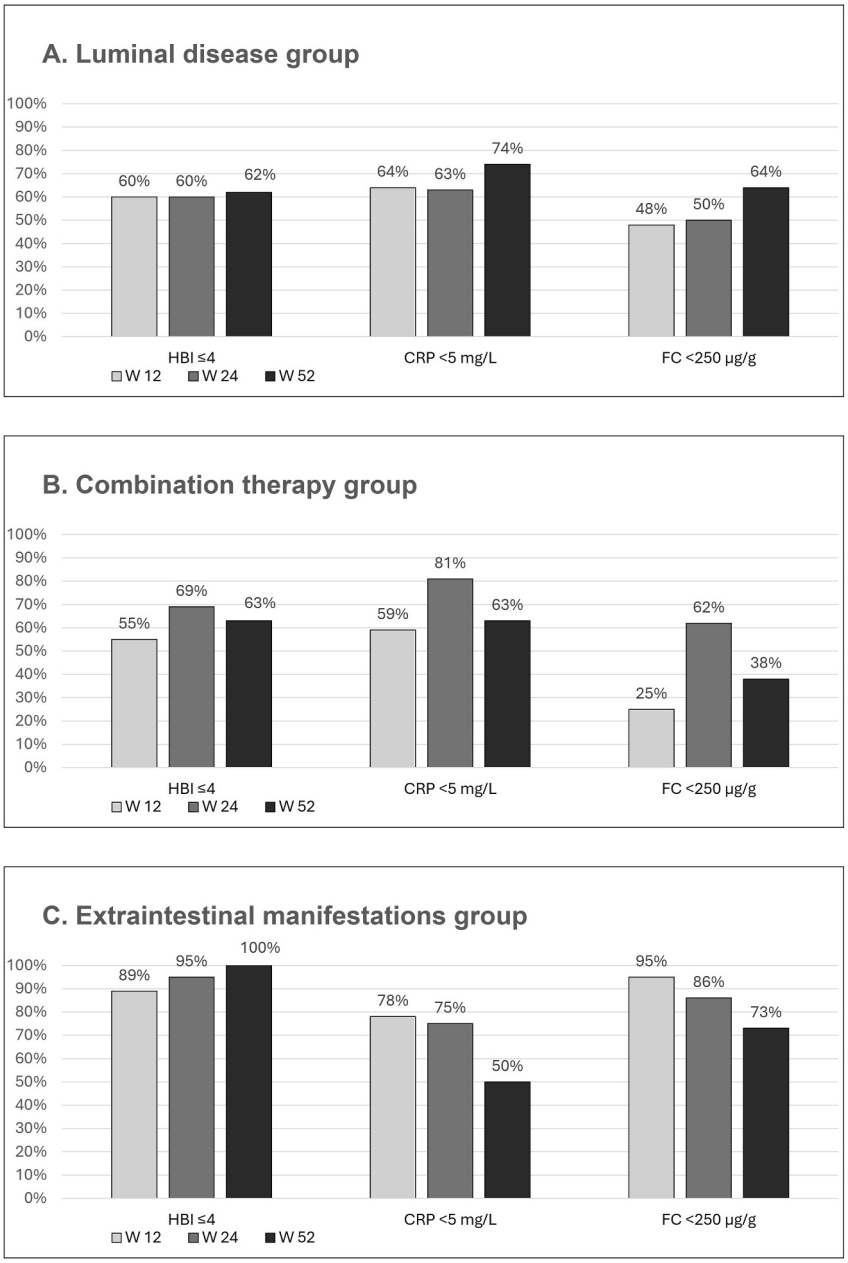

FIGURE 2 | Clinical remission and biochemical normalization rates at weeks 12, 24, and 52 according to treatment group. (A) Luminal disease group; (B) combination therapy group; (C) extraintestinal manifestations group. Clinical remission was defined as a Harvey-Bradshaw Index (HBI) score ≤ 4, and normalization thresholds for FC and CRP were < 250 µg/g and < 5 mg/L, respectively. The number of patients with available data at each timepoint is indicated in the figure, and percentages were calculated based on available observations at each timepoint.

associated with meaningful clinical, biochemical, and endoscopic benefits, particularly in patients with active luminal disease and in those treated for EIMs. Given the heterogeneity of the study population, the main conclusions of this study are primarily driven by the luminal disease cohort, while findings in the EIM and combination therapy groups should be interpreted as exploratory.

Clinical remission and biomarker normalization rates in patients with active luminal disease were comparable to or slightly higher than those reported in Phase 3 trials (U-EXCEL, U-EXCEED, and U-ENDURE), in which week 52 remission ranged between 37% and 48% among biologic-experienced patients [3–5]. When contextualized within available real-world evidence (Table 5), our findings are broadly consistent with recently published cohorts, with remission rates of approximately 60%–67% at one year in similar, often heavily pretreated populations [6, 8–11, 19], supporting the external validity of UPA effectiveness in routine clinical practice. Endoscopic remission was achieved in 16% of patients, a lower proportion than in some real-world cohorts [6, 7, 9]. However, this finding should be interpreted in the context of non-systematic

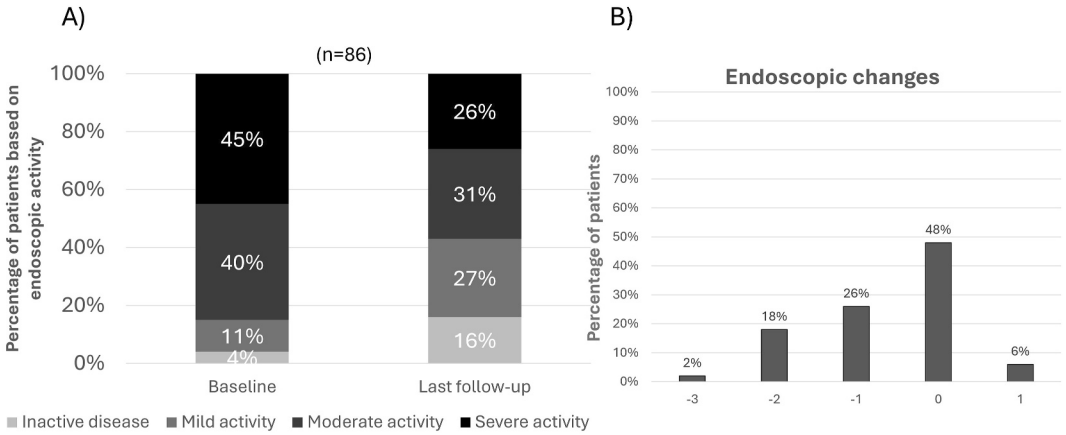

FIGURE 3 | Endoscopic outcomes in patients with Crohn's disease were treated with upadacitinib. (A) Distribution of endoscopic activity at baseline and at the end of follow-up ($n = 86$). (B) Degree of endoscopic change compared to baseline.

TABLE 3 | Multivariate analysis of predictive factors for treatment outcomes in patients with luminal Crohn's disease ($n = 250$).

Factor	Outcome assessed	OR (95% CI)	*p*-value	Association with FC/CRP normalization or endoscopic improvement
Fistulizing behavior	Lower clinical remission	0.14 (0.04–0.54)	0.004	NS
Number of risk factors (per unit increase)	Lower clinical remission	0.62 (0.41–0.95)	0.028	NS
Corticosteroid use at baseline	Lower clinical remission	0.23 (0.08–0.70)	0.009	NS
Disease location	Clinical remission	NS	—	NS
Cause of discontinuation of prior biologics	Clinical remission	NS	—	NS
Disease duration	Clinical remission	NS	—	NS
Sex	Clinical remission	NS	—	NS
Clinical remission at week 12	Clinical remission at week 52	8.1 (2.15–36.45)	0.0004	Associated with endoscopic improvement (OR 2.7; 95% CI: 1.1–6.7; $p = 0.03$)
FC normalization at week 12	FC normalization at week 52	5.9 (1.26–33.78)	0.011	Associated with endoscopic improvement (OR 2.6; 95% CI: 0.98–6.95; $p = 0.05$)
CRP normalization at week 12	CRP normalization at week 52	7.3 (1.16–57.24)	0.016	Associated with endoscopic improvement (OR 4.2; 95% CI: 1.63–11.82; $p = 0.004$)
Complete response at week 12 (clinical remission + FC & CRP normalization)	Complete response at week 52	9.4 (1.53–78.34)	0.0057	Not associated with endoscopic improvement ($p = 0.08$)

Note: None of the analyzed baseline factors, including those associated with reduced clinical remission (fistulizing behavior, higher number of risk factors, corticosteroid use at baseline), showed a significant association with normalization of fecal calprotectin (FC) or C-reactive protein (CRP) levels, nor with endoscopic improvement.
Abbreviation: NS, not significant.

endoscopic reassessment in routine daily practice, where follow-up endoscopy is often reserved for patients with suboptimal clinical or biochemical responses. Importantly, early clinical and biomarker response at week 12 was strongly associated with subsequent endoscopic improvement, reinforcing the relevance of early treat-to-target strategies even when endoscopy is not routinely performed.

Patients treated for EIMs showed the most pronounced and sustained benefit, with high remission rates and preservation of

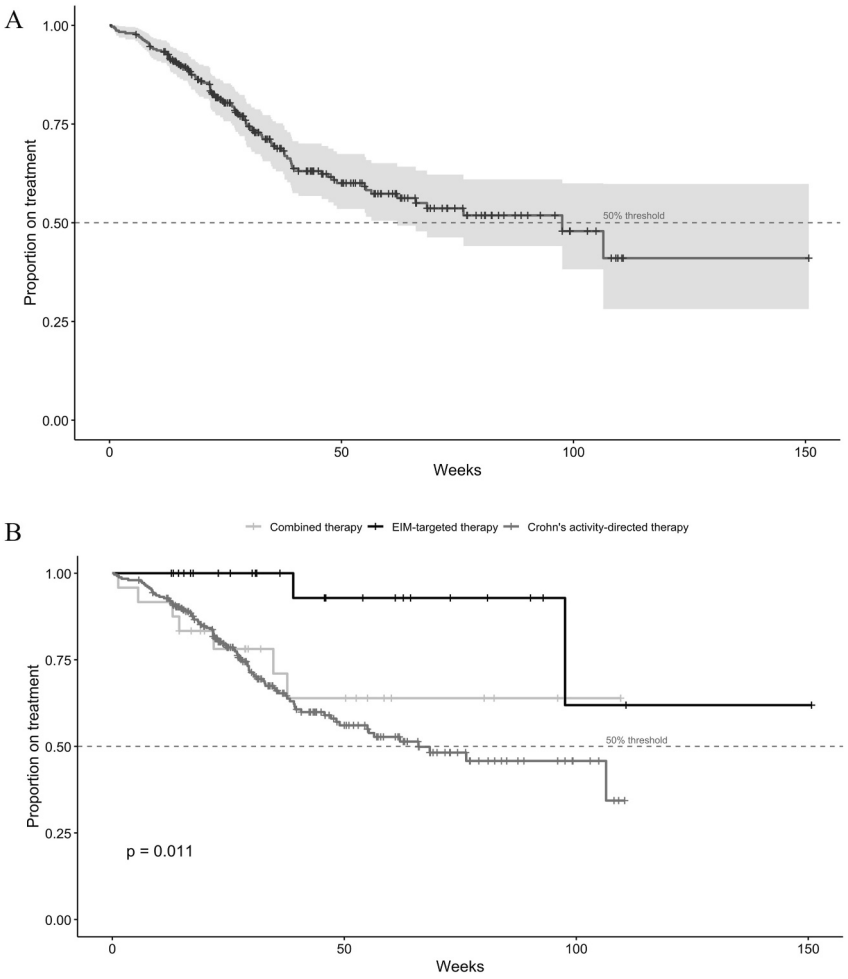

FIGURE 4 | Persistence of upadacitinib in the overall cohort (A) and by treatment group (B): Crohn's disease activity-directed therapy (luminal disease, dark gray), combined therapy (upadacitinib plus biologic, light gray), and extraintestinal manifestations-targeted therapy (extraintestinal manifestations without luminal disease, black).

intestinal remission throughout follow-up. It should be noted that most EIMs in our cohort were musculoskeletal, particularly peripheral arthropathy, whereas dermatologic and ophthalmologic manifestations were less frequent. Therefore, these findings should primarily be interpreted in the context of rheumatologic manifestations. As these patients initiated UPA in the absence of active luminal disease, this subgroup allowed independent evaluation of extraintestinal outcomes. These findings support the role of JAK1 inhibition in controlling systemic inflammatory activity and are consistent with post hoc analyses of clinical trials and small real-world series reporting favorable outcomes in EIMs [21–25]. Moreover, the effectiveness observed in CD-associated EIMs appears broadly comparable to outcomes reported in non-IBD populations treated with UPA for other IMIDs, suggesting that underlying IBD does not negatively affect therapeutic response [26].

Advanced combination therapy (ACT), defined as the concomitant use of UPA with another biological agent, represents an emerging strategy for selected patients with refractory CD or difficult-to-control EIMs [27–29]. Although evidence remains limited, early observational series [30, 31] and the VEGA trial in UC support the potential for enhanced efficacy without major safety trade-offs [32]. In our cohort, combination therapy was associated with early clinical improvement but did not consistently translate into sustained remission, highlighting the need for optimized treatment protocols, clearer patient selection criteria, and longer follow-up to better define its role in clinical practice [33]. However, given the small sample size and heterogeneity of this subgroup, these findings should be considered exploratory and interpreted with caution. Further prospective studies are needed to better define the role of advanced combination therapy in clinical practice, including its safety and health-economic implications.

Predictive analyses identified fistulizing disease behavior, higher cardiovascular risk burden, and baseline corticosteroid use as factors associated with lower remission rates, in line with previous real-world studies [6, 8]. Notably, the reason for prior biological discontinuation did not influence UPA outcomes, although this finding should be interpreted cautiously given the heterogeneity of the underlying mechanisms and the exploratory nature of the analysis.

Interestingly, while a higher number of prior advanced therapies were associated with lower treatment persistence, it did not

TABLE 4 | Adverse events by system/organ class and their impact on treatment discontinuation ($N = 300$).

System/Organ class (*n*, %)	Adverse Event	*n* (%)	Discontinuation *n* (%)
Infections (16, 5.3%)	Respiratory infection	8 (2.7%)	3 (37.5%)
	Herpes zoster (incl. Ophthalmic)	3 (1%)	2 (66.7%)
	Herpes labialis	1 (0.3%)	—
	Gastroenteritis E. coli + HUS	1 (0.3%)	Yes
	Otitis	1 (0.3%)	Yes
	Anal abscess	1 (0.3%)	—
	Skin infection	1 (0.3%)	Yes
	Viral infection	1 (0.3%)	—
Dermatologic (13, 4.3%)	Acne	10 (3.3%)	3 (30%)
	Alopecia	1 (0.3%)	Yes
	Rash	2 (0.7%)	1 (50%)
Hematologic (3, 1%)	Severe anemia	2 (0.7%)	Yes
	Leukopenia	1 (0.3%)	Dose reduction
Gastrointestinal (17, 5.7%)	Worsening disease	6 (2%)	4 (66%)
	Abdominal pain	6 (2%)	2 (33%)
	Subocclusion	5 (1.7%)	Yes
	Diarrhea	1 (0.3%)	—
	GI bleeding	2 (0.7%)	1 (50%)
	Vomiting	1 (0.3%)	—
	Transaminase elevation	1 (0.3%)	Yes
	Perforation	1 (0.3%)	Yes
Endocrine (7, 2.3%)	Dyslipidemia	7 (2.3%)	—
Cardiovascular/Thrombotic (2, 0.7%)	Hypertension	1 (0.3%)	—
	Upper limb thrombosis	1 (0.3%)	Yes
Carcinoma (5, 1.7%)	Skin squamous cell carcinoma	2 (0.7%)	1 (50%)
	Basal cell carcinoma	1 (0.3%)	—
	Renal carcinoma	1 (0.3%)	—
	Suspected melanoma (not confirmed)	1 (0.3%)	Yes
Others (14, 4.7%)	Fever	5 (1.7%)	3 (60%)
	Headache	2 (0.7%)	—
	Asthenia	2 (0.7%)	Yes
	Angioedema	1 (0.3%)	Yes
	Flu-like syndrome	1 (0.3%)	—
	Cough	1 (0.3%)	Yes
	Metrorrhagia	1 (0.3%)	—
	SAPHO syndrome	1 (0.3%)	Yes
	Edema	1 (0.3%)	—

Abbreviations: HUS, hemolytic uremic syndrome; SAPHO syndrome, (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis).

significantly affect remission rates. This discrepancy may reflect that persistence and remission capture different dimensions of treatment effectiveness, particularly in heavily pretreated patients.

The relatively high discontinuation rate observed in our cohort likely reflects the highly refractory nature of the study population, with nearly all patients previously exposed to anti-TNF agents (98%), 71% to ustekinumab, and 59% to three or more advanced therapies. This likely explains the lower persistence compared with other real-world cohorts. The safety profile observed was consistent with known class effects of JAK inhibitors and comparable to previous real-world reports [6, 9], and most commonly included infections and dermatologic

TABLE 5 | Real-world studies assessing upadacitinib in Crohn's disease (luminal activity).

Study (Year)	*n* (CD)	Clinical Remission (w12)	Clinical Remission (w52)	FC normalization	CRP normalization	Endoscopic Remission
Present study (2025)	250	60%–62%	62%	48% (w12) 64% (w52)	64% (w12) 74% (w52)	16%
Danso 2025 [13]	312	50%	N/1a	↓ (significant)	↓ (significant)	6%–12% (W24)
Wu 2025 [7]	156	77.8%	N/A	↓ (significant)	↓ (significant)	19.4%
Richard 2025 [8]	197	56%	N/A	52% biomarker	52% biomarker	47% (endo/radio)
Devi 2025 [6]	334	52.1%	55.9% (6 months)	N/A	N/A	42.7%
Papathanasioua 2025 [18]	24	85% (response)	N/A	N/A	W12: 84.6%	N/A
García 2025 [12]	49	54%	38%	N/A	N/A	N/A
Farkas 2024 [9]	115	76.2%	66.7%	↓ (significant)	↓ (significant)	54.5%
Elford 2024 [11]	93	64%	38%	↓ (significant)	↓ (significant)	N/A
Bezzio 2024 [19]	64	52% (SFCR)	61% (w24)	36%–38%	36%–38%	21.8% deep remission
Friedberg 2023 [10]	17	70.6% (w8)	N/A	62% (w8)	64% (w8)	N/A
Chugh 2022 [20]	45	27.2%	N/A	↓ (non-significant)	↓ (significant)	28.6%

Note: ↓ (significant): statistically significant reduction reported in the original study, without available numerical data.
Abbreviations: CRP, C-reactive protein; FC, fecal calprotectin; N/A, not applicable; SFCR, teroid-free clinical remission; w, week.

events such as acne, both of which are well-described for this drug class [34, 35]. Serious adverse events were infrequent, and no safety signal emerged in patients receiving combination therapy. No increased cardiovascular or thrombotic risk was identified, although careful patient selection and monitoring remain essential [34, 36]. Herpes zoster events were uncommon, which may in part reflect routine vaccination practices in patients initiating JAK inhibitors in our setting.

This study has several limitations, including its retrospective analysis of prospectively collected registry data, incomplete endoscopic follow-up, and restricted multivariate analyses. The relatively short median follow-up (29 weeks), reflecting the recent approval of UPA and the real-world nature of data collection, may limit the assessment of long-term effectiveness and durability of response. Endoscopic reassessment was not performed systematically and was more frequently undertaken in patients with suboptimal clinical or biochemical responses, which may have influenced the observed rates of endoscopic remission. In addition, strategies such as UPA reinduction or high-dose maintenance were not systematically evaluated, as they were not yet standardized during the study period, potentially affecting treatment persistence [37]. Nevertheless, this represents one of the largest real-world analyses of UPA in CD and provides valuable insights into underrepresented clinical scenarios.

In conclusion, UPA is an effective real-world therapeutic option for CD, including highly treatment-refractory patients, achieving sustained clinical and biochemical remission with an acceptable safety profile. Favorable outcomes were also observed in patients treated for EIMs and in selected combination strategies. Early clinical and biomarker responses emerged as a key predictors of long-term outcomes, supporting early reassessment strategies to optimize disease control.

Author Contributions

Planning and/or conducting the study, collecting and/or interpreting data, and/or drafting the manuscript: M.I. and P.N. Collecting and/or interpreting data: all authors. All authors approved the final version of the manuscript. Guarantor of the article: M.I.

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The authors have nothing to report.

Ethics Statement

This cohort study was based on data from the ENEIDA database [17]. The use of the database was approved by the ethics committee of each participating center in 2006, after which data were collected prospectively. All patients included in ENEIDA signed an informed consent document authorizing the use of their clinical data for research. This project was approved by the Scientific Committee of GETECCU in September 2023.

Conflicts of Interest

M.I. reports grants and personal fees from MSD, Janssen, Takeda, Kern Pharma, AbbVie, Lilly, and Chiesi during the conduct of the study. B.B. received financial support for traveling and educational activities from Johnsson and Johnsson, AbbVie, Takeda, Alfasigma, Faes Farma and Ferring. M.D.M.-A. has served as a speaker, a consultant and advisory member for or has received research funding from for MSD, Abbvie, Takeda, Lilly, Pfizer, Shire Pharmaceuticals, Faes Farma, Johnson and Johnson and Ferring. D.C. has no conflicts to declare. C.M.-P. has no conflicts to declare. A.G. has no conflicts to declare. P.V. received financial support for traveling and educational activities from Johnson

and Johnson, Abbvie, Pfizer, Takeda, Lilly and Faes Farma. M. Moreta has no conflicts to declare. E.B.-M. has served as a speaker and consultant for Janssen and Chiesi, Kern, Takeda and Alfasigma. Y.G.L. has received financial support for traveling and educational activities and has received fees for being speaker, consultant or advisory board member from MSD, Abbvie, Pfizer, Ferring, Shire Pharmaceuticals, Takeda, Tillots, Jannsen, Alfasigma, Sandoz and Lilly. G.E.R.G. has served as speaker from Johnson and Johnson and received financial support for traveling and educational activities from Johnsson and Johnsson, AbbVie, Kern Pharma, Takeda, Lilly, Chiesi, Dr. Falk and Ferring. MV has no conflicts to declare. 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Data Availability Statement

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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