Annals of Gastroenterology (2025) **38,** 306-310

Induction with upadacitinib in Crohn's disease: real-world experience from an early-access program in Greece

Evgenia Papathanasiou[a], Alexandros Ioannou[a], Pavlos Pardalis[a], Giorgos Leonidakis[a], George Michalopoulos[b], Spilios Manolakopoulos[c], Spyridon Siakavellas[c], Angeliki Theodoropoulou[d], Athanasia Tasovasili[e], Olga Giouleme[f], Maria Tzouvala[g], Eftychia Tsironi[h], Nikos Viazis[i], Spyridon Michopoulos[a], Evanthia Zampeli[a]

"Alexandra" General Hospital of Athens; "G. Gennimatas" General Hospital of Athens; 2nd Academic Department of Internal Medicine, Hippocration General Hospital of Athens, University of Athens Medical School; Venizeleio General Hospital, Heraklion; "Agioi Anargyroi" General and Oncology Hospital of Kifisia, National and Kapodistrian University of Athens; Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki; "Agios Panteleimon" General Hospital of Nikaia–Piraeus, "Agia Varvara" General Hospital of West Attica, Athens–Piraeus; Metaxa Memorial General Hospital; Evangelismos General Hospital, Athens, Greece

Abstract

Background Upadacitinib is a selective Janus kinase-1 inhibitor, approved for the management of Crohn's disease (CD) by the United States Food & Drug Administration. In Greece, upadacitinib was initially available through an early-access program. Our goal was to describe the real practice experience.

Methods This was a multicenter retrospective cohort study of patients with moderate-to-severe CD. The primary endpoint was clinical response, defined as a reduction ≥3 in the Harvey-Bradshaw index. Secondary endpoints included biochemical improvement. Outcomes were assessed at 4, 8 and 12 weeks.

Results A total of 24 CD patients received upadacitinib and were included in the analysis. Their mean age was 42.2 years (range 24-63). Eleven patients (45.8%) had ileocolonic CD and 5 (20.8%) CD colitis. Fourteen patients had active extraintestinal manifestations. The majority of patients (19/24) had ≥3 failed biologics. All of them had failed treatment with anti-tumor necrosis factor and 19 (79%) with ustekinumab. At 12 weeks, nearly all patients achieved a clinical response (85%). Of 13 patients with C-reactive protein >5 mg/L at baseline, 11 (84.6%) achieved normalization by week 8. Adverse events occurred in 3 patients (14.2%).

Conclusion In a small cohort of resistant CD patients, the short-term clinical efficacy of upadacitinib was high.

Keywords Upadacitinib, Crohn's disease, Greece

Ann Gastroenterol 2025; 38 (3): 306-310

Conflict of Interest: None

Correspondence to: Evgenia Papathanasiou, Vas Sofias 80 & Lourou, 11528 Athens, Greece, e-mail: evgeniapapathanasiou@gmail.com

Received 30 December 2024; accepted 16 April 2025; published online 28 April 2025

DOI: https://doi.org/10.20524/aog.2025.0969

Introduction

Crohn's disease (CD) is a chronic disease defined by transmural inflammation of the gastrointestinal tract [1]. Although its etiopathogenesis is not clear, a key role for environmental factors, inducing an aberrant immune response in genetically predisposed individuals, has been identified [2-4]. The disease is characterized by alternating periods of flare and remission. Disease management aims at controlling inflammation in both the short and long term. Treatment options have expanded over the past few years [5,6]. However, current treatment modalities are often unsuccessful

in more than half of CD patients worldwide [7]. Anti-tumor necrosis factor-α agents were the first available biologics for CD treatment, followed by anti-integrins and anti-interleukin 12/23 agents. Orally administered Janus kinase (JAK) inhibitors have recently been approved for a wide range of inflammatory conditions. Upadacitinib (UPA) is a selective JAK inhibitor, licensed for the treatment of rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis and inflammatory bowel disease [8,9]. In a phase 2, double-blind, randomized controlled trial (RCT), significantly more CD patients who received UPA achieved clinical remission compared to placebo [10]. A phase 3 RCT by Loftus *et al* [8] demonstrated that induction and maintenance therapy with UPA was superior to placebo in moderate-to-severe CD. Moreover, UPA maintained its superiority over placebo regarding all secondary endpoints, including quality-of-life outcomes. The aim of this study was to assess the effectiveness and safety of UPA in CD patients who have failed multiple treatments.

Materials and methods

Patient selection

This was a retrospective cohort study from 9 tertiary centers. Patients with CD who received at least 12 weeks of UPA between March 2022 and December 2023 were included. All patients had clinically active CD. UPA was available through an early-access program.

Demographic and clinical data

Data were collected from patients' medical records. The following patient- and disease-related data were included: age, sex, age at CD diagnosis, disease duration, disease phenotype (according to the Montreal classification), surgical history, smoking history, and prior treatment modalities (immunosuppressants, biologics and small molecules were considered advanced treatment). All data were registered in a standard form. A predefined treatment evaluation protocol was used to retrospectively collect disease activity scores using the Harvey-Bradshaw index (HBI). Laboratory results were recorded at baseline (before UPA initiation) and at weeks 4, 8 and 12 of follow up. Clinically active disease was defined as HBI≥5. Clinical response was defined as a decrease ≥3 in baseline HBI score. Clinical remission was defined as HBI<5. Corticosteroid-free clinical remission (CSFR) was defined as clinical remission in those patients not receiving any form of systemic corticosteroid at the specific time point. C-reactive protein (CRP) normalization was defined as below cutoff value. Fecal calprotectin (FCP) response and remission were empirically defined as <250 mg/g and <50 mg/g, respectively. Endoscopic data were scarce. Before initiation of treatment, activity was defined as lack of endoscopic remission, whereas after completion of induction, endoscopic improvement was based on a physician's assessment. Adverse events (AE) were recorded as treatment-related AE and serious AE, defined as any complication that led to a patient's hospitalization, surgery or death. The data were collected with the approval of each participating center's ethics committee.

Statistical analysis

For categorical variables, total counts and percentages are presented. Continuous variables that were normally distributed were represented as mean value ± standard deviation are presented, while for those not normally distributed, median values and interquartile range (IQR) were used. For the comparison of continuous variables, the parametric paired-sample t-test and the non-parametric Wilcoxon test were performed. A P-value of 0.05 was used as the threshold of statistical significance. Statistical analysis was performed using the statistical package SPSS 23 (IBM, Armonk, NY, USA).

Results

The analysis included a total of 24 CD patients, who received UPA and were followed up for at least 12 weeks (Table 1). Fourteen patients (58.3%) were female. Five patients (20.8%) were current smokers. The mean age at UPA initiation was 42.2±12.6 years and the mean age at CD diagnosis was 30.1±15.1 years. The mean disease duration was 11.5±8.3 years (Table 1). Eleven (45.8%) had ileocolonic disease (Montreal L3), whereas 5 (20.8%) had colonic disease (L2). In addition, 4 (16.6%) had perianal involvement (p), 3 (12.5%) fibrostenotic phenotype (B2), and 4 (16.6%) penetrating disease (B3). Seven (29.1%) had prior CD- related surgery.

Nine patients (37.5%) had received 4 and 19 (79%) 3 advanced therapies. All patients were exposed to at least 2 biologics. Specifically, 21 (87.5%) patients had been exposed to infliximab, 21 (87.5%) to adalimumab, 19 (79.2%) to

[a]Department of Gastroenterology, "Alexandra" General Hospital of Athens, Athens (Evgenia Papathanasiou, Alexandros Ioannou, Pavlos Pardalis, Giorgos Leonidakis, Spyridon Michopoulos, Evanthia Zampeli); [b]Department of Gastroenterology, "G. Gennimatas" General Hospital of Athens, Athens (George Michalopoulos); [c]Hepatogastroenterology Unit, 2nd Academic Department of Internal Medicine, Hippocration General Hospital of Athens, University of Athens Medical School (Spilios Manolakopoulos, Spyridon Siakavellas); [d]Department of Gastroenterology, Venizeleio General Hospital, Heraklion (Angeliki Theodoropoulou); [e]Academic Department of Internal Medicine, Hepatogastroenterology Unit, "Agioi Anargyroi" General and Oncology Hospital of Kifisia, National and Kapodistrian University of Athens (Athanasia Tasovasili); [f]Second Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki (Olga Giouleme); [g]Department of Gastroenterology, "Agios Panteleimon" General Hospital of Nikaia–Piraeus, "Agia Varvara" General Hospital of West Attica, Athens–Pireaus (Maria Tzouvala); [h]Department of Gastroenterology, Metaxa Memorial General Hospital (Eftychia Tsironi); [i]Department of Gastroenterology, Evangelismos General Hospital, Athens (Nikos Viazis), Greece

Table 1 Demographic characteristics

Characteristics	Value
Mean age years (±SD)	42.2±12.6
Mean age at IBD diagnosis (±SD)	30.1±15.1
Mean disease duration years (±SD)	11.5±8.3
Sex	
Female, n (%)	14 (58.3)
Male, n (%)	10 (41.6)
Smoking history	
Current, n (%)	5 (20.8)
Former, n (%)	3 (12.5)
History of bowel resection, n (%)	7 (29.1)
Disease phenotype	
Ileocolonic, n (%)	11 (45.8)
Colonic, n (%)	5 (20.8)
Ileal, n (%)	8 (33.3)
Perianal, n (%)	4 (16.6)
Non stricturing, non-fistulizing, n (%)	17 (70.8)
Fibrostenotic, n (%)	3 (12.5)
Penetrating, n (%)	4 (16.6)
EIMs, n (%)	14 (58.3)
Arthralgia, n (%)	13 (54.2)
Psoriasis, n (%)	1 (4.1)
Atopic dermatitis, n (%)	2 (8.2)
Medication history	
Biologic exposed, n (%)	100
Infliximab, n (%)	21 (87.5)
Adalimumab, n (%)	21 (87.5)
Ustekinumab, n (%)	19 (79.2)
Vedolizumab, n (%)	11 (45.8)
Ozanimod, n (%)	1 (4.1)
Guselkumab, n (%)	1 (4.1)
Certolizumab, n (%)	1 (4.1)
Etanercept, n (%)	1 (4.1)
Number of prior advanced therapies	
≥3 biologics, n (%)	19 (79.1)
4 biologics, n (%)	9 (37.5)
Concomitant CD-related medications on UPA initiation	
Steroids, n (%)	7 (29.2)
None, n (%)	17 (70.8)
UPA indication	
Active luminal disease, n (%)	21 (87.5)
Extraintestinal manifestation, n (%)	3 (5)

SD, standard deviation; IBD, inflammatory bowel disease; EIM, extraintestinal manifestation; CD, Crohn's disease; UPA, upadacitinib

ustekinumab and 11 (45.8%) to vedolizumab. Of the 24 patients, 21 (87.5%) were prescribed UPA for CD management and 3 (5%) for an additional indication. All patients received 45 mg UPA as an induction dose for 12 weeks, whereas the starting maintenance dose was planned to be 30 mg. Seven patients (29.2%) were on corticosteroids at onset. At baseline, mean HBI was 6.9 (IQR 5.5-8.5), mean CRP level was 22.45 mg/L (IQR 3-35 mg/L) and median FCP level was 470 mg/g (IQR 147-1010 mg/g).

At Week 4, follow-up data were available for 21 patients. Sixteen (76.19%) and 12 (57.1%) patients with active disease at baseline achieved clinical response or remission, respectively. Three out of 7 patients (42.8%) were weaned off steroids and achieved CSFR. At Week 8, follow-up data were available for 21 patients. All patients with clinically active disease at baseline achieved clinical remission, while 7 on steroids achieved CSFR. The median HBI decreased from 6.9 (IQR 5.5-8.5) at baseline, to 2 (IQR 0-4) at week 8. The median FCP level decreased from 470 mg/g (IQR 147-1010 mg/g) at baseline, to 165 mg/g (IQR 155-430 mg/g) at week 12. Of 11 patients with FCP >250 mg/g at baseline, 9 (81.8%) and 7 (63.6%) had values <250 and <50 mg/g, respectively, at week 8. The mean CRP decreased from 22.45 mg/L (IQR 3-35 mg/L) at baseline to 3.38 mg/L (IQR 2-4 mg/L) at week 8 (P=0.012). Of 13 patients with CRP >5 mg/L at baseline, 11 (84.6%) achieved normalization by week 8. At Week 12, follow-up data were available for 19 patients. With the exception of 1 patient who discontinued UPA because of a poor response, all had a clinical response at week 12. The mean HBI decreased to 0.83. No patient required steroids, whereas 8 underwent endoscopy, which showed improvement.

The mean HBI before UPA administration was 6.95±2.08, whereas the mean HBI after 12 weeks of treatment was 0.83±1.09 (Fig. 1A). We observed a significant decrease in HBI with a mean difference of 6.22±2.34 (95% confidence interval [CI] 5.05-7.38, P<0.001). The median FCP level was 470 mg/g (IQR 147-1010 mg/g) and after 12 weeks of treatment the median FCP was 165 mg/g. There was a significant reduction of 615±401.6 (95%CI 193.48-1036.1, P=0.013) (Fig. 1B). In addition, all patients showed a decrease in serum CRP levels: from mean CRP 22.45 mg/dL (IQR 3-35 mg/dL) at baseline to 3.75 mg/dL (IQR 1.75-4.75 mg/dL) at week 12 (P=0.009) (Fig. 1C).

At week 12, 4 of 5 patients (80%) with no small bowel disease (L2) achieved clinical remission. Among 19 patients with small intestinal involvement, 19 (100%) and 14 (74%) experienced clinical response and remission, respectively.

Safety data were available for all patients at week 12. Mild and reversible AE were observed in 3 patients (14.2%): neutropenia, acne and abdominal pain. No discontinuation due to AEs was recorded. There were no incidences of herpes zoster or other infections.

Discussion

This small case series provides solid evidence about the short-term efficacy and safety of UPA in difficult-to-treat CD. After 12 weeks of treatment, the vast majority of these refractory patients showed a clinical and biochemical response to UPA, without steroids. UPA was well tolerated and no serious AE were noted during an induction period of 12 weeks.

The efficacy of UPA was first evaluated in the CELEST study, a phase 2 multicenter randomized trial involving 220 patients, who were offered an immediate release formulation of UPA [10]. During the induction period, the dose of 24 mg twice daily demonstrated the best results, and 22% of patients achieved clinical and endoscopic remission.

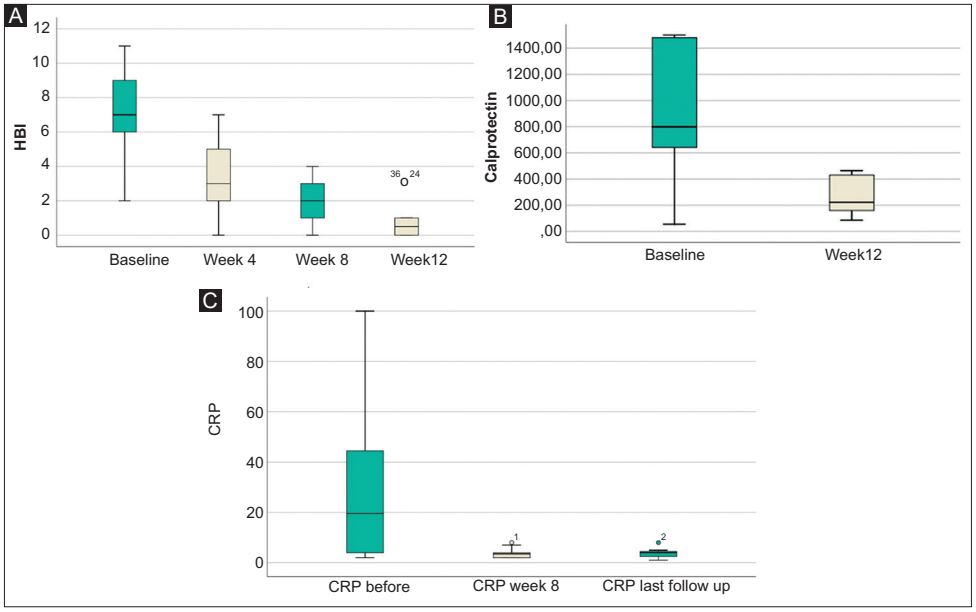

Figure 1 (A) Changes in Harvey-Bradshaw index (HBI) during follow up; (B) changes in fecal calprotectin during follow up; (C) changes in C-reactive protein (CRP) during follow up

Most recently, 2 Phase 3 clinical trials, the U-EXCEED and the U-EXCEL, have confirmed the efficacy of UPA in CD [11,12]. Patients in the intervention group achieved clinical remission rates of 39% and 49%, respectively, during the induction period [8].

The CELEST trial further proved that UPA in a maintenance dose of 12 mg twice daily, achieved high rates of clinical and endoscopic remission (up to 63% and 38%, respectively) at 52 weeks of surveillance [13]. A recent update of the trial confirms the long-term efficacy and safety of UPA [14].

The University of Chicago's induction experience was largely positive, as 70.6% achieved clinical remission (HBI<5), 64% achieved CRP remission and 62% achieved FCP remission [15]. The observed clinical remission rates for induction were higher compared with U-EXCEL (49.5%), U-EXCEED (38.9%) and a multicenter United States (US) cohort (27.2%). However, these were different cohorts with different methods for assessing clinical remission. The multicenter US cohort's lower clinical remission rates for induction may partially be explained by the fact that numerous patients received less than 45 mg daily for induction [13].

Our study had some limitations. The retrospective study design, the small sample size, the heterogeneity of follow up and the limited endoscopic data, narrow the power of our conclusions. On the other hand, we showed that UPA was highly efficient in inducing a clinical response in difficult-to-treat CD patients. Notably, almost 80% of our study population had failed at least 3 biologics with no less than 2 different mechanisms of action. This is not infrequent in everyday clinical practice, whereas these patients are usually excluded from clinical trials.

One may assume that such a potent drug is a suitable option as second-line and an equally good choice as first-line treatment in patients with severe CD. In our small series, patients managed to wean off steroids, which is another essential observation in favor of UPA. UPA, as a fast-acting agent, may be useful in cases of steroid contraindication or intolerance and perhaps as a short-term bridge to a less potent and safer agent in older patients or patients with comorbidities. Another interesting observation was the drug's good performance in colonic disease, although this needs to be confirmed in larger numbers of patients.

In conclusion, in this cohort of biologic-refractory CD patients, treatment with UPA showed excellent short-term efficacy.

Summary Box

What is already known:

- Upadacitinib is a second-generation, selective Janus kinase (JAK) inhibitor, approved by the United States Food & Drug Administration, for treating various chronic inflammatory conditions
- Upadacitinib is the only JAK inhibitor approved for Crohn's disease (CD) and the first advanced oral treatment option for patients with CD
- Real-world efficacy and safety data are of critical importance

What the new findings are:

- Upadacitinib demonstrated high rates of clinical response in difficult-to-treat CD patients
- No new safety signals were identified
- The benefit profile of upadacitinib supports its use and further study in CD patients

References

1. Chang JT. Pathophysiology of inflammatory bowel diseases. *N Engl J Med* 2020;**383**:2652-2664.
2. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017;**389**:1741-1755.
3. Veauthier B, Hornecker JR. Crohn's disease: diagnosis and management. *Am Fam Physician* 2018;**98**:661-669.
4. Avedillo-Salas A, Corral-Cativiela S, Fanlo-Villacampa A, Vicente-Romero J. The efficacy and safety of biologic drugs in the treatment of moderate-severe Crohn's disease: a systematic review. *Pharmaceuticals (Basel)* 2023;**16**:1581.
5. Bastida G, Garrido A, Valero E, del Pozo P. Crohn's disease. *Medicine* 2020;**13**:603-612.
6. Yebra Carmona J, Poza Cordón J, Suárez Ferrer C, et al. Correlation between endoscopy and intestinal ultrasound for the evaluation of postoperative recurrence of Crohn's disease. *Gastroenterol Hepatol* 2022;**45**:40-46.
7. Sulz MC, Burri E, Michetti P, Rogler G, Peyrin-Biroulet L, Seibold F; on behalf of the Swiss IBDnet, an official working group of the Swiss Society of Gastroenterology. Treatment algorithms for Crohn's disease. *Digestion* 2020;**101**(Suppl 1):43-57.
8. Loftus EV Jr, Panés J, Lacerda AP, et al. Upadacitinib induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2023;**388**:1966-1980.
9. Parmentier JM, Voss J, Graff C, et al. *In vitro* and *in vivo* characterization of the JAK1 selectivity of upadacitinib (ABT-494). *BMC Rheumatol* 2018;**2**:23.
10. Sandborn WJ, Feagan BG, Loftus EV Jr, et al. Efficacy and safety of upadacitinib in a randomized trial of patients with Crohn's disease. *Gastroenterology* 2020;**158**:2123-2138.
11. Upadacitinib (RINVOQ®) achieved primary and key secondary endpoints in first Phase 3 induction study in patients with Crohn's disease. North Chicago, IL: AbbVie Inc.; 2021. Available from: https://news.abbvie.com/2021-12-06-Upadacitinib-RINVOQ-R-Achieved-Primary-and-Key-Secondary-Endpoints-in-First-Phase-3-Induction-Study-in-Patients-with-Crohns-Disease [Accessed 28 April 2025].
12. Second Phase 3 induction study confirms upadacitinib (RINVOQ®) improved clinical and endoscopic outcomes in patients with Crohn's disease. North Chicago, IL: AbbVie Inc.; 2022. Available from: https://news.abbvie.com/2022-02-24-Second-Phase-3-Induction-Study-Confirms-Upadacitinib-RINVOQ-R-Improved-Clinical-and-Endoscopic-Outcomes-in-Patients-with-Crohns-Disease [Accessed 28 April 2025].
13. Chugh R, Braga-Neto MB, Fredrick TW, et al. Multicentre real-world experience of upadacitinib in the treatment of Crohn's disease. *J Crohns Colitis* 2023;**17**:504-512.
14. D'Haens G, Panés J, Louis E, et al. Upadacitinib was efficacious and well-tolerated over 30 months in patients with Crohn's disease in the CELEST extension study. *Clin Gastroenterol Hepatol* 2022;**20**:2337-2346.
15. Friedberg S, Choi D, Hunold T, et al. Upadacitinib is effective and safe in both ulcerative colitis and Crohn's disease: prospective real-world experience. *Clin Gastroenterol Hepatol* 2023;**21**:1913-1923.