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Effectiveness and Safety of a Second JAK Inhibitor in Ulcerative Colitis: The J2J Multicentre Study

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ABSTRACT

Background: While three Janus kinase inhibitors (JAKi) have demonstrated efficacy in ulcerative colitis (UC), scarce data exist regarding JAKi intraclass switching.

Aim: To evaluate the effectiveness and safety of a second JAK inhibitor in UC.

Methods: This was a multicentre, retrospective, observational cohort including patients with moderate to severe UC who received a second-line of JAKi after failure or intolerance of a first. The primary outcome was steroid-free clinical remission (SFCR) at Weeks 8–14, defined as a partial Mayo score of 2 or less with no individual sub-score above 1.

Results: Among the 169 patients from 28 participating centres, 105 received upadacitinib, 54 filgotinib and 10 tofacitinib as a second-line of JAKi. Overall, 81/169 achieved SFCR at Weeks 8–14: 58/105 with upadacitinib, 18/54 with filgotinib and 5/10 with tofacitinib ($p = 0.03$). In the multivariate analysis, upadacitinib was independently associated with higher odds of SFCR than filgotinib (OR = 3.15, 95% CI [1.52–6.79]). With a median follow-up duration of 96 days, drug persistence at 6 months was 72.8% with upadacitinib, 57.2% with filgotinib and 66.7% with tofacitinib ($p = 0.099$). 24.3% of patients (41/169) experienced at least one adverse event leading to treatment withdrawal in 9 patients (5%). No cases of death, cancer, or major acute cardiovascular events were reported.

Conclusion: A second-line of JAKi provided clinical remission in about half of patients after induction, and was well tolerated.

1 | Introduction

Janus Kinase inhibitors (JAKi) are small molecules that act intracellularly by blocking the JAK-signal transducer of activators of transcription (STAT) signalling pathway, thereby inhibiting several inflammatory pathways and blocking the production of numerous pro-inflammatory cytokines. There are three FDA- and EMA-approved molecules with distinct JAK selectivity profiles [1]. Tofacitinib is a pan-JAKi, while filgotinib and upadacitinib are two selective JAK1 inhibitors.

Investigator group is listed in "Appendix" section.

For affiliations refer to page 9.

These three drugs have demonstrated their efficacy in treating ulcerative colitis (UC) through randomised controlled phase 3 trials [2–4] and real-world cohort studies [5–8]. They are orally administered with a quick mechanism of action and are effective on extra-intestinal symptoms, particularly joints. However, recent safety concerns have emerged regarding JAKi, particularly a potential increased risk of cardiovascular events and cancer [9].

Although the therapeutic armamentarium has been expanding with an increasing number of available treatments and different mechanisms of action to treat patients with UC, a significant proportion of patients remain refractory [10], and end up in surgery. In cases of multiple treatment failure, one potential strategy is to initiate a new drug with a previously experienced mode of action. This intra-class switching approach has long been utilised in inflammatory bowel diseases (IBD), particularly with anti-tumour necrosis factor (TNF) agents [11, 12]. However, only scarce data exist regarding JAKi intra-class switching. Indeed, to date, there is limited data investigating the efficacy and safety of a JAKi in UC previously exposed to another JAKi. Therefore, we conducted a study with the aim of evaluating the effectiveness and safety of a second JAKi in patients with UC.

2 | Methods

2.1 | Study Design

The JAKi after JAKi (J2J) study was a multicentre, retrospective, observational cohort studying the effectiveness and safety of a second-line of JAKi in patients with active moderate-to-severe UC who have already been exposed to a first line of JAKi.

This study was coordinated by the GETAID (Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif), across 28 Belgian and French centres. Patients were retrospectively recruited from July 2019 to December 2024. Data were collected via a shared platform using a questionnaire completed by the medical research teams from the different centres. Data were collected until last news or loss of follow-up. A minimum of 8 weeks of follow-up was required to be eligible. The study was made in accordance with local ethical regulatory rules (MR004).

2.2 | Patients

Consecutive adults with UC who experienced failure or intolerance with a first JAKi (tofacitinib, filgotinib, or upadacitinib) and were subsequently treated with another JAKi—either tofacitinib, filgotinib, or upadacitinib—were eligible. Additional inclusion criteria were active UC regardless of its extent (defined as a partial Mayo score of at least 3).

Exclusion criteria included diagnosis of Crohn's disease, ileoanal anastomosis, the presence or suspicion of malignancy and history of neoplasia other than basal carcinoma of the skin or carcinoma in situ of the cervix.

Baseline corresponded to the first day of initiation of the second JAKi.

2.3 | Outcome Measures

The primary outcome was steroid-free clinical remission after induction (SFCR) (Weeks 8–14), defined as a partial Mayo score of 2 or less with no individual sub-score above 1.

Secondary endpoints included clinical remission and response at Weeks 8–14. Clinical response was defined by a decrease of at least 30% of the partial Mayo score from baseline. Biomarkers (CRP and faecal calprotectin) were collected when available, and rates of colectomy were reported. Additionally, we assessed factors associated with treatment success.

A safety analysis was performed by studying adverse events. Severe adverse events were defined as adverse events requiring hospitalisation and/or treatment discontinuation.

2.4 | Statistical Analysis

Categorical variables were described as percentages, while continuous variables were reported as medians (interquartile range (IQR)). The proportions between groups were compared using a chi squared test or Fisher exact test when expected counts were < 5. We also assessed the persistence rates of second-line treatments using the Kaplan–Meier method and a log-rank test. A logistic regression analysis was conducted to examine the factors associated with achieving SFCR. Continuous variables were imputed using their respective means. Variables with a p-value of 0.10 or less in the univariate logistic regression, with less than 30 missing data, were included in the multivariate analysis. Analyses were done with R (version 4.4.0). Statistical significance was interpreted by a 95% confidence interval (CI) and p-value < 0.05.

3 | Results

3.1 | Baseline Characteristics

Among the 179 eligible patients, 10 were excluded due to missing data at baseline ($n = 2$) or at evaluation at Weeks 8–14 ($n = 8$). A total of 169 patients were analysed and followed with a median follow-up duration of 96 days (IQR [62.8–309.5]).

Among them, 38% were women ($n = 65$), with a median age at inclusion of 34.6 years (IQR [26.4–46.8]), and a median age at diagnosis of UC of 24 years (IQR [18.4–35.6]). At the time of second JAKi initiation, the median disease duration was 7.4 years (IQR [4.2–12.6]). More than half of the patients included (50.9%) had extensive E3 disease, and 93.5% had been exposed to at least two biologics (excluding JAKi) at baseline.

In the overall cohort, 67.5% of patients received tofacitinib as first JAKi, 27.2% received filgotinib and 5.3% received upadacitinib. Discontinuation of the first JAKi occurred due to loss of response in 57% and primary failure in 39%. The median

duration of the first course of JAKi was 162 days (IQR [82–362.5]). Of 169 included patients, 105 received upadacitinib as second-line JAKi, 54 received filgotinib and 10 received tofacitinib (Figure S1). The median partial Mayo score at baseline was 6 [5–8]. Baseline patient characteristics are shown in Table 1.

3.2 | Primary Outcome

SFCR was achieved in 81 (47.9%) patients at Weeks 8–14. In the group receiving upadacitinib as a second-line JAKi, SFCR was achieved in 58 patients (55.2%). In the group receiving filgotinib as a second-line JAKi, SFCR occurred in 18 patients (33.3%). SFCR rate was at 5 (50%) in the tofacitinib group. The rate of SFCR was significantly higher in the upadacitinib group as compared to filgotinib ($p = 0.0088$, chi squared test). No statistically significant differences were found when comparing other groups (upadacitinib vs. tofacitinib, $p = 1$; filgotinib vs. tofacitinib: $p = 0.52$) (Figure 1A).

Within the subgroup of patients treated with upadacitinib, 32 (49.2%) patients who received tofacitinib previously achieved SFCR, whereas 26 (65%) in those who received filgotinib ($p = 0.16$).

Focusing on patients who received tofacitinib as first JAKi, 17 (34.7%) patients treated with filgotinib in second-line reached SFCR after induction compared to 32 (49.2%) for patients treated with upadacitinib in second-line ($p = 0.12$).

3.3 | Secondary Outcomes

At Weeks 8–14, 118 patients (69.8%) presented a clinical response, and 104 patients (61.5%) had a clinical response without steroids. Similarly, 89 patients (52.7%) were in clinical remission. Details across treatment groups are presented in Figure 1B–D.

During the follow-up period, 52 patients discontinued treatments: 19 patients on upadacitinib (18%), 29 patients on filgotinib (54%) and 4 patients on tofacitinib (40%).

In the overall population, the median CRP dropped from 5 mg/L (IQR [1.7–14], $n = 138$) to 2 (IQR [1–6.4], $n = 114$). Regarding faecal calprotectin, it went from 721 µg/g (IQR [390–1800], $n = 43$) to 748 (IQR [92–1767], $n = 38$).

Among the 52 patients who discontinued the treatment in the overall cohort, the same number of patients—21 (40.4%) – stopped due to primary failure and secondary failure. Primary failure was the most common case of discontinuation in the upadacitinib group, accounting for 52.6% of cases. Secondary failure was the leading cause of treatment withdrawal in the filgotinib and tofacitinib groups. Causes of treatment withdrawal are presented in Table 2.

3.4 | Persistence

Regarding treatment persistence, in the overall cohort, the survival without treatment withdrawal at 6 months was 64% (95% CI [55.3–74.1]). It was estimated at 72.8% (95% CI [61.8–85.7]), 57.2% (95% CI [44.7–73.2]) and at 66.7% (95% CI [36.2–100]) at 6 months for upadacitinib, filgotinib and tofacitinib, respectively ($p = 0.099$) (Figure 2).

3.5 | Factors Associated With Treatment Success

In univariate logistic regression, steroids at baseline (odds ratio (OR) = 0.28, 95% CI [0.12–0.58]) were significantly inversely associated with SFCR. Regarding first JAKi, tofacitinib was associated with less chance of SFCR than filgotinib (OR = 0.48, 95% CI [0.24–0.97]). Type of second-line JAKi was also significantly associated with SFCR in the univariate analysis. Details of the univariate logistic regression are presented in Table 3.

In multivariate analysis, steroids at baseline (OR = 0.24, 95% CI [0.10–0.54], $p < 0.001$), type of second JAKi and ileorectal anastomosis (OR = 0.10, 95% CI [0.01–0.69], $p = 0.017$) were independent factors associated with SFCR. Regarding second-line JAKi, upadacitinib had significantly better odds of SFCR than filgotinib (OR = 3.15, 95% CI [1.52–6.79]) while there was no significant difference between filgotinib and tofacitinib (OR = 2.13, 95% CI [0.49–9.53]) (Table 4).

3.6 | Safety

Forty one patients (24.3%) experienced at least one adverse event, and a total of 47 adverse events were observed. The most commonly observed adverse events were infections (7.7% of patients) and dermatological lesions (8.3% of patients): 13 infections were reported in total, including 8 with upadacitinib and 5 with filgotinib, and 14 patients presented dermatological lesions, including 11 with upadacitinib. Acne was the most frequent skin manifestation (9 out of 14 skin lesions) and was particularly observed with upadacitinib (7.6% of patients on upadacitinib).

Two cases of ophthalmic herpes zoster were found in the upadacitinib group that did not lead to treatment permanent withdrawal. Dyslipidemia was detected in two patients, one with tofacitinib and one with filgotinib. Details of adverse events are displayed in Table 5.

Nine patients (5%) presented a severe adverse event requiring discontinuation of treatment (Table 5). Among them, four occurred with upadacitinib and five with filgotinib.

During follow-up, 11 colectomies were performed (7% of patients): 9 with upadacitinib and 2 with tofacitinib. No cases of death, neoplasia, or major acute cardiovascular events were reported.

4 | Discussion

Here we report the largest experience to date of intraclass switching of JAKi. We show that 47.9% of patients present a SFCR after the induction period. Moreover, using a multivariate analysis model, we report that steroids at baseline as well as ileorectal anastomosis were independently associated with

TABLE 1 | Patient characteristics at baseline.

Patient characteristics at baseline	Overall $N=169$	Upadacitinib $N=105$	Filgotinib $N=54$	Tofacitinib $N=10$
Women, *n* (%)	65 (38)	39 (37)	24 (44)	2 (20)
Age at UC diagnosis (in years), median [IQR]	24 [18.4–35.6]	25.7 [20–38.2]	23.6 [17.4–31]	21.1 [17.6–33.1]
Age at inclusion (in years), median [IQR]	34.6 [26.4–46.8]	35.6 [29–47.5]	31.9 [25.2–42]	32.2 [21.9–45.9]
Disease duration at baseline (in years), median [IQR]	7.4 [4.2–12.6]	7.7 [4.2–12.4]	7.4 [4.4–12.5]	3.8 [2.4–15.4]
Disease extent				
E1	12 (7)	4 (3)	7 (13)	1 (10)
E2	68 (40)	42 (40)	20 (37)	6 (60)
E3	86 (50)	57 (54)	26 (48)	3 (30)
Smoking status				
Active smoker	9 (5.3)	5 (4.8)	2 (3.7)	2 (20)
Extra-intestinal manifestation ≥ 1	40 (23.7)	24 (22.9)	14 (25.9)	2 (20)
Previous drug exposure (excluding JAKi)				
Oral 5-ASA	130 (77)	86 (82)	39 (72)	5 (50)
Systemic steroids	136 (81)	84 (80)	44 (82)	8 (80)
Thiopurines	116 (69)	76 (72)	36 (67)	4 (40)
Methotrexate	31 (18)	17 (16)	13 (24)	1 (10)
Infliximab	143 (85)	92 (88)	44 (82)	7 (70)
Adalimumab	89 (53)	56 (53)	29 (54)	4 (40)
Golimumab	41 (24)	25 (24)	15 (28)	1 (10)
Vedolizumab	144 (86)	89 (85)	46 (85)	9 (90)
Ustekinumab	119 (71)	74 (71)	39 (72)	6 (60)
Exposure ≥ 2 biologics	158 (93)	99 (94)	50 (93)	9 (90)
Ileo-rectal anastomosis	7 (4)	3 (3)	4 (7)	0
First line of JAKi				
Tofacitinib	114 (68)	65 (62)	49 (91)	—
Filgotinib	46 (27)	40 (38)	—	6 (60)
Upadacitinib	9 (5)	—	5 (9)	4 (40)
Reason for discontinuation of the first JAKi				
Primary failure	65 (39)	40 (38)	20 (37)	5 (50)
Secondary failure	97 (57)	63 (60)	32 (59)	2 (20)
Adverse event	5 (3)	2 (2)	1 (2)	2 (20)
Other	2 (1)	0 (0)	1 (2)	1 (10)
Median duration of exposure to the first JAKi (days)	162 [82–362.5]	162 [73.3–407.5]	184 [108–307]	75 [62.3–118.3]
Median time (days) between the two lines of JAKi	16 [1–235]	5 [1–132.5]	130 [2.5–529.8]	4.5 [1.5–105.8]
Concomitant drug exposure at baseline, *n* (%)				
None	91 (54)	54 (51.4)	31 (57.4)	6 (60)
Systemic steroids	43 (25)	31 (29.5)	10 (18.5)	2 (20)

(Continues)

TABLE 1 | (Continued)

Patient characteristics at baseline	Overall $N=169$	Upadacitinib $N=105$	Filgotinib $N=54$	Tofacitinib $N=10$
≥20 mg	34 (20.1)	24 (22.8)	8 (14.8)	2 (20)
<20 mg	7 (4.1)	6 (5.7)	1 (1.9)	0 (0)
Oral 5-ASA	24 (14)	15 (14.3)	7 (13.0)	2 (20)
CRP, median [IQR]	5 [1.7–14]	5.8 [2.1–12.3]	4 [1.1–14]	5.5 [1.7–19.3]
n = data available	$n=138$	$n=88$	$n=42$	$n=8$
Faecal calprotectin, median [IQR]	721 [390–1800]	1000 [500–1800]	647 [371–1701]	380.5 [310–1296]
n = data available	$n=43$	$n=25$	$n=14$	$n=4$
Partial Mayo score, median [IQR]	6 [5–8]	6 [5–8]	6 [5–7]	7 [5.3–7]
UCEIS, median [IQR]	5 [4–6]	5 [4–6]	4 [3–5]	4 [4–5]
n = data available	$n=94$	$n=65$	$n=24$	$n=5$

Abbreviations: 5-ASA = 5-aminosalicylic acid, CRP = C-reactive protein, JAKi = Janus Kinase inhibitor, UC = ulcerative colitis, UCEIS = Ulcerative Colitis Endoscopic Index of Severity.

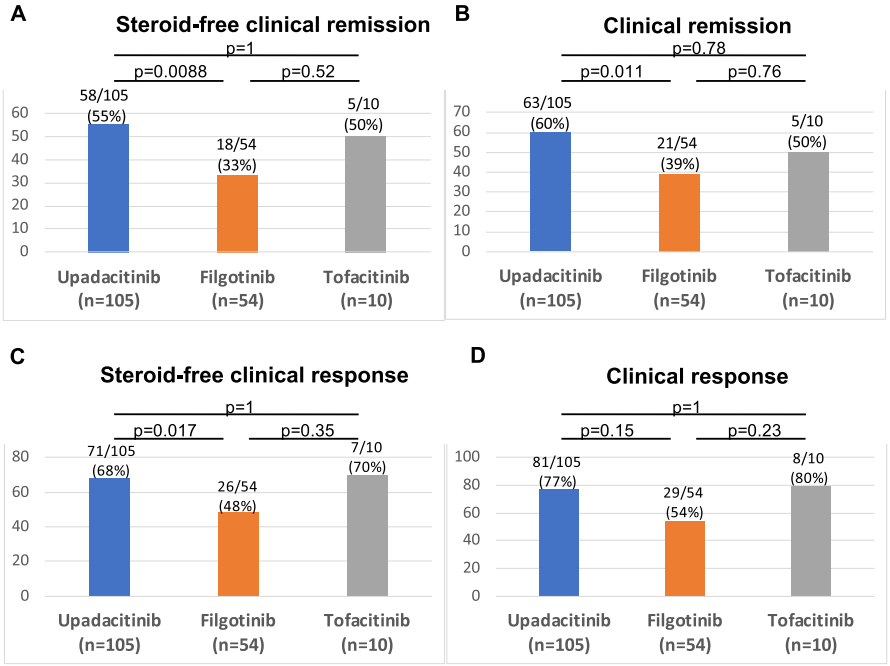

FIGURE 1 | Clinical remission and response rated at Weeks 8–14. (A) Steroids-free clinical remission. (B) Clinical remission. (C) Steroids-free clinical response. (D) Clinical response.

TABLE 2 | Reason for discontinuation of second-line JAKi.

Reason for discontinuation of second-line JAKi, N (%)	Overall $N=52/169$ (31)	Upadacitinib $N=19/105$ (18)	Filgotinib $N=29/54$ (54)	Tofacitinib $N=4/10$ (40)
Primary failure, n (%)	21 (40.4)	10 (52.6)	10 (34.5)	1 (25)
Secondary failure	21 (40.4)	5 (26.3)	13 (44.8)	3 (75)
Adverse event/intolerance	9 (17.3)	4 (21)	5 (17.2)	0 (0)
Other, n (%)	1 (1.9)	0	1 (3.4)	0 (0)

a poorer outcome while second-line upadacitinib was associated with a higher rate of treatment success when compared to filgotinib.

Previous studies including patients with second-line JAKi presented similar results regarding the highest level of efficacy demonstrated by upadacitinib. Indeed, Akiyama et al.

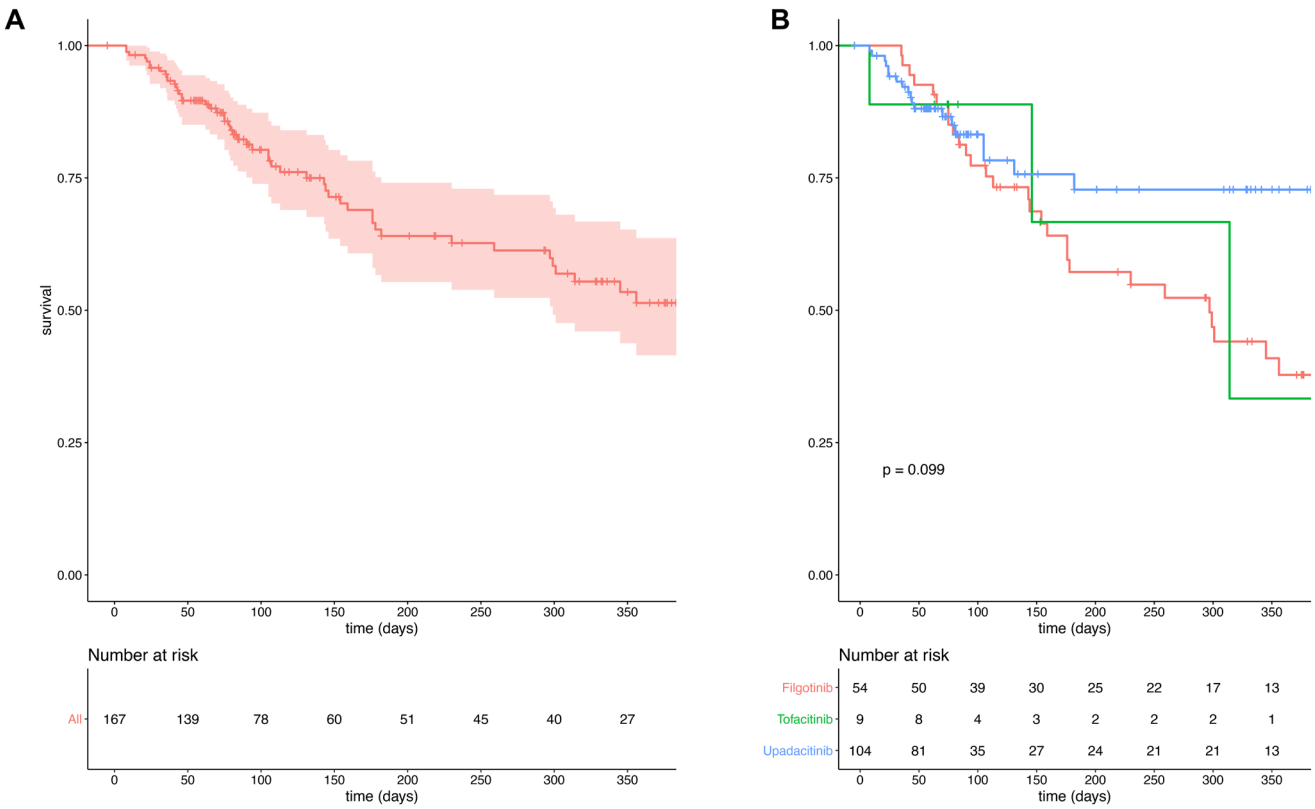

FIGURE 2 | Survival without second-JAK inhibitor discontinuation. Survival was estimated within the Kaplan–Meier analysis for the overall cohort (A) or according to type of second-line JAKi (B).

reported outcomes for 92 patients treated with upadacitinib after prior exposure to other JAKi, including tofacitinib ($n = 31$), filgotinib ($n = 54$), or both ($n = 7$). Among these patients, clinical remission was achieved in 57.3% (43/75) at Week 10 and 82.9% (34/41) at Week 58. Regarding filgotinib, 21 patients received treatment following previous JAKi exposure: tofacitinib ($n = 19$), upadacitinib ($n = 1$), or both ($n = 1$). Clinical remission rates for filgotinib were 28.6% (4/14) at Week 10 and 62.5% (5/8) at Week 58 [5].

Additional smaller observational studies have evaluated JAKi use in patients previously treated with another JAKi, primarily focusing on upadacitinib in individuals refractory to tofacitinib. For instance, Levine et al. reported that 36% of 16 tofacitinib-refractory patients achieved both clinical remission and SFCR with upadacitinib [13]. The real-world study by Friedberg et al. found in a subgroup of nine patients exposed to tofacitinib that upadacitinib showed efficacy, with a clinical remission rate of 77.8% at Week 8 [8].

Similarly, Gilmore et al. provided real-world data from a multicentre Australian study on upadacitinib. Among 152 patients, 42 had prior exposure to tofacitinib, with clinical remission rates of 24% (10/42) at baseline and 72% (30/42) at Week 8. In comparison, tofacitinib-naïve patients had remission rates of 19% (21/110) at baseline and 78% (86/110) at Week 8, with no statistically significant difference between the groups ($p = 0.17$) [14].

Another study from the UK presented by Danso et al. [15] reported an overall rate of steroids-free clinical remission at 48.8% (40 out of 82 patients) after induction with a second JAKi consistent with our findings.

Outside of the second-line, it was demonstrated in several indirect and direct comparisons that upadacitinib may be the best-in-class in terms of effectiveness [16, 17].

It is interesting to note that upadacitinib may be as efficient as first-line or second-line JAKi. In their real-world study, Boneschansker et al. found a similar remission rate with upadacitinib between patients already exposed to JAKi and those naïve to JAKi (42% vs. 39%; OR, 0.79; 95% CI, 0.08–7.96) [16].

Although both filgotinib and upadacitinib are designed to preferentially inhibit JAK1, they do not exhibit identical biological activity, as demonstrated by Traves et al. Indeed, in vitro studies have shown that the potency and selectivity of JAKi to block specific JAK–STAT pathways vary between agents. This variability also depends on the cell type and the cytokine stimulus [18].

In addition, our study shows that second-line JAKi is well tolerated, with more than 75% of patients having no side-effects during follow-up. The most common adverse events were infections (7.7% of patients) and dermatological lesions (8.3% of patients), but these were mainly mild and did not result in hospitalisation. Only nine patients (5% of the total sample) had to discontinue second-line JAKi due to adverse events. Notably, two patients developed ophthalmic zoster; however, both were able to resume upadacitinib, which remained effective in treating

TABLE 3 | Factors associated with steroid-free clinical remission after induction.

Characteristics	*N*	OR	95% CI	*p*
Sex	169			0.7
Woman		—	—	
Man		0.90	0.48, 1.68	
Smoking status	168			0.6
Active		—	—	
Never		0.65	0.15, 2.58	
Past smoker		0.93	0.20, 3.99	
History of extra intestinal manifestation	169			0.4
At least one		—	—	
None		1.33	0.65, 2.76	
Age at diagnosis	168	1.07	0.96, 1.20	0.2
Age at inclusion	168	1.40	0.80, 2.50	0.2
Disease extent	154			0.9
E2		—	—	
E1		1.06	0.29, 4.01	
E3		0.86	0.44, 1.66	
Ileorectal anastomosis	169			0.055
No		—	—	
Yes		0.17	0.01, 1.03	
Past exposure to 2 or more biotherapies at inclusion	168			0.6
No		—	—	
Yes		1.34	0.49, 3.86	
First line JAKi	169			0.12
Filgotinib		—	—	
Tofacitinib		0.48	0.24, 0.97	
Upadacitinib		0.51	0.11, 2.19	
Reason for first JAKi withdrawal	169			0.18
Primary failure		—	—	
Secondary failure		1.44	0.76, 2.72	
Adverse event/ intolerance		3.52	0.70, 25.86	
Second-line JAKi	169			0.030
Filgotinib		—	—	
Tofacitinib		2.00	0.50, 8.08	
Upadacitinib		2.47	1.26, 4.97	
Duration of first line JAKi	163	1.02	1.00, 1.05	0.10
UC duration	169	0.93	0.76, 1.08	0.4
Systemic steroids at baseline	169	0.28	0.12, 0.58	<0.001
Oral 5-ASA at baseline	169	0.74	0.30, 1.77	0.5
Partial Mayo at baseline	169	0.85	0.70, 1.02	0.077
C-reactive protein at baseline	138	0.92	0.81, 1.01	0.073
Albumin level at baseline	77	1.26	0.84, 1.98	0.3
Faecal calprotectin at baseline	43	1.03	1.00, 1.06	0.060

Note: Results from the logistic regression univariate analysis.
Abbreviations: CI = confidence interval, OR = unadjusted odds ratio.

TABLE 4 | Independent factors associated with steroid-free clinical remission after induction.

Characteristics	OR	95% CI	*p*
Duration of first line JAKi	1.01	0.98, 1.05	0.4
Steroids at baseline	0.24	0.10, 0.54	<0.001
Partial Mayo at baseline	0.85	0.69, 1.05	0.13
Second-line JAKi			
Filgotinib	—	—	0.008
Tofacitinib	2.13	0.49, 9.53	
Ileorectal anastomosis			
No	—	—	0.017
Yes	0.10	0.01, 0.69	

Note: Results from the logistic regression multivariate analysis.
Abbreviations: CI = confidence interval, OR = odds ratio.

their UC. Neither patient had received the recombinant VZV vaccine, as it was not reimbursed in France at the time.

The strategy of using a second JAKi has also been explored and reported in rheumatoid arthritis. In a real-world study involving 400 patients with rheumatoid arthritis previously treated with a JAKi, switching to a second JAKi was associated with higher drug retention compared to switching to an anti-TNF [19].

Our study has several strengths, including its multicentre recruitment and large sample size, with 169 patients included. It

TABLE 5 | Adverse events under second-line JAKi: total sample and by type of second-line JAKi received.

Adverse events under second-line JAKi	Total sample (*N* = 169)	Upadacitinib (*N* = 105)	Filgotinib (*N* = 54)	Tofacitinib (*N* = 10)
None, *n* (%)	128 (75.7)	81 (77.1)	39 (72.2)	8 (80)
Infection, *n* (%)	13 (7.7)	8 (7.6)	5 (9.2)	0 (0)
• Campylobacter colitis	1 (0.6)	1 (1)	0 (0)	
• CMV colitis	3 (1.8)	1 (1)	2 (3.7)	
• HSV	1 (0.6)	1 (1)	0 (0)	
• Ophthalmic zoster	2 (1.2)	2 (1.9)	0 (0)	
• Acute bacterial pyelonephritis	1 (0.6)	0 (0)	1 (1.9)	
• Others	5 (3.0)	3 (2.9)	2 (3.7)	
Dermatological lesions excluding shingles	14 (8.3)	11 (10.5)	3 (5.6)	0 (0)
• Acne, *n* (%)	9 (5.3)	8 (7.6)	1 (1.9)	
• Other skin lesions, *n* (%)	5 (3.0)	3 (2.9)	2 (3.7)	
Diffuse interstitial lung disease, *n* (%)	1 (0.6)	1 (1)	0 (0)	0 (0)
External hemorrhoidal thrombosis, *n* (%)	1 (0.6)	0 (0)	0 (0)	1 (10)
Dyslipidemia, *n* (%)	2 (1.2)	0 (0)	1 (1.9)	1 (10)
Hepatic cytolysis, *n* (%)	1 (0.6)	1 (1)	0 (0)	0 (0)
Abdominal pain, *n* (%)	3 (1.8)	2 (1.9)	1 (1.9)	0 (0)
Nausea, *n* (%)	2 (1.2)	0 (0)	2 (3.7)	0 (0)
Headache, *n* (%)	1 (0.6)	0 (0)	1 (1.9)	0 (0)
Dizziness, *n* (%)	1 (0.6)	0 (0)	1 (1.9)	0 (0)
Asthenia, *n* (%)	5 (3.0)	2 (1.9)	3 (5.6)	0 (0)
Others, *n* (%)	3 (1.8)	2 (1.9)	1 (1.9)	0 (0)
Adverse events requiring discontinuation of JAKi, *n* (%)	9 (5.3)	4 (3.8)	5 (9.3)	0 (0)
• Diffuse interstitial lung disease	1 (0.6)	1 (1.0)	0 (0)	
• Dizziness	1 (0.6)	0 (0)	1 (1.9)	
• Dermatological and mucosal lesions excluding shingles	3 (1.8)	1 (1.0)	2 (3.7)	
• Fever, abdominal pain	1 (0.6)	1 (1.0)	0 (0)	
• Recurrent infections	1 (0.6)	0 (0)	1 (1.9)	
• Others (unspecified)	2 (1.2)	1 (1.0)	1 (1.9)	

is a real-world study, making the results highly translatable to routine clinical practice.

However, the study also has limitations. The sample size was insufficient to analyse each specific JAKi sequencing strategy in detail, particularly for patients who received upadacitinib as a first-line treatment and tofacitinib as a second-line therapy. Additionally, our study is subject to the inherent limitations of real-world retrospective observational studies, including missing data on faecal calprotectin and endoscopic outcomes. Another limitation is the lack of long-term follow-up data.

In the future, further analyses with a larger number of patients in each specific subgroup and extended follow-up will be necessary to refine our findings.

In conclusion, our multicentre, real-world study demonstrated that approximately half of patients with multi-refractory UC benefited from a second JAKi after induction, with higher remission rates observed with upadacitinib. This effectiveness is accompanied by an acceptable safety profile. Further prospective studies are needed to refine sequencing strategies in UC, particularly for patients who have been exposed to multiple lines of advanced therapies.

Author Contributions

Mathilde Osty: investigation, writing – original draft. **Romain Altwegg:** investigation, writing – review and editing. **Mélanie Serrero:** investigation, writing – review and editing. **Alban Benezech:** investigation, writing – review and editing. **Albane Lecomte:** investigation, writing – review and editing. **Guillaume Cadiot:** investigation, writing – review and editing. **Lucine Vuitton:** writing – review and editing, investigation. **Anne Wampach:** investigation, writing – review and editing. **Stéphane Nancey:** investigation, writing – review and editing. **Anthony Buisson:** investigation, writing – review and editing. **Catherine le Berre:** investigation, writing – review and editing. **Clea Rouillon:** investigation, writing – review and editing. **Cyrielle Gilletta:** investigation, writing – review and editing. **Felix Goutorbe:** investigation, writing – review and editing. **Mathurin Fumery:** investigation, writing – review and editing. **Nassim Hammoudi:** investigation, writing – review and editing. **Ludovic Caillo:** investigation, writing – review and editing. **Mathias Vidon:** investigation, writing – review and editing. **Nadia Arab:** investigation, writing – review and editing. **Gaelle Sickersen:** investigation, writing – review and editing. **Maryan Cavicchi:** investigation, writing – review and editing. **Sophie Vieujean:** investigation, writing – review and editing. **Maeva Charkaoui:** investigation, writing – review and editing. **Nicolas Richard:** investigation, writing – review and editing. **Pauline Wils:** investigation, writing – review and editing. **Bénédicte Caron:** investigation, writing – review and editing. **Aurélien Amiot:** investigation, writing – review and editing. **Alexandre Nuzzo:** investigation, writing – review and editing. **David Laharie:** investigation, writing – review and editing. **Julien Kirchgesner:** investigation, writing – review and editing, methodology, formal analysis, data curation. **Mathieu Uzzan:** investigation, conceptualization, writing – review and editing, formal analysis, methodology, data curation, supervision.

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Conflicts of Interest

M.U. declares counselling, boards or fees for AbbVie, Amgen, Celltrion, Janssen, Lilly and Takeda. R.A. declares counselling, boards or fees for AbbVie, Alphasigma, Amgen, Biogen, Celltrion, Ferring, Janssen, Lilly, MSD, Pfizer, Sandoz and Takeda. M.S. declares boarding or lecture fees for Abbvie, Alfasigma, Amgen, Biogen, Celltrion, Ferring, Janssen, MSD, Pfizer and Takeda. A.B. declares boards or fees for AbbVie, Amgen, Janssen and Takeda. G.C. declares boards for Johnson and Johnson, Lilly; and lectures for Abbvie, Takeda. C.R. has received lecture/consultant fees from Abbvie, Lilly, Janssen, Biogen, Amgen, Takeda and Galapagos. M.F. received lecture and/or consulting fees from Sandoz, Biogen, Amgen, Alfasigma, Galapagos, Ferring, Tillots, Nordic-Pharma, Celltrion, Janssen, Amgen, Lilly, Pfizer, Janssen, Abbvie, Takeda, Lilly and Gilead. N.H. has served as a consultant/advisory board member to Abbvie, Celltrion, Fresenius Kabi, Janssen and Lilly and as a speaker for Abbvie, Galapagos and Takeda. L.C. declares counselling, boards or fees for AbbVie, Amgen, Celltrion, Johnson & Johnson, Lilly, Pfizer and Takeda. M.C. declares counselling and boards for AbbVie, Janssen, Lilly, Pfizer, MSD and lecture fees for Ferring, Alfasigma, Takeda, Pfizer, Amgen, Lilly, Tillotts and Abbvie. N.R. declares counselling, boards or fees for AbbVie, Amgen, Celltrion, Ferring, Janssen and Takeda. S.V. received lecture and/or consulting fees from AbbVie, Alfasigma, Celltrion, Ferring, Janssen, Lilly and Takeda. P.W. declares lecture fees from Abbvie, Ferring, Takeda, Amgen, Biogen and Janssen. B.C. received lecture and/or consulting fees from AbbVie, Amgen, Celltrion, Ferring, Galapagos, Janssen, Lilly, Nordic Pharma, Pfizer and Takeda. A.A. received consulting fees from Abbvie, Pfizer, Takeda, Adacyte, Sandoz, Tillotts Pharma, Janssen and Sandoz as well as lecture fees and travel accommodations from Abbvie, Janssen, Pfizer, Takeda, Biogen, Fresenius Kabi, Amgen, Adacyte, Ferrin, Biogen and Celltrion. A.N. has received lecture and/or consulting fees from Abbvie, Amgen, Celltrion, Janssen, Alfasigma, Lilly and a grant from MSD-Avenir. D.L. declares counselling, boards, transports, or fees from Abbvie, Alfasigma, Amgen, Celltrion, Ferring, Janssen, Lilly, Medac, MSD, Pfizer, Sandoz and Takeda. J.K. received lecture fees from Janssen and Lilly, and consulting fees from Roche, Pfizer, Janssen, Abbvie, Takeda, Lilly and Gilead. The other authors declare no conflicts of interest.

Data Availability Statement

Individual anonymized data will be provided upon request to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix A

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