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Effectiveness and safety of upadacitinib in a real-world cohort of patients with Crohn's disease in the UK: a multicentre retrospective cohort study

Yaa Danso ,[1] Chandni Radia ,[2,3] Alex Elford,[4,5] Jie Han Yeo,[6] Thomas Morris,[1] Chirag Patel,[7] Kimberley Butler,[8] Sonia Kalyanji,[9] Katie Yeung,[10] Chaonan Dong,[11] Karishma Sethi-Arora,[12] Alice Hewitt,[13] Lushen Pillay,[14] Susan Ritchie,[15] Mohammed Allah-Ditta,[16] Lucy Hicks,[17] Phil Harvey ,[18] Fiona Rees,[19] Emma Johnston,[20] Ruth Rudling,[21] Charlie Lees,[4,22] Jennifer Toft,[6] Sara Mccartney,[6] Xinyi Choon,[7] Richard C G Pollok ,[9] Dania Al-Zarrad ,[10] Melissa Hale,[8] Christopher Andrew Lamb ,[11,23] R Alexander Speight ,[11,23] Jimmy Limdi,[12] Hannah Trodden-Mittnacht,[13] Konstantina Rosiou ,[13] Tim Raine,[14] Anjan Dhar ,[24,25] Puneet Chhabra,[16] Nick N Burr ,[21] Paul Harrow,[6] Kamal V Patel ,[9] Mark Samaan,[7] Polychronis Pavlidis,[2] Alexandra Kent ,[2] Klaartje Bel Kok,[1] Christian Selinger[13]

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For numbered affiliations see end of article.

Correspondence to
Dr Yaa Danso;
yaa.danso@nhs.net

ABSTRACT

Objective Upadacitinib is the first Janus kinase inhibitor and oral advanced therapy licensed for Crohn's disease (CD). Following NICE approval in 2023, real-world data on outcomes are limited. The effectiveness and safety of upadacitinib in a cohort of patients with CD was assessed.

Methods A multicentre retrospective cohort analysis across 19 UK hospitals. Adult patients with active CD who started upadacitinib between April 2023 and October 2023 were included. Outcomes were reviewed over 24 weeks. The primary endpoint was clinical remission (Harvey Bradshaw Index (HBI) <4) at 12 and 24 weeks. Biochemical remission (faecal calprotectin <200 µg/g and C-reactive protein ≤5) and endoscopic remission (Simple Endoscopic Score for Crohn's Disease ≤3) were assessed at the same intervals. Adverse events (AEs) were recorded until 24 weeks or drug withdrawal.

Results 312 patients were included, with a minimum follow-up of 12 weeks. The cohort had difficult-to-treat disease; 64% failing 3 or more biologics, 51% exhibiting penetrating or stricturing disease and 41% requiring prior resection. 50% (113/227) of patients achieved clinical remission at 12 weeks and 45% (77/172) at 24 weeks. Patients with colonic disease had higher remission rates at 24 weeks compared with other disease locations. At 24 weeks, 51 patients (16%) had discontinued upadacitinib. Treatment persistence was 90.3% at 12 weeks and 84.1% at 24 weeks. 28% had AEs, with 18% experiencing serious AEs and 16.6% requiring hospitalisation.

Conclusion This is a large real-world study reporting outcomes in patients with CD treated with upadacitinib. Our data demonstrated good short-term effectiveness and tolerance in a clinically refractory population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Upadacitinib is the first oral advanced therapy for Crohn's disease (CD).

⇒ U-EXCEED and U-EXCEL phase III induction trials and the long-term maintenance trial U-ENDURE showed promising clinical outcomes, but there remains scarce robust long-term real-world data.

WHAT THIS STUDY ADDS

⇒ Our data demonstrated good effectiveness—clinical remission rate of 45% and was well tolerated in a highly refractory, large real-world cohort of patients with CD in the UK.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The high drug persistence rates of 90.3% at 12 weeks and 84.1% at 24 weeks alongside favourable steroid-free clinical remission outcomes indicate a positive role for upadacitinib in managing challenging CD cases.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition requiring long-term and tailored management. The mainstay of advanced therapy for CD has been focused on biologics and especially tumour necrosis factor (TNF) inhibitors, also known as anti-TNF therapy.[1] Although anti-TNF therapy generally has a strong efficacy and safety profile, some patients eventually experience

a loss or inadequate response to treatment.[2 3] Despite the availability of several biologic therapies for CD targeting different immune pathways, a substantial proportion of patients with CD do not achieve a sufficient initial or maintained response, and further treatment options are required.[4] Upadacitinib has recently become available as the first Janus kinase (JAK) inhibitor approved for use in CD. As the first advanced oral therapy for CD, it holds a number of advantages: a rapid onset of action, lack of immunogenicity and convenience of administration.[5]

The U-EXCEED and U-EXCEL phase III induction trials demonstrated week 12 remission was achieved in 38.9% and 49.5%, respectively. All patients recruited to U-EXCEED had previous biologic failure, with 31.1% of patients having failed 3 or more. In the U-EXCEL cohort, 46% had also failed a biologic, and 14.6% had failed 3 or more,[6] thus showing the potential of upadacitinib to provide sustained benefits for patients who have not responded to other treatments.

While the clinical trial outcomes are promising but with scarce medium to long-term real-world data,[7] the broader effectiveness and safety in everyday practice over extended periods remains uncertain. Within clinical practice, many patients receiving new therapies do not fit the strict eligibility criteria of randomised clinical trials. Real-world data are crucial to complement clinical trial findings and understand treatment outcomes in the broader population.[8 9]

This is a study of a large real-world cohort of patients with CD across multiple sites within the UK. The objective was to assess the effectiveness, persistence and safety of upadacitinib in patients with moderate to severe CD over 24 weeks.

METHODS

Study design and setting

This is a multicentre retrospective cohort analysis. Patients were recruited from 19 hospitals across the UK, including district general hospitals, teaching hospitals and tertiary inflammatory bowel disease (IBD) centres. Patient outcomes were reviewed over 24 weeks. Reporting followed the STROBE (STrengthening the Reporting of OBservational Studies in Epidemiology) statement for observational studies (online supplemental file).

Inclusion criteria

Patients aged 18 years and older with a confirmed diagnosis of clinically, biochemically or endoscopically active CD who started on upadacitinib were included (table 1). Patients were followed up until week 24 or drug withdrawal.

Patients were identified via local electronic medical records. All sites used either structured databases or manual review to identify patients with CD who had initiated upadacitinib between April 2023 and October 2023. Patients were included if they had received at least 12 weeks of treatment or earlier if the drug had been discontinued.

Exclusion criteria

Patients who had ulcerative colitis (UC), IBD unclassified or without active disease in any of the parameters listed in table 1 were excluded.

Data collection

Patient electronic medical records were reviewed to collect retrospective data at each hospital.

Patients received upadacitinib with a standard induction dosage of 45 mg once daily for 12 weeks, followed by a maintenance dosage of 15 mg once daily or 30 mg once daily.

Clinical outcomes

Baseline clinical parameters (table 1) were recorded within the 3 months prior to starting upadacitinib. The primary endpoint of clinical remission, defined as a HBI <4, was assessed at 12 weeks (±4 weeks) and 24 weeks (±4 weeks). Clinical response was defined as a HBI reduction of ≥3 from baseline. Biochemical response was defined as ≥50% reduction in FCP or CRP, with no increase in either parameter. FCP <200 µg/g and CRP ≤5 mg/L defined biochemical remission. While endoscopic response and remission was defined as ≥50% reduction in Simple Endoscopic Score for CD (SES-CD) and SES-CD ≤3, respectively.[10]

All response data are shown combined with remission data. This is to show the overall proportion of patients who derived clinical benefit from upadacitinib, whether this was through a response alone or achieving remission. Secondary endpoints included drug persistence, corticosteroid-free clinical remission, safety data and

Table 1 Clinical, biochemical and endoscopic parameters used to assess disease activity and outcomes

	Scoring system	Active disease	Response	Remission
Clinical	**HBI**	**≥4**	**Reduction ≥3**	**<4**
Biochemical	FCP and CRP	FCP ≥200 µg/g and CRP >5 mg/L	FCP or CRP reduction of 50% and no increase in either parameter	FCP <200 µg/g and CRP ≤5 mg/L
Endoscopic	SES-CD	SES-CD >3	Reduction of 50% or more	≤3

Baseline scores were all recorded within 3 months prior to starting upadacitinib.
CRP, C reactive protein; FCP, faecal calprotectin; HBI, Harvey Bradshaw Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.

assessment of baseline factors potentially associated with the endpoint of clinical remission.

An intention-to-treat analysis approach was used, including all patients that reached the 12 weeks endpoint as part of the induction analysis and all those that reached the 24 weeks endpoint for the maintenance analysis. Patients who discontinued the drug were considered treatment non-responders for all subsequent time points (non-responder imputation). Patients who had continued on the drug but had not yet reached 12 weeks at the time of analysis were not included.

Abdominal pain score and stool frequency score as per HBI were recorded within 3 months prior to commencing upadacitinib. For patients with a stoma, daily stoma bag emptying was used to account for stool frequency as part of the HBI score. Patients with stomas are an important cohort of the Crohn's population and we endeavoured to include them within this dataset. This was a pragmatic but unvalidated approach to this part of the data collection.[11 12]

Steroid-free clinical remission was defined as clinical remission without steroid use at the end of 12 or 24 weeks. Patients who were included in the cohort and did not have either remission or response were deemed as non-responders. Start and stop dates of upadacitinib were recorded, drug persistence defined as the number of patients continuing upadacitinib at any given time point. Baseline demographic data, including age, sex, smoking status, disease duration, disease location in accordance with Montreal classification, number of previous biologics and steroid use at each interval, were all recorded. A serious adverse event (SAE) was defined as one that caused hospitalisation, morbidity or death.

Bias

All eligible patients across the 19 sites were included, without restriction based on disease severity or other variables to reduce selection bias. We used standardised clinical outcomes with uniform criteria across centres. We addressed potential confounding variables such as disease location and prior biologic failure by exploring results within subgroup analyses.

Statistical analysis

Statistical analysis was performed using RStudio V.2022.12.0+353 and Prism V. Prism was also used to create data graphs. Descriptive statistics were presented as medians with IQRs for continuous variables and frequencies as percentages for categorical variables. The Wilcoxon matched-pairs signed-rank test was used to assess significance between paired data scores at baseline, 12 weeks and 24 weeks. Univariate analysis was performed using logistic regression. All analyses were two-tailed, and a $p<0.05$ was considered to be significant for all statistical tests. Patients with missing data were still included for any analyses for which they had data.

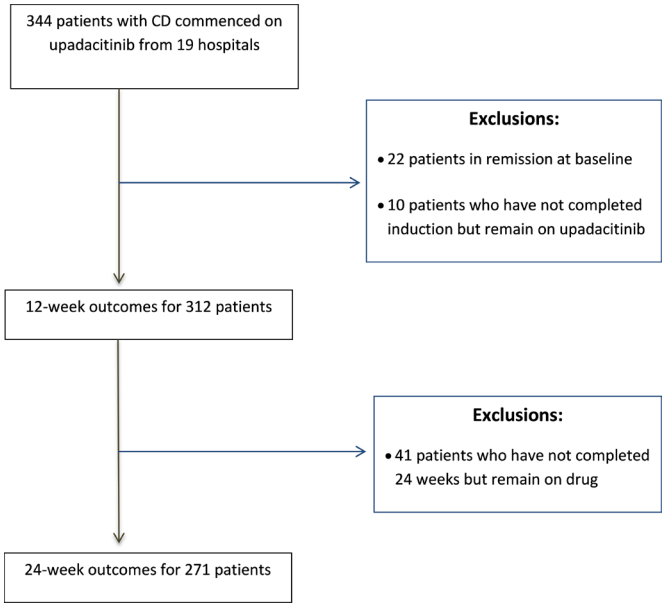

Figure 1 Flowchart showing patient selection for analysis. CD, Crohn's disease.

Ethical considerations

The data collected were anonymised and collected as part of routine clinical care. There was no change in patient treatment. Data were collected as part of a service evaluation at each site. This study was covered under the NHS Health Research Authority.[13] All collection, use and transfer of patient data required for this study received approval from the local data protection teams.

RESULTS

Patient characteristics

Data were collected from 344 patients across 19 hospitals. Figure 1 shows the patient selection process, outlining the initial patient numbers and the exclusions at both 12 and 24 weeks. Following exclusions, 312 patients were evaluated for the 12-week outcomes, and 271 patients were evaluated for the 24-week outcomes. All 312 patients were included in the safety data.

Descriptive data

Of the 312 patients included in the analysis (table 2), 58% were male with a median age of 31–35. The majority (57%) had ileo-colonic disease, and an inflammatory phenotype was the most frequently observed—present in 48%. 59% had not had a previous resection and 17% had two or more resections. 99% had prior biologic exposure before commencing upadacitinib, with a median number of 3 (IQR 2–4) prior advanced therapies. 34% of patients were on corticosteroids at the time of starting upadacitinib, and 8% were on exclusive enteral nutrition. The median HBI score was 9 (IQR 6–12), indicating moderate disease activity. This was reflected in the Simple Endoscopic Score for Crohn's Disease (SES-CD); median 8 (IQR 5–16). The median FCP level was 1055 µg/g (IQR

Table 2 Baseline demographic data

N=312		n (%)	
Age		31–35 (median range)	
Gender			
Male		180 (58)	
Female		132 (42)	
Smoking			
Current		23 (8)	
Ex-smoker		45 (16)	
Never		208 (75)	
Unknown		36	
Disease location			
L1		56 (18)	
L2		71 (23)	
L3		177 (57)	
L4		6 (2)	
Perianal disease		99 (32)	
Stoma		46 (15)	
Steroids on commencing upadacitinib			
Yes		105 (34)	
No		102 (66)	
No data		5	
Number of previous advanced therapies (excluding upadacitinib)			
Bio naive		4 (1)	
1		46 (15)	
2		63 (20)	
3 (median)		91 (29)	
4		89 (29)	
5		18 (6)	
6		1 (0.3)	
EEN on commencing upadacitinib			
Yes		26 (8)	
No		284 (92)	
No data		2	
Induction completed			
Yes		280 (90)	
No		32 (10)	
24 weeks completed			
Yes		220 (92)	
No		51 (8)	
No data		41	
Baseline disease activity scores		Median (IQR)	
HBI (total cohort with stoma)	HBI (available data for stoma patients only n=30)	9 (6–12)	8 (6–10)
CRP		11 (3–29)	
FCP		1055 (371–1715)	
SES-CD		8 (5–16)	

CRP, C reactive protein; EEN, exclusive enteral nutrition; FCP, faecal calprotectin; HBI, Harvey Bradshaw Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.

371–1715 µg/g), and the median CRP was 11 mg/L (IQR 3–29 mg/L).

All remission outcomes were assessed at week 12 and week 24. This included all patients with available data regardless of their baseline values. However, a response result required a comparison of follow-up values (either week 12 or week 24) to baseline values and is therefore limited to only patients with paired baseline and follow-up data. Patients who only had follow-up data (without baseline) that had not reached remission could not be included within the response outcomes. As such, denominators for remission and response analysis differ.

Induction results

At week 12, clinical remission was achieved in 50% (113/227) of patients, with 93% of those in steroid-free clinical remission (figure 2A). Additionally, 17% (38/222) demonstrated a clinical response. Five patients lacked paired data for clinical response assessment.

Biochemical remission was observed in 28% (59/213) of patients, while 7% (10/141) of those with paired baseline and week 12 data showed a biochemical response. Endoscopic remission was achieved in 6% (3/46), and among the 43 patients with paired baseline and week 12 endoscopic data, 5% (2/43) had an endoscopic response.

Maintenance results at 24 weeks

Out of 172 patients, 77 (45%) were in clinical remission at week 24, with 96% (74/77) of these patients attaining steroid-free clinical remission. Further, 18% (30/165) of patients were in biochemical remission and 12% (8/66) of patients achieved endoscopic remission (figure 2B).

The comparative scores of all recorded parameters from baseline, 12 weeks and 24 weeks are shown in figure 3, and the full results at each stage can be found in the online supplemental data.

Significant reductions in HBI, FCP and CRP were observed at both 12 and 24 weeks compared with baseline. At induction, clinical remission was reflected in a median HBI reduction from 9 to 3 (p<0.0001). At 24 weeks, the median HBI decreased further to 2 (IQR 1–5; p<0.0001). FCP also had a marked improvement with a median reduction from 1055 µg/g at baseline to 212 µg/g at 12 weeks (p<0.0001) and an overall median reduction to 288.5 at 24 weeks from baseline (p<0.0001). Among 237 paired CRP measurements, median CRP levels dropped by 8 mg/L from baseline to 12 weeks (p<0.0001). At 24 weeks, CRP decreased from 11 mg/L (IQR 3–29) at baseline to 4 mg/L (IQR 1–12; p<0.0001). There was limited data available for endoscopic scoring (SES-CD), with only three patients having paired data by 24 weeks. Among these, the median SES-CD decreased from 8 (IQR 5–16) at baseline to 2 (IQR 0–5), although this was not statistically significant (p=0.17). Figure 3B shows the overall median endoscopic scores over time.

Patient severity scores were recorded for abdominal pain (APS) and stool frequency (SFS). The median APS decreased from a baseline score of 2 (IQR 1–2) to 0 (IQR

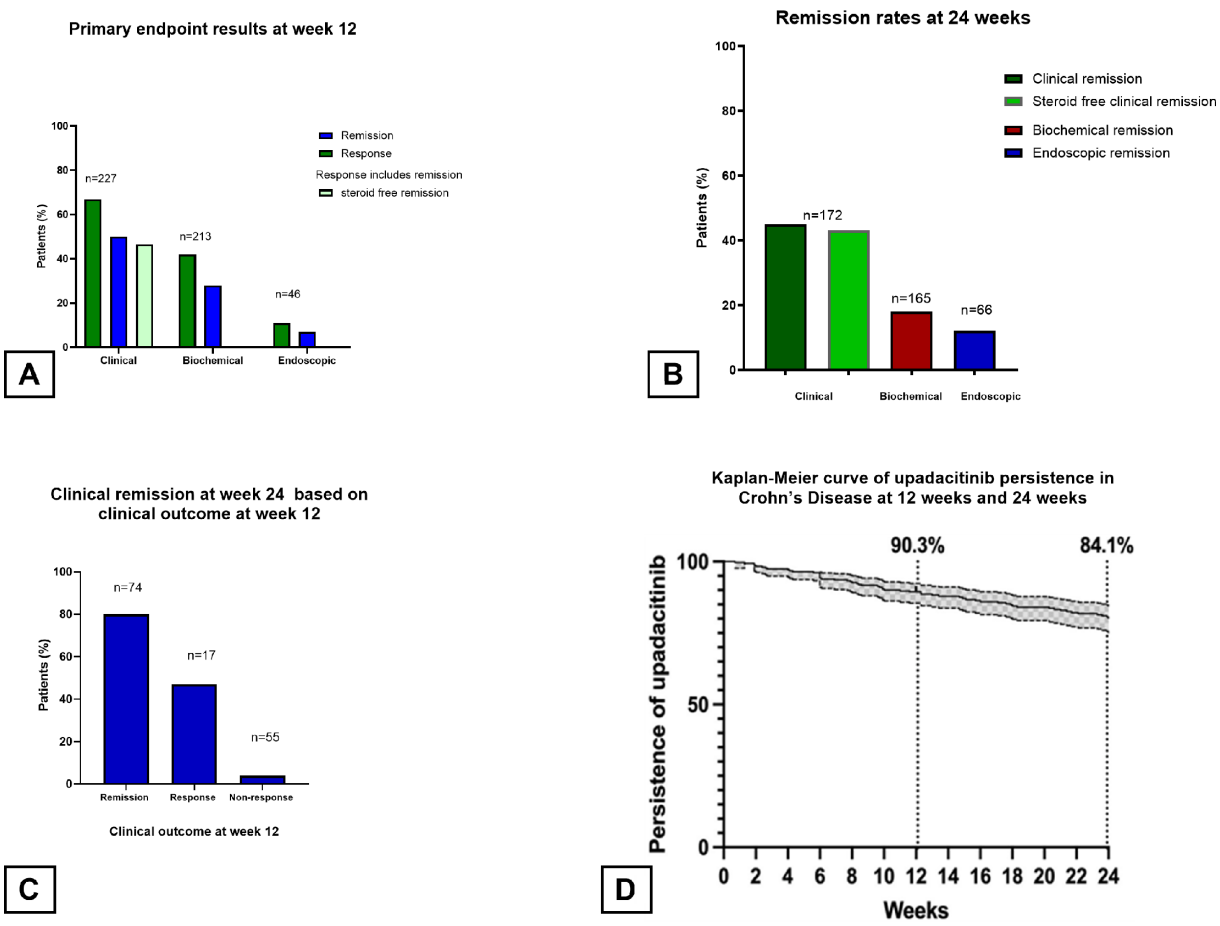

Figure 2 (A) Clinical outcomes at week 12. (B) Clinical outcomes at week 24. (C) Clinical remission at week 24 based on clinical outcome at week 12. (D) Kaplan-Meier curve of upadacitinib persistence in Crohn's disease at 12 weeks and 24 weeks.

0–1) at 12 weeks (p<0.0001), and this reduction was sustained at 24 weeks. A similarly significant reduction was observed in SFS, which dropped from a baseline of 5 (IQR 2.25–8) to 2 (IQR 1–4) at 12 weeks (p<0.0001). This median score was also sustained at 24 weeks, remaining at 2 (IQR 1–3).

A total of 32 patients discontinued upadacitinib before 12 weeks; 15 patients (47%) stopped due to adverse events (AEs) and 15 (47%) due to primary non-response. In two cases, the reason for cessation was not documented.

Of the 271 patients with the 24-week outcomes, 19 patients (7%) did not reach 24-week follow-up. Of these, six patients required admission. The mean duration of upadacitinib in these patients was 14.9 weeks. Drug persistence rates were 90.3% at 12 weeks and 84.1% at 24 weeks (figure 2D).

Subgroup analysis

10% (22/221) of patients required an extended induction, and of those with available data, 45% (5/11) reached clinical remission at 24 weeks. The remaining 11 patients who required an extended induction included one patient who discontinued upadacitinib before the 24-week follow-up and another 10 patients who did not have HBI scores recorded at the 24-week follow-up and clinical remission could not be calculated. In comparison, of the patients who underwent a standard induction, 59% (71/120) achieved clinical remission at 24 weeks. Using Fisher's exact test, no statistically significant difference was found in clinical remission rates between patients who received standard and extended inductions (p=0.5253).

Data were analysed comparing clinical remission in those with and without a stoma. Of the patients with available data who did not have a stoma (n=226), the median HBI was reduced from 9 to 3 at 12 weeks (p<0.0001), reflecting clinical remission. By 24 weeks, clinical remission was sustained as the median HBI was further decreased to 2 (IQR 1–5; p<0.0001). For patients with a stoma, a similar baseline HBI of 8 (IQR 6–10) was seen, which improved to 5 (IQR 3–8) and 6 (IQR 3–10) at 12 and 24 weeks. These changes were not statistically significant. Interpretation within the stoma subgroup is limited, although these findings are important due to the under-representation of stoma patients in many real-world cohorts.

The results of univariate and multivariate logistic regression to identify predictors of clinical remission at 24 weeks are provided in the online supplemental data.

A key finding was patients with colonic disease (L2) and ileocolonic disease (L3) had higher odds of achieving

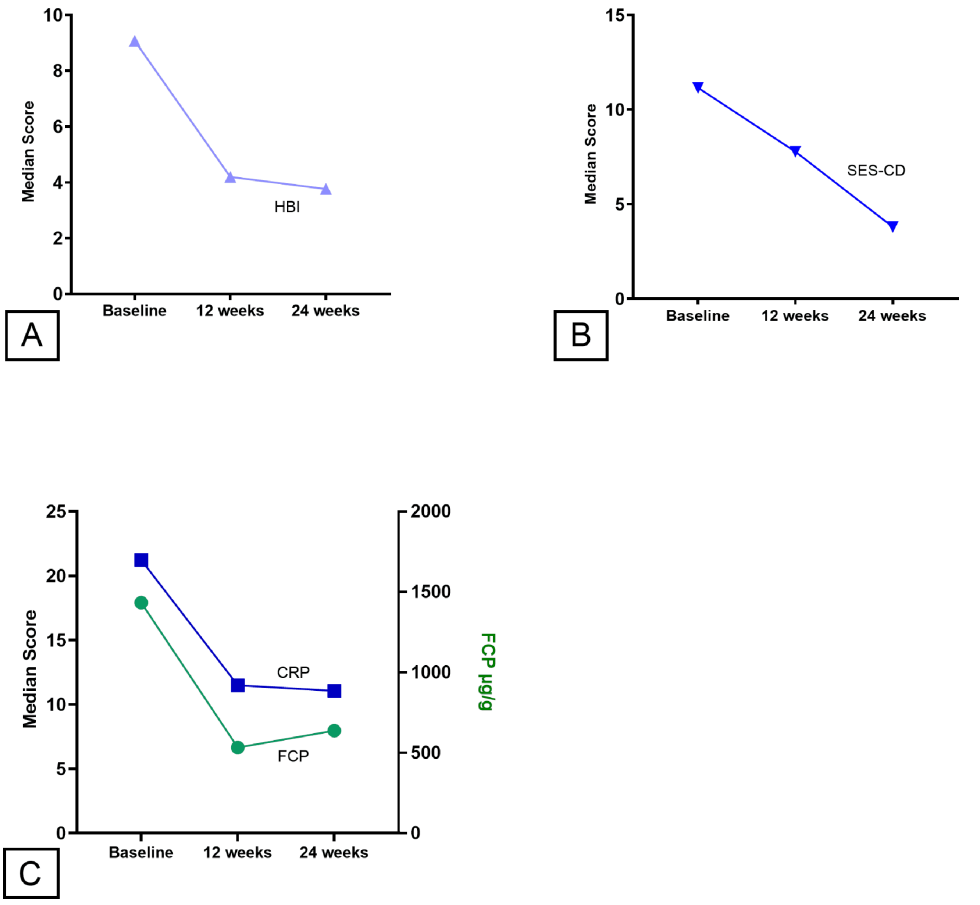

Figure 3 Total cohort comparative scores between baseline, 12 weeks and 24 weeks for (A) Harvey Bradshaw Index (HBI), (B) Simple Endoscopic Score for Crohn's Disease (SES-CD), (C) faecal calprotectin (FCP) and C reactive protein (CRP).

clinical remission compared with those with isolated ileal disease. In the univariate analysis, this was only statistically significant for colonic disease (p=0.005). After adjusting for clinically relevant variables in the multivariate analysis, both L2 and L3 disease remained significant predictors of clinical remission at 24 weeks. Patients with colonic disease (L2) had 9.16 times the odds of clinical remission compared with those with ileal disease (L1) (p=0.003) followed by those with ileocolonic disease (OR=3.44, p=0.043). This suggests that having isolated colonic disease was associated with the greatest likelihood of remission.

The univariate analysis showed ex-smokers had significantly lower odds of achieving remission compared with never smokers at 24 weeks. After adjusting for other factors, ex-smokers had significantly lower odds of achieving clinical remission compared with never-smokers (OR=0.08, p=0.006), suggesting a negative impact of prior smoking. Interestingly, active smoking showed no significant association with remission (OR=0.64, p=0.560) reflected in both the univariate and multivariate analyses, although the study may not have been powered with enough active smokers to confidently detect a statistical association. Patients with a stoma, even after accounting for other variables, had significantly lower odds of achieving clinical remission at 24 weeks compared with patients without (OR 0.16, p=0.016).

Age and previous resection lost statistical significance after accounting for confounding variables in the multivariate analysis.

Gender, age at diagnosis, disease behaviour, perianal disease, number of prior advanced therapies, baseline FCP levels, HBI scores and steroid use were not found to be significantly associated with remission outcomes at 24 weeks.

Clinical remission based on clinical outcome at 12 weeks

In patients who achieved clinical remission at 12 weeks, 80% (59/74) maintained remission at week 24 (figure 2C). In those with a clinical response (but not in remission) at 12 weeks, 47% (8/17) reached clinical remission at 24 weeks. Only 4% (2/55) of patients who did not have a clinical response at 12 weeks were in clinical remission at 24 weeks.

Adverse events

AEs occurred in 28% (86/312) of patients and SAEs occurred in 18% (55/312) of patients. A total of 124 AEs were recorded overall (table 3), with some patients experiencing more than one E. The most common AEs were infections (7.7%), lipid abnormalities (4.8%) and acne (4.5%). Other dermatological conditions (excluding acne) and full blood count abnormalities also occurred in 4% of patients each.

Table 3 Adverse events

AE	N (%)	SAE	N (%)
n=312			
Infection*	24 (7.7)	Resection†	17 (5.4)
Lipid abnormalities	15 (4.8)	Worsening symptoms*†	15 (4.8)
Acne	14 (4.5)	Obstruction†	7 (2.2)
Dermatological (non-acne)*	12 (3.9)	Anaemia†	6 (1.9)
Full blood count abnormalities*	12 (3.9)	Infection*†	5 (1.6)
Headache*	8 (2.6)	Venous thromboembolism*†	3 (1.0)
Myalgias*	6 (1.9)	Cancer*	3 (1.0)
Liver function test abnormalities	5 (1.6)	Perianal complications†	3 (1.0)
Nausea	4 (1.3)	Zoster*†	1 (0.3)
Zoster	4 (1.3)	Steven-Johnson syndrome*†	1 (0.3)
Herpes simplex virus*	3 (1.0)	Herpes simplex virus*†	1 (0.3)
Perioral symptoms*	3 (1.0)	Major adverse cardiovascular events	0
Vertigo*	2 (0.6)		
Insomnia*	2 (0.6)		
Shortness of breath*	2 (0.6)		
Fatigue*	2 (0.6)		
Weight gain*	2 (0.6)		
Allergic reaction*	1 (0.3)		
Creatine kinase abnormalities	1 (0.3)		
Mental health symptoms*	1 (0.3)		
			25 (8.0)
			52 (16.6)

Percentages are rounded to 1 decimal place.
*AE causing permanent cessation of drug.
†AE causing hospitalisation.
AE, adverse event; FCP, faecal calprotectin; SAE, serious adverse event.

The most common SAEs included surgical resections (5.4%), worsening symptoms (4.8%) and obstruction not requiring resection (2.2%); of note, one patient was admitted twice for obstruction. These AEs also made up the majority of hospitalisations, suggesting uncontrolled disease was a key driver rather than direct side effects of upadacitinib.

Out of 312 patients, 32 (10%) discontinued treatment due to AEs before completing the induction phase. Notably, the primary reason for discontinuation was worsening symptoms, with eight patients requiring resections. There was also one case each of zoster, cancer, thrombosis and Stevens-Johnson syndrome.

The most common reasons for discontinuing the drug during both the induction and maintenance phases were worsening symptoms and infections. Three patients (1%) developed cancer, one patient had a zoster infection requiring hospitalisation and three patients experienced venous thromboembolism. Overall, 8% of patients had to stop upadacitinib due to side effects or complications.

DISCUSSION

This is the largest European real-world experience of upadacitinib in CD, providing insight into the effectiveness and safety in clinical practice within a highly refractory population. Upadacitinib demonstrated effectiveness by achieving clinical remission in 45% of patients at 24 weeks. These findings are particularly encouraging for both patients and clinicians, as they illustrate upadacitinib's effectiveness in a difficult-to-treat cohort of CD, with 64% of patients having had at least three prior advanced therapies (excluding upadacitinib) and 51% exhibiting either penetrating or stricturing disease behaviour.

The clinical remission rate of 45% at 24 weeks mirrors findings from previous real-world studies such as Elford *et al* which reported a clinical remission rate of 48% at 24 weeks.[14] A more recent study from the US over 24 weeks showed 55.9% clinical remission at follow-up. Interestingly, when looking at patients with more refractory disease, characterised as those with two or more prior advanced therapy exposures, which was more in

keeping with the cohort in this study, the clinical remission rate was similar at 40.5%.[15] In contrast, Friedberg *et al* reported a clinical remission rate of 71% in those with active disease.[16] However, this was taken at an earlier time point of 8 weeks which may capture an early therapeutic response due to the rapid onset of upadacitinib, potentially resulting in a higher proportion of patients in clinical remission. In controlled trial settings, such as in U-EXCEL, U-EXCEED and U-ENDURE, upadacitinib demonstrated slightly lower clinical remission rates, with 50% and 39% at week 12 and 37–48% at week 52, which may reflect the stringent criteria and specific population groups observed in randomised controlled trials compared with real-world cohorts.[6]

When comparing remission rates with biologics typically used as second-line treatments, a study reported clinical remission rates of 42.1% for ustekinumab and 44.8% for vedolizumab at 26 weeks[17] and another 30% for vedolizumab at 30 weeks.[18] Upadacitinib was at least a third-line therapy for 64% of patients in this cohort and achieved a similar remission rate. These findings suggest that upadacitinib may offer a potential advantage in achieving remission in clinically difficult-to-treat CD, particularly as upadacitinib does not exhibit the diminishing effectiveness that is frequently seen with sequential use of biologics in IBD.

While clinical remission matters, those who also exhibit biomarker remission have better long-term outcomes than those not in biomarker remission.[19] This cohort demonstrated clinically significant reductions in CRP and faecal calprotectin at 24 weeks.

The rate of endoscopic remission at 24 weeks in this study was relatively low, at 12%, notably less than the endoscopic outcomes in clinical trials such as CELEST,[20] where endoscopic remission was reported as 44–55% at 12 months. In real-world cohorts, Elford *et al* showed similar results where one out of four patients achieved endoscopic remission.[14] This may reflect the challenges of treating a real-world population; however, the large amount of missing data may reflect the different protocols in hospitals for endoscopic assessment. It is conceivable that endoscopy at 12 or 24 weeks was prioritised for patients with an insufficient clinical response, thereby reporting with a bias towards non-remission.

Disease location appeared to significantly affect clinical outcomes. Patients with colonic disease (L2) had numerically higher remission rates compared with those with ileal (L1) and ileo-colonic (L3) disease both at 12 and 24 weeks which aligns with prior literature, as seen in Friedberg *et al*[16] and also Elford *et al*.[14] This outcome shows the need for tailored therapeutic approaches, as disease location could be an important factor in predicting treatment outcomes.[19] It would also be important to note that some patients with L1 and L3 disease may have undergone resections which could contribute to consequent bile acid diarrhoea. Unfortunately, we did not collect data on patients with a confirmed diagnosis of bile acid diarrhoea, but its presence may have affected clinical remission rates due to increased stool frequency among this group.

Patients who were in remission at 12 weeks had numerically higher rates of remission at 24 weeks compared with those who had a response or non-response at week 12, reflecting similar findings in U-EXCEL, U-EXCEED and U-ENDURE post hoc analysis[21] where early responders predicted better longer-term outcomes.

JAK inhibitors exhibit a different safety profile compared with other biologics; an increased risk of herpes zoster infections,[22] risk of thromboembolic events, cardiovascular events and potential increased malignancy risk.[23] Due to teratogenicity in animal studies, JAK inhibitors are contraindicated during pregnancy and lactation.[24] In this cohort, 28% of patients experienced AEs, and 18% experienced SAEs. The most common AEs included infections, lipid abnormalities and acne. These findings are consistent with the safety data reported in the CELEST extension study,[20] Elford *et al* and Sandborn.[25] Upadacitinib has recently been approved for CD, but approved for rheumatoid arthritis previously in 2020.[26] A review of the safety profile of upadacitinib across multiple arthritis groups indicated that the most common AEs were also related to acne and infections.[27] This suggests that upadacitinib's safety profile could be comparable in real-world use to what has been observed in clinical trial settings.

Our data highlighted that 8% of patients had to discontinue upadacitinib due to AEs. These results are similar to those in Elford *et al*,[14] which showed discontinuation rates of 10%, but contrast the results of the U-ENDURE trial, which had discontinuation rates of 14–19%.[6] This may reflect the robust mechanisms for reporting AEs and strict discontinuation criteria in clinical trials which differ with retrospective real-world data which is more flexible and also vulnerable to recollection bias.

This study offers a real-world insight from a UK cohort, showcasing results from a clinically challenging group of patients often encountered in clinical practice.[28] The inclusion of patients who had undergone multiple resections, a number of prior advanced therapies, with complex disease behaviours, shows how upadacitinib can be beneficial in challenging cases. A disadvantage of this study is that it did not differentiate outcomes based on dosage variations. The modification of the HBI to equate stoma bag changes with stool frequency is not a validated method. Stoma output patterns differ from natural bowel movements, with patients emptying their bag multiple times even during times of remission. We recognise this method of data collection has meant by virtue of having an ileostomy and increased stoma bag emptying these patients could receive a score of 4 alone for stool frequency (average bag emptying frequency for those with a stoma),[29] which limits their ability to achieve the clinical remission: HBI <4. A key limitation was the retrospective collection of safety data. AEs were identified through routine clinical monitoring documented in electronic health records during standard care visits, rather

than systematic screening visits. Abnormalities were only captured when clinically indicated during standard care, potentially leading to underestimation of their true incidence. Showcasing research within ethnically diverse populations is important for generalisability of findings. This study did not collect data on patient ethnicity and thus limits the ability to assess the representativeness of the cohort across different ethnic groups.

In conclusion, upadacitinib was effective in inducing and maintaining clinical remission in this large, pan-UK real-world cohort with highly refractory CD. The high drug persistence rates and favourable steroid-free remission outcomes indicate a positive role for upadacitinib in managing challenging CD cases. Nonetheless, the AE profile warrants cautious patient selection and ongoing safety monitoring.

Author affiliations
[1]Barts Health NHS Trust, London, UK
[2]King's College Hospital NHS Foundation Trust, London, UK
[3]King's College London Faculty of Life Sciences & Medicine, London, UK
[4]Edinburgh IBD Unit, Western General Hospital, Edinburgh, UK
[5]The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, Melbourne, Victoria, Australia
[6]University College London Hospitals NHS Foundation Trust, London, UK
[7]Guy's and St Thomas' NHS Foundation Trust, London, UK
[8]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[9]St George's University Hospitals NHS Foundation Trust, London, UK
[10]St Mark's the National Bowel Hospital and Academic Institute, London, UK
[11]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[12]Gastroenterology, Northern Care Alliance NHS Foundation Trust, Manchester, UK
[13]Leeds Teaching Hospitals NHS Trust, Leeds, UK
[14]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[15]County Durham and Darlington NHS Foundation Trust, Darlington, UK
[16]Calderdale and Huddersfield NHS Foundation Trust, Huddersfield, UK
[17]Imperial College Healthcare NHS Trust, London, UK
[18]Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK
[19]University Hospitals Sussex NHS Foundation Trust, Worthing, UK
[20]Department of Gastroenterology, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK
[21]Mid Yorkshire Teaching NHS Trust, Wakefield, UK
[22]Centre for genomics and experimental medicine, Institute of Genetics and Cancer, University of Edinburgh, Western General Hospital, Edinburgh, UK
[23]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[24]Gastroenterology, County Durham and Darlington NHS Foundation Trust, Darlington, UK
[25]School of Health and Life Sciences, Teesside University, Middlesbrough, UK

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ORCID iDs
Yaa Danso http://orcid.org/0009-0009-8572-131X
Chandni Radia http://orcid.org/0009-0002-1572-2172
Phil Harvey http://orcid.org/0000-0002-1192-9910
Richard C G Pollok http://orcid.org/0000-0001-6452-6763
Dania Al-Zarrad http://orcid.org/0009-0001-4349-4341
Christopher Andrew Lamb http://orcid.org/0000-0002-7271-4956
R Alexander Speight http://orcid.org/0000-0003-3184-9181
Konstantina Rosiou http://orcid.org/0000-0001-7260-1866
Anjan Dhar http://orcid.org/0000-0001-8964-2031
Nick N Burr http://orcid.org/0000-0003-1988-2982
Kamal V Patel http://orcid.org/0000-0003-2611-4260
Alexandra Kent http://orcid.org/0000-0003-0577-6177

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