



Original research

Real-world effectiveness of upadacitinib in Crohn's disease: a UK multicentre retrospective cohort study

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ABSTRACT

Background Upadacitinib is a Janus kinase inhibitor, which has recently been approved for treating Crohn's disease. There are limited real-world studies on the outcomes of upadacitinib in Crohn's disease.

Objective Our aim was to evaluate the outcomes of upadacitinib in a real-world Crohn's disease cohort.

Methods We conducted a retrospective, multicentre, cohort study over a 2-year period across National Health Service (NHS) Lothian and Royal Devon University Healthcare NHS Foundation Trust. The primary outcome was treatment persistence at week 24. Secondary endpoints were corticosteroid-free clinical remission (Harvey-Bradshaw Index (HBI) <5) and biomarker remission (C-reactive protein (CRP) ≤5 mg/L and faecal calprotectin (FCAL) <250 µg/g) at 12, 24 and 52 weeks. We recorded adverse events.

Results 135 patients commenced upadacitinib as of the 1 January 2024, of which 93 patients with active Crohn's disease were included with a minimum of 12 weeks follow-up. The median follow-up time was 25 weeks (IQR 15–42 weeks). 82% of the cohort had exposure to at least two classes of advanced therapies, and 52% had exposure to at least three classes of advanced therapies. Treatment persistence was 87.1% at week 12, 81.7% at week 24 and 62.8% at week 52. Rates of clinical remission were 64% (42/66), 48% (22/46) and 38% (8/21) at weeks 12, 24 and 52, respectively. Significant reductions in HBI, CRP and FCAL were observed during follow-up. 14% (13/91) had a hospitalisation due to Crohn's disease. Adverse events occurred in 40% (37/93) of the cohort, of which 12% (11/93) were serious.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Upadacitinib has been demonstrated to have efficacy for Crohn's disease in phase 3 clinical trials, but real-world data are lacking.

WHAT THIS STUDY ADDS

⇒ Our data demonstrate that upadacitinib was an effective treatment option, in a real-world, highly medically refractory, Crohn's disease cohort with good persistence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Upadacitinib remains an effective drug in Crohn's patients who have failed multiple other advanced therapies. Our data support 30 mg as the preferred maintenance dose for most Crohn's patients.

Conclusion Upadacitinib was effective in a real-world, highly refractory, Crohn's disease cohort with good persistence.

INTRODUCTION

Upadacitinib is a second-generation oral small molecule with preferential inhibition of Janus kinase (JAK) type 1.¹ Upadacitinib recently received approval for the treatment of Crohn's disease by the UK Medicines and Healthcare products Regulatory Agency,² based on positive results in the phase 3 clinical trials, where clinical remission rates of 49.5% (U-EXCEL) and 38.9% (U-EXCEED) were observed for induction and 47.6% for maintenance therapy (U-ENDURE).³ Upadacitinib is

the first JAK inhibitor to demonstrate efficacy for the treatment of Crohn's disease and possesses numerous benefits of being a small molecule including oral administration and no immunogenicity.⁴

To date, there have been limited studies assessing the real-world efficacy of upadacitinib in moderate to severe Crohn's disease.^{5,6} These studies have largely focused on induction data. The Lothian IBD and Royal Devon University Healthcare units have been using upadacitinib over the last 2 years for moderate to severe Crohn's disease. Our aim was to audit the treatment persistence, effectiveness and safety of upadacitinib in our population of patients with moderate to severe Crohn's disease.

METHODS

Study design

We conducted a multicentre retrospective cohort analysis involving five hospitals across two National Health Service (NHS) health organisations in the UK (NHS Lothian and Royal Devon University Healthcare NHS Foundation Trust). Data were retrospectively collected at each hospital by review of electronic medical records. The prevalence of Crohn's disease has previously been reported as 283.3 and 265.94 per 100 000 in Lothian,⁷ and Devon, respectively.⁸

Participants

We identified all adult (≥ 18 years old) patients with Crohn's disease who received upadacitinib from 1 September 2021 to 1 January 2024 via pharmacy dispensing records and electronic medical health records: TrakCare patient management (InterSystems) at NHS Lothian and Epic (Epic Systems Corporation, Verona, Wisconsin, USA) at Royal Devon University Healthcare NHS Foundation Trust). Inclusion criteria were as follows: (a) confirmed diagnosis of Crohn's disease (based on standard clinical, radiological, endoscopic and histological criteria); (b) upadacitinib started for the indication of active Crohn's disease, defined by either a Harvey-Bradshaw index (HBI) ≥ 5 and/or C-reactive protein (CRP) > 5 mg/L and/or endoscopic/radiographic assessment and/or faecal calprotectin (FCAL) ≥ 250 μ g/g and (c) minimum of 12 weeks follow-up after initiation of upadacitinib as of 1 January 2024. Patients who ceased the drug prior to 12 weeks were still included for analysis. Exclusion criteria were as follows: (1) commencement of upadacitinib primarily for a different indication and (2) patient moving service and follow-up data subsequently not available.

Data collection

We collected baseline demographic data, disease characteristics, concomitant comorbidities, prior therapies and follow-up data from the electronic medical records. We used the Harvey-Bradshaw to assess clinical disease activity. We recorded biomarkers of disease

activity including CRP; serum albumin and FCAL. All FCAL samples were measured using standard ELISA (Lothian: Calpro AS, Norway (quantifiable range 25–1250 μ g/g); Devon: Immundiagnostik, Bensheim, Germany (quantifiable range 6–2100 μ g/g)). We recorded endoscopic assessment and cross-sectional imaging which occurred 3 months prior to commencing the medication or during follow-up. We recorded changes to upadacitinib dose and prescription of corticosteroids (both at discretion of the treating clinician). We recorded adverse events including surgery, hospitalisation and mortality. We followed patients until their most recent clinical interaction or until upadacitinib was discontinued.

Primary and secondary outcomes

Our primary outcome was treatment persistence at week 24. Secondary outcomes included treatment persistence at weeks 12 and 52, clinical remission, CRP remission, FCAL remission and normal serum albumin, at week 12 (± 4 weeks), week 24 (± 8 weeks) and week 52 (± 8 weeks). Other secondary outcomes assessed were upadacitinib dosing regimens, corticosteroid use, adverse events, hospitalisation and surgery. We assessed baseline predictors for treatment persistence.

Definitions

We defined clinical remission as an HBI of < 5 in the absence of corticosteroids.⁹ We defined CRP remission as a CRP ≤ 5 mg/L and FCAL remission as a FCAL < 250 μ g/g.⁹ Normal serum albumin level was defined as ≥ 36 g/L as per our laboratory reference range. High cholesterol was defined as a serum cholesterol ≥ 5 mmol/L. Severity of endoscopic and radiological changes was based on the formal scoring system the clinician used (such as the Simple Endoscopic Score for Crohn's disease) or, if no formal scoring system was used, was based on the clinician's description of changes such as mild, moderate or severe inflammation. We categorised radiological and endoscopic disease as inactive, mild, moderate or severe. We defined the induction period as the first 12 weeks of therapy.³ The maintenance period was considered beyond 12 weeks. For disease treatment cessation, we defined primary non-response as failure to achieve clinical and/or biomarker (CRP or FCAL) remission and subsequent cessation of the drug. We defined secondary loss of response as obtaining clinical and/or biomarker remission (minimum one parameter) and subsequently losing response and ceasing therapy. Serious adverse events were defined as those that led to hospitalisation, cessation of drug, disability or death. For phenotype location subanalysis, we used the Montreal classification. If a patient had ileocolonic disease and had previously undergone a colectomy, we considered that patient as having ileal disease in the phenotype subanalysis.

Statistical analysis

We used SPSS V.25 (IBM) and Prism V.10.0 (Graphpad Software, San Diego, California, USA) for statistical analyses and generation of graphs. We present descriptive statistics as medians with IQR for continuous variables, and frequencies with percentages for categorical variables. For comparison of non-parametric continuous variables, we used the Kruskal-Wallis test. We assessed primary outcomes using the Kaplan-Meier survival analysis. Patients were censored at failure or at last follow-up. Patients who discontinued therapy for any reason were considered non-remission for all indices after the time point they ceased treatment. We used Cox proportional hazard regression analyses to identify potential baseline predictors of persistence. Variables for analysis were chosen a priori and are listed in online supplemental table 1. Variables from the univariable analysis with a $p < 0.20$ were fitted, and a stepwise backward selection approach was adopted to identify significant predictors. We considered a $p < 0.05$ to be significant for all statistical tests.

Ethical considerations

We regarded this work as a clinical service evaluation. All data were collected as part of routine clinical care. Our study is covered under the NHS Health Research Authority.¹⁰

RESULTS

Patient selection

135 patients with Crohn's disease were started on upadacitinib. A total of 42 patients were excluded from primary analysis (online supplemental figure 1). The number of patients included for analysis was 93.

Patient population

Patient demographics, disease characteristics and comorbidities are summarised in table 1. The median age of the cohort was 36 years old (IQR 26–49). 55 % of the cohort were male. Most patients (98%, 91/93) had been treated with anti-TNF therapy (figure 1, table 1 and online supplemental table 4). 76% (71/93), 53% (49/93) and 12% (11/93) had been treated with an IL-12/23 p40 or IL-23 p19 inhibitor, anti-integrin or JAK inhibitor, respectively. 16% (15/93), 30% (28/93), 41% (38/93) and 11% (10/93) had been treated with 1, 2, 3 and 4 different classes of advanced therapies. Baseline disease activity is presented in table 1. Median HBI was 8 (IQR 5–11), median CRP was 10 mg/L (IQR 3–30), median FCAL was 615 µg/g (IQR 211–1229) and median albumin was 35 g/L (IQR 32–40). All patients who underwent baseline endoscopic assessment (32%, 30/93) had luminal inflammation. See online supplemental tables 2 and 3 for radiological and endoscopic severity data.

Table 1 Phenotype at initiation

All patients (n=93)	
Male sex	51 (55%)
Age, years, median (IQR)	36 (26–49)
Disease duration, years, median (IQR)	12 (6–16)
Smoking status	
Never	72 (77%)
Current	10 (11%)
Previous IBD-related luminal surgery	29 (31%)
Age at diagnosis	
≤16 years (A1)	23 (25%)
17–40 years (A2)	57 (61%)
>40 years (A3)	13 (13%)
Disease location	
Ileal (L1)	15 (16%)
Colon (L2)	35 (38%)
Ileocolonic (L3)	43 (46%)
Upper gastrointestinal involvement (L4)	24 (26%)
Disease behaviour	
Non-stricturing, non-penetrating (B1)	54 (58%)
Stricturing (B2)	26 (28%)
Penetrating (B3)	13 (14%)
Perianal disease (p)	24 (26%)
Extraintestinal manifestations (EIM)	
Total number of patients with EIMs	50 (54%)
Enteropathic arthritis	24 (26%)
Dermatological	11 (12%)
Oral	8 (9%)
Primary sclerosing cholangitis	4 (7%)
Ocular	3 (3%)
Comorbidities	
Total number of patients with comorbidities	37 (40%)
Immune-mediated inflammatory diseases	13 (14%)
Metabolic syndrome/obesity/dyslipidaemia	11 (12%)
Respiratory	10 (11%)
Cardiac/vascular	6 (6%)
Renal	4 (4%)
Venous thromboembolism	3 (4%)
Other	14 (15%)
Prior advanced therapy class exposure*	
Anti-TNF	91 (98%)
IL-12/23 and IL-23 inhibitors	71 (76%)
Anti-integrin	49 (53%)
JAK inhibitor	11 (12%)
Calcineurin inhibitor	2 (2%)
Upadacitinib induction dose	
45 mg	92 (99%)
15 mg†	1 (1%)
Corticosteroid use during induction	32 (34%)
Baseline disease severity	
Median HBI (n=37)‡	8 (5–11)
Median CRP, mg/L (n=62)	10 (3–30)

Continued

Table 1 Continued

All patients (n=93)	
Median albumin, g/L (n=62)	35 (32–40)
Median FCAL, µg/g (n=50)	615 (211–1229)
*Prior drug exposure listed in online supplemental table 4.	
†13 patients had a stoma, therefore, HBI could not be calculated.	
‡Induction dose of 15 mg due to stage 4 chronic kidney disease.	
Anti-TNF, anti-tumour necrosis factor; CD, Crohn's disease; CRP, C-reactive protein; EIM, extraintestinal manifestations; FCAL, faecal calprotectin; HBI, Harvey-Bradshaw Index; IL, interleukin; JAK, Janus kinase.	

Upadacitinib persistence

The cohort had a median follow-up period of 25 weeks (IQR 15–42 weeks). Persistence rates were 87.1% at week 12, 81.7% at week 24 and 62.8% at week 52 (figure 2). On univariable Cox regression analysis, only disease duration was negatively associated with persistence (HR 0.99, 95% CI 0.99 to 1.00, $p=0.04$), therefore, multivariable analysis could not be performed. Reasons for treatment cessation included primary non-response 13% (12/93), secondary loss of response 3% (3/93) and adverse events 10% (9/93).

Effectiveness outcomes

Rates of clinical remission were 64% (42/66) at week 12, 48% (22/46) at week 24 and 38% (8/21) at week 52 (online supplemental figure 2). CRP remission rates were 55% (40/73) at week 12, 38% (20/53) at week

24 and 19% (6/22) at week 52. FCAL remission rates were 50% (24/48) at week 12, 36% (15/42) at week 24 and 19% (3/16) at week 52. Rates of albumin normalisation were 65% (46/71) at week 12, 45% (25/55) at week 24 and 22% (33/68) at week 52. We observed a significant reduction in HBI, CRP and FCAL during follow-up (figure 2). A minority of patients had endoscopic and radiological assessment during the study period (online supplemental tables 2 and 3 for outcomes).

When considering disease location, clinical remission rates at week 12 were 45% (5/11), 77% (17/22), 65% (20/31) for ileal, colonic and ileocolonic disease, respectively (online supplemental figure 3). Rates of clinical remission at week 24 were 27% (3/11), 53% (9/17) and 56% (10/18) for ileal, colonic and ileocolonic disease respectively. CRP remission rates at week 12 were 48% (10/21), 68% (15/22) and 50% (15/30) for ileal, colonic and ileocolonic disease, respectively. CRP remission rates at week 24 were 36% (5/14), 40% (6/15) and 38% (9/24) for ileal, colonic and ileocolonic disease, respectively. FCAL remission rates at week 12 were 64% (9/14), 50% (7/14) and 40% (8/20) for ileal, colonic and ileocolonic, respectively. FCAL remission rates at week 24 were 30% (3/10), 50% (8/16) and 25% (4/16) for ileal, colonic and ileocolonic disease, respectively.

Dosing regimens

All patients were commenced on 45 mg daily except for one patient, who was commenced on 15 mg daily due to stage 4 chronic kidney disease. One patient

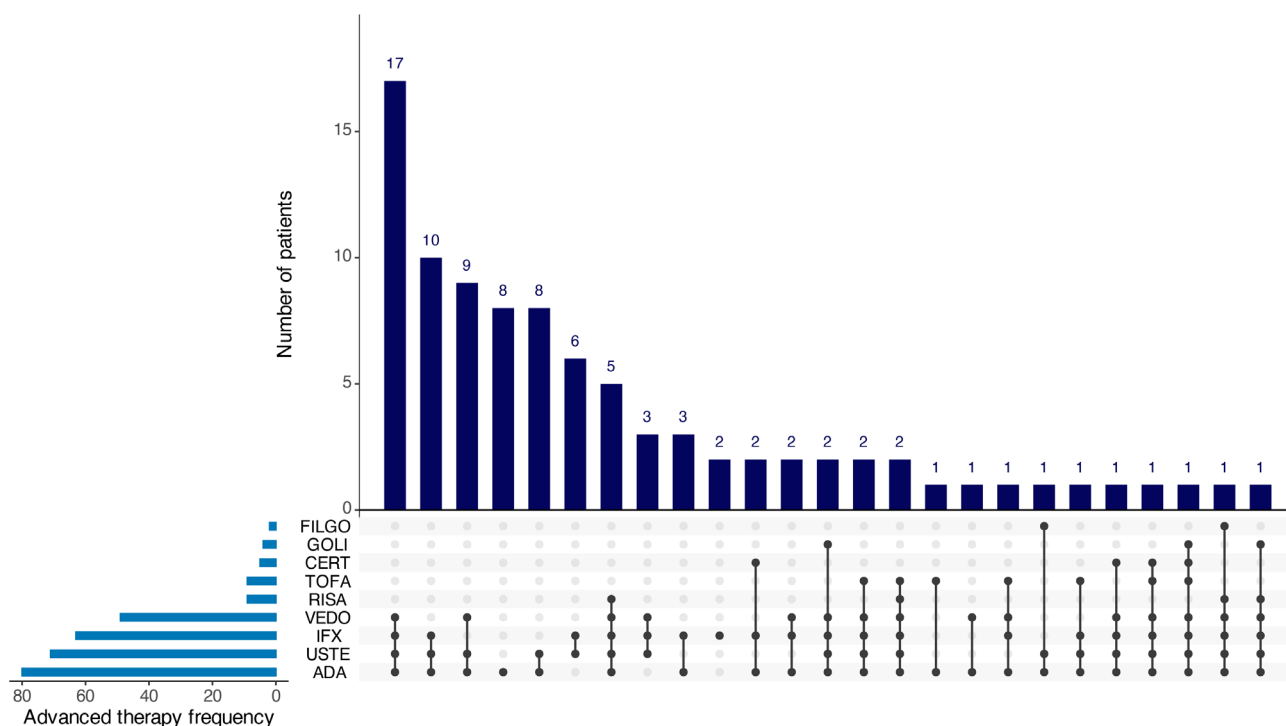


Figure 1 UpSet plot demonstrating advanced therapy exposure and combinations of advanced therapies.

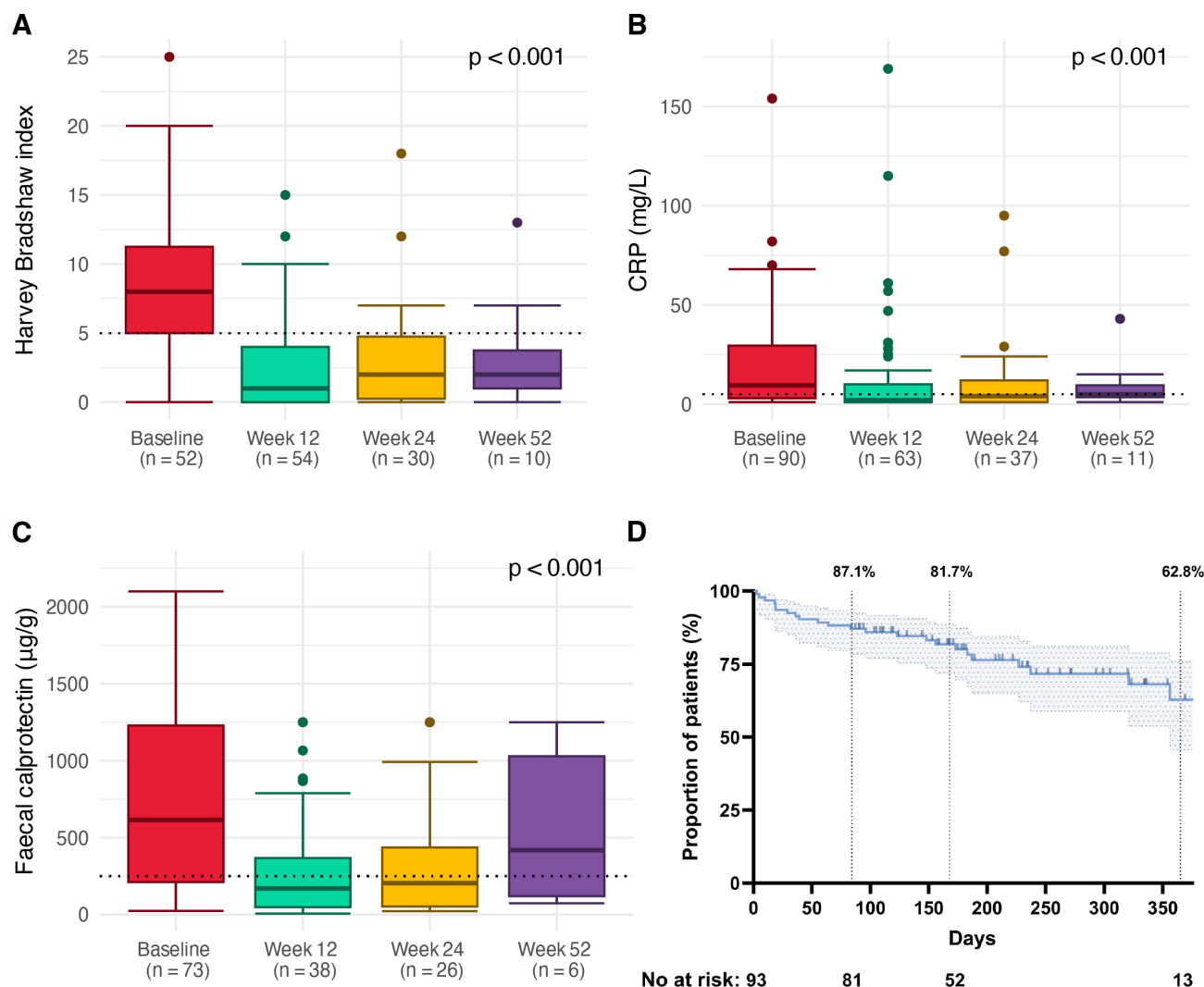


Figure 2 (A) Changes in Harvey-Bradshaw Index (HBI) during follow-up; (B) changes in CRP during follow-up; (C) changes in faecal calprotectin during follow-up (graphs are depicted as Tukey plots. Kruskal-Wallis test used to determine significant differences between the three time points). (D) Kaplan-Meier curve showing persistence of upadacitinib therapy. Kaplan-Meier curve showing persistence of upadacitinib therapy (dotted line depicts persistence at weeks 12, 24 and 52, respectively). CRP, C-reactive protein.

underwent an extended induction (45 mg daily for 16 weeks total) due to inadequate response. This patient ultimately ceased medication for primary non-response. Of the 81 patients who proceeded to maintenance therapy, 22% (18/81) and 78% (63/81) patients were reduced to 15 mg and 30 mg daily, respectively. One per cent (1/81) were de-escalated from 30 mg to 15 mg during follow-up. 17% (14/81) of patients had their dose escalated during follow-up; 10% (8/81) from 15 mg to 30 mg daily, and 7% (6/81) from 30 mg to 45 mg daily. For those who escalated to 45 mg of therapy during the maintenance period, two are still completing their temporary dose escalation of 45 mg, two subsequently ceased therapy for primary non-response, and two patients are currently maintained on 30 mg daily after no more than 8 weeks of 45 mg daily. Of the 52 patients who were on therapy for 24 weeks or more, only 17% (6/52) were on 15 mg daily as a maintenance dose.

Steroid prescription, Crohn's disease-related hospitalisation and surgery

During the maintenance period, 11% (9/81) were prescribed corticosteroids. Six per cent (5/81) commenced corticosteroids between 12 and 24 weeks for primary non-response. Eight per cent (4/52) commenced corticosteroids beyond 24 weeks; 4% (2/52) for primary non-response and 4% (2/52) for loss of response. One of the primary non-responders who commenced corticosteroids beyond 24 weeks was the patient who had the extended upadacitinib induction regimen. 15% (14/93) were hospitalised due to a flare of Crohn's disease. Eight per cent (7/93) underwent Crohn's disease-related resectional surgery during the study period. Three per cent (3/91) underwent emergency surgery; one subtotal colectomy for luminal flare, one total colectomy for refractory proctitis with recurrent perianal sepsis and the other an emergency laparotomy with small bowel resection for

perforations. Four per cent (4/93) underwent elective surgery for resection of symptomatic fibrotic strictures, which were present prior to commencing upadacitinib. 13% (3/24) of patients with perianal disease developed perianal abscesses and required an examination under anaesthesia. For patients with a history of extraintestinal manifestations (EIM) of disease still on upadacitinib at the end of the study, 79% (22/28) of patients with non-PSC EIMs were inactive at last follow-up. No patients ceased medication primarily due to an active EIM of disease. 31% (4/13) of patients with stomas (11 ileostomies and 2 colostomies) reported the tablet regularly came through the stoma. This exclusively occurred in patients with end ileostomies. Three of the four patients essentially had their full small bowel length, with only one of these four patients having had additional small bowel resected. Three of the four patients remain on upadacitinib, with one having ceased due to primary non-response. Of the three patients who continue on drug, two have normalised their biomarkers, with the other patient's clinical symptoms and CRP improved.

Safety

43 adverse events were recorded across 40% (37/93) of the cohort (table 2). Serious adverse events occurred in 12% (11/93) of the cohort. One (1%) adverse event was associated with mortality; a patient with small bowel perforation. This occurred in a patient who was commenced on upadacitinib in hospital for a severe small bowel Crohn's flare. The patient developed worsening abdominal pain and was found to have evidence of a bowel perforation on cross-sectional imaging, which was not present on cross-sectional imaging 9 days earlier.

DISCUSSION

In this highly medically refractory cohort, where 82% of the cohort had exposure to at least two classes of advanced therapies, and 52% had exposure to at least three classes of advanced therapies, persistence rates were 81.7% at 24 weeks. Response to induction was 64% of patients achieving clinical remission, 55% achieving CRP remission and 50% achieving FCAL remission. Sustained remission occurred in a substantial proportion of patients. Patients with colonic disease responded best, with a signal towards ileal disease responding less well. Most patients with a perianal phenotype did not experience a deterioration of perianal disease.

Our data add valuable information to the phase 3 trial data³ and the previously two published real-world cohorts.^{5,6} The University of Chicago's induction experience was largely positive, where 70.6% achieved clinical remission (HBI<5), 64% achieved CRP remission and 62% achieved FCAL remission.⁵ The observed clinical remission rates for induction were higher compared with U-EXCEL (49.5%),

Table 2 Adverse events (AEs)

Adverse events	All patients (n=93)
Total number of AEs	43
Total number of patients with AEs	37 (40%)
Infection*	14 (15%)
Herpes zoster reactivation*	3 (3%)
Headache*	4 (4%)
Acne	6 (6%)
New hypercholesterolaemia	5 (5%)
Dermatological (not acne)	4 (4%)
Deranged liver function tests†	2 (2%)
Venous thromboembolism*	1 (1%)
Large retinal detachment*	1 (1%)
Small bowel perforation*	1 (1%)
Nausea and vomiting	1 (1%)
Myalgias*	1 (1%)
AE causing temporary medication cessation	12 (13%)
Serious adverse events (n=93)	
Total number of patients with serious AEs	11 (12%)
AE causing permanent medication cessation	9 (10%)
AE causing hospitalisation	4 (4%)
Nausea and vomiting*	1 (1%)
Abscess*	2 (2%)
Influenza	1 (1%)
*Adverse events that led to permanent cessation of upadacitinib; nausea and vomiting, headache, large retinal detachment, small bowel perforation, venous thromboembolism, Stevens-Johnson syndrome, multifocal abscess, myalgias and herpes zoster reactivation with a superimposed bacterial infection.	
†These LFT derangements were all mild elevations of ALTs, however, all less than 100 U/L (reference range=10–50 U/L).	
AE, adverse event; LFT, liver function tests.	

U-EXCEED (38.9%)³ and a multicentre US cohort (27.2%),⁶ however, these were different cohorts with different methods for assessing clinical remission. The multicentre US cohort's lower clinical remission rates for induction may partially be explained by numerous patients receiving less than 45 mg daily for induction.⁶

Most of our cohort received 30 mg as maintenance therapy, particularly among those who were on therapy for greater than 24 weeks. This is not surprising given the highly refractory nature of the cohort and upadacitinib's increasing effectiveness in IBD with higher dosing.¹¹ Our data suggest that patients with Crohn's disease are less likely to do well with 15 mg dosing. This finding is also suggested in the real-world multicentre US study.⁶ Higher rates of clinical remission occurred in 30 mg dosing than 15 mg dosing at 1 year in the U-ENDURE trial (47.6% vs 37.3%).³ In the absence of safety and tolerance concerns, our centres favour using 30 mg as a maintenance dose in light of the above data. There is currently a paucity of data to describe outcomes of de-escalating dosing from 30 mg for 15 mg during maintenance dosing and is an area of future research.

One issue observed in our cohort was patients with stomas encountering problems absorbing the drug. 30% of these patients reported the tablet passing through the stoma. This is a novel finding as the clinical trials excluded patients with stomas.^{3,12} The tablets used in Crohn's disease are extended-release formulations designed to decrease the peak-to-trough fluctuations in plasma concentrations of once daily dosing.¹³ Strategies used across our centres to counter this problem have included taking the tablet at night and using low-dose loperamide if considered safe to do so. A strategy akin to that of the phase two clinical trial of upadacitinib in Crohn's disease (CELEST),¹² where immediate release tablets were prescribed twice daily may be a more effective strategy for stoma patients and warrants further exploration.

Adverse events occurred in 40% of our cohort, which is higher than observed in other real-world cohorts (32.4% and 27%).^{5,6} The majority of these were not severe, in line with real-world data and the phase 3 trial data.³ The most observed adverse event was infection. Upadacitinib was generally well tolerated with 10% ceasing because of adverse events. It is unclear whether the bowel perforation was related to upadacitinib; this event occurred in an already hospitalised patient with severe Crohn's disease where only two doses of upadacitinib were given as salvage therapy.

A frequently occurring problem in clinical practice is choosing subsequent advanced therapies for patients with severe Crohn's disease. Responses to advanced therapy seem to max out between 30% and 60%,¹⁴ and a substantial number of patients will subsequently lose response to therapy over time.^{15–17} There is usually a diminishing return in efficacy after subsequent biologics, particularly after anti-TNF therapy.^{18,19} These problems create the issue of the 'therapeutic ceiling'.¹⁴ Our data demonstrate that upadacitinib remains effective for patients with Crohn's disease who have failed other advanced therapies. There are increasing data supporting that JAK inhibitors maintain effectiveness in patients with IBD with prior advanced therapy failure, as demonstrated by several real-world tofacitinib studies, where its effectiveness in ulcerative colitis was not negatively affected by the previous number of biologic therapies.^{20–22}

Strengths and limitations

Our cohort is highly refractory with most patients having failed multiple classes of advanced therapies, including previous JAK inhibitors. We present the first real-world study to our knowledge to report on persistence of upadacitinib in Crohn's disease, explore reasons for treatment cessation and to report weeks 24 and 52 data.

The limitations of this study primarily relate to its retrospective nature which limited detailed assessment of response, including EIMs which are best assessed with validated scoring systems. Data were not

available for all time points; however, all patients had clinical or biochemical data points which described their response to upadacitinib. Endoscopic and radiological data were not universally scored using formal scoring systems; however, this is a common limitation of real-world studies given formal scoring systems are not frequently used by clinicians. There were a low number of FCALs available for week 52 outcomes, potentially biasing the result to be lower, given 47% (11/23) of week 52 patients had ceased upadacitinib and were therefore considered non-remission for this outcome.

CONCLUSION

We have demonstrated in a real-world, highly, medically refractory cohort that upadacitinib is effective in achieving clinical remission and has good treatment persistence. We observed no new safety signals.

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