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ORIGINAL ARTICLE

Patients with Crohn's Disease and Ileostomy Can Respond to Upadacitinib

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Abstract

Background Recent studies have established a role for Janus kinase (JAK) inhibitors in the management of patients with inflammatory bowel disease. However, these studies excluded patients with an ileostomy.

Aim We sought to evaluate the clinical response of patients with Crohn's disease (CD) and ileostomy who were treated with upadacitinib.

Methods This retrospective study included patients with CD who had an ileostomy secondary to medically refractory CD and who were treated with upadacitinib. Patients who underwent ileostomy takedown and continued taking upadacitinib were analyzed separately from patients with an ileostomy throughout upadacitinib treatment duration. The primary endpoint was clinical response defined by either continuation or discontinuation of upadacitinib. The secondary endpoint was identifying variables that lead to discontinuation of upadacitinib.

Results A total of 48 patients, between the ages of 17–70 years met our inclusion criteria of having CD, an ileostomy, and upadacitinib use after ileostomy creation. Of the 48 patients, 32 (67%) had clinical improvement in CD activity with upadacitinib use based on review of clinical documentation. Upadacitinib was discontinued in 16 patients (33%) for various reasons including refractory symptoms related to CD, deep vein thrombosis, anemia/leukopenia, insurance denial, pregnancy planning, headache/back pain, or squamous cell carcinoma of the skin.

Conclusion We evaluated the efficacy of upadacitinib in patients with CD and ileostomy. Two-thirds of our cohort experienced improvement in CD-related symptoms with upadacitinib use. Further studies are needed to evaluate if altered gastrointestinal anatomy significantly impacts absorption and efficacy of upadacitinib in patients with CD.

Keywords Upadacitinib · Janus kinase inhibitors · Crohn's disease · Ileostomy

Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is an immune-mediated condition characterized by inflammation of the gastrointestinal tract that requires medical management and at times surgical intervention [1, 2]. Biologic agents and small molecules have improved rates of achieving clinical remission as well as mucosal healing, which subsequently lead to improved patient outcomes [3, 4]. Although advanced therapies can successfully treat patients with IBD, there are a subset of patients who do not respond. Approximately, 10–40% of patients are primary non-responders, while 50% will experience secondary loss of response within the first year of initiating biologic treatment [5, 6].

Recent studies have established a role for Janus kinase (JAK) inhibitors in the management of patients with IBD [7–11]. JAK inhibitors are small molecules that penetrate cells to act on multiple intracellular cytokine-dependent inflammatory signaling cascades associated with IBD activity [12]. These small molecules have proven efficacious in both biologic-naïve and exposed patients [13]. There are four JAK enzymes, JAK1, 2, and 3 and tyrosine kinase 2,

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each of which can be preferentially acted on by a cytokine depending on the setting [14]. JAK1 selectivity has shown to have targeted activity against interleukin (IL)-6 and interferon gamma, resulting in clinical improvement in IBD with a lower-risk profile compared to other JAK inhibitors with less selectivity [15].

Upadacitinib is a selective JAK1 inhibitor that has been shown to induce and maintain clinical remission and endoscopic response in patients with moderate-to-severe CD; however, these studies explicitly excluded patients with an ileostomy [8–11]. There have been concerns around the efficacy of JAK inhibitors in patients with an ileostomy given the possibility for altered intestinal transit and malabsorption [16–18]. We aimed to evaluate the clinical response of patients with CD who have an ileostomy to treatment with upadacitinib.

Methods

Study Population

This retrospective study included patients diagnosed with CD aged 17 to 70 years with an ileostomy secondary to medically refractory CD. Patients were required to have documentation of inadequate response, loss of response, or intolerance to at least one anti-tumor necrosis factor (anti-TNF) agent prior to initiation of upadacitinib. All patients with an ileostomy received upadacitinib for at least one month. Patients were evaluated within our multi-site hospital system between November 2018 and February 2024. Patients who received upadacitinib prior to intestinal surgery were excluded. Of note, patients who underwent ileostomy takedown and continued taking upadacitinib were analyzed separately from patients with an ileostomy throughout treatment duration. Each chart was evaluated for concomitant use of loperamide, proton pump inhibitor, and/or opioid with upadacitinib.

Endpoints

The primary endpoint was clinical response defined by either continuation or discontinuation of upadacitinib. The secondary endpoint was identifying variables that necessitated discontinuation of upadacitinib.

Results

Participants' Characteristics

A total of 48 patients met our inclusion criteria of having CD, ileostomy, and upadacitinib use after ileostomy creation. Demographic variables for all patients are presented in Table 1. The median patient age was 40 years (range 17–70 years) and 54% of patients were male. The median years of active CD was 18 years (range 3–56 years).

There were two patients whose ileostomy creation predated the electronic medical record and did not have details on therapies prior to ileostomy creation documented in their chart.

Medication Use for Crohn's Disease

Table 2 provides data on ileostomy age and medications used before and after ileostomy creation. Median age of ileostomy was 30 months (range 5–312 months). Of the 48 patients, 4 patients underwent ileostomy takedown. In the patients who had previous treatment data available, the most common medications trialed and failed before ileostomy creation were infliximab (78%), adalimumab (69%), and thiopurines (69%). The most common medication initiated after ileostomy creation was upadacitinib in 19 patients (40%). It should be noted that all of these 19 patients had been treated with at least one anti-TNF agent prior to ileostomy creation. Other medications used after ileostomy creation that failed before initiating upadacitinib included ustekinumab (38%), adalimumab (23%), and thiopurines (23%). The median duration of upadacitinib use in patients with an ileostomy was 6 months (range 1–33 months). Of the four patients who underwent ileostomy takedown, all continued taking upadacitinib after ileostomy takedown with median duration of use of 14.5 months (range 9–21 months).

Patient Response to Upadacitinib

Data on patient response to upadacitinib use are provided in Table 3. Of the 48 patients, 32 (67%) had clinical improvement in CD activity with upadacitinib use based on review of clinical documentation. None of these 32 patients reported visualizing upadacitinib tablets in their ileostomy output. Of these patients, median duration of upadacitinib use was 6.5 months (1–33), and all patients continued upadacitinib use. Upadacitinib was discontinued in 16 (33%) patients for various reasons. The most

Table 1 Patient demographics

	N (number of patients)	Median (range) or number (%) of patients
Age (years)	48	40 (17–70)
Sex	48	26 (54% Male)
Crohn's disease	48	48 (100%)
Active Crohn's disease (years)		18 (3–56)

Table 2 Medication use before and after ileostomy creation

	N (number of patients)	Median (range) or number (%) of patients
Ileostomy age (months)	48	30 (5–312)
Ileostomy takedown		4 (8%)
Pre-ileostomy failed medications	48	
5-Aminosalicylic acid		21 (44%)
Thiopurine (6-mercaptopurine, azithromycin)		33 (69%)
Methotrexate		15 (31%)
Infliximab		38 (78%)
Adalimumab		33 (69%)
Certolizumab		12 (25%)
Tofacitinib		3 (6%)
Risankizumab		0 (0%)
Ustekinumab		23 (48%)
Vedolizumab		21 (44%)
None of these		1 (2%)
Unknown/not documented		2 (4%)
Post-ileostomy medications failed before upadacitinib	48	
5-Aminosalicylic acid		2 (4%)
Thiopurine (6-mercaptopurine, azithromycin)		11(23%)
Methotrexate		8 (16%)
Infliximab		10 (21%)
Adalimumab		11(23%)
Certolizumab		8 (16%)
Tofacitinib		1 (2%)
Risankizumab		5 (10%)
Ustekinumab		18 (38%)
Vedolizumab		10 (21%)
None of these		19 (40%)
Unknown/not documented		0 (0%)
Upadacitinib duration with ileostomy (months)	48	6 (1–3)
Upadacitinib duration with and without Ileostomy (months)	4	14.5 (9–21)

common cause for discontinuation was refractory symptoms related to CD (56%). Of the nine patients with refractory symptoms related to CD, four noted seeing full upadacitinib tablets with their ileostomy output. Per chart review, none of these patients were counseled on trialing loperamide or other antidiarrheals in an attempt to slow intestinal transit and optimize absorption. There were 20 patients taking loperamide, 15 patients taking a proton pump inhibitor, and 18 patients taking an opioid.

Other reasons for upadacitinib discontinuation were deep vein thrombosis, anemia/leukopenia, insurance denial, pregnancy planning, headache/back pain, or squamous cell carcinoma of the skin. In the 16 patients who discontinued upadacitinib, the median duration of use was 5 months (range 2–10 months).

Discussion

This study evaluated the efficacy of upadacitinib in patients with CD and ileostomy secondary to medically refractory CD. Both phase 2 [8, 9] and phase 3 [10, 11] trials demonstrated that upadacitinib use for induction and maintenance of remission in patients with moderate-to-severe CD and UC was superior to placebo. However, all of these trials excluded patients with an ileostomy [9–11]. Approximately, 60% of patients with CD will require surgery. Nearly one third of patients with an ileostomy secondary to medically refractory CD experience clinical recurrence that may require subsequent medical therapy, with another 16% requiring additional surgeries [19].

Table 3 Response to upadacitinib

	Median (range) or number (%) of patients
Response to upadacitinib	32 (67%)
Ileostomy intact	28 (89%)
Ileostomy intact, post-takedown	4 (11%)
Duration of upadacitinib use (months)	6.5 (1–33)
Discontinued upadacitinib	16 (33%)
Refractory IBD	9 (53%)
Whole pills in ileostomy output	4 (44%)
Anemia/leukopenia	2 (12%)
Deep vein thrombosis	1 (6%)
Insurance denial	1 (6%)
Pregnancy planning	1 (6%)
Headache/back pain	1 (6%)
Skin squamous cell carcinoma progression	1 (6%)
Duration of upadacitinib use (months)	5 (2–10)

Currently, there are no clinical trials of advanced therapies for CD that include patients with an ileostomy [20]. The recruitment of patients with an ileostomy is likely absent due to contemporaneous indices for measuring outcomes in patients with CD not having been developed or validated in these patients [20]. Therefore, investigation into the outcomes of these post-surgical patients with the various available medical therapies is a presently unmet need [21, 22].

The clinical response to upadacitinib demonstrated in our cohort is encouraging given the paucity of pharmacologic options in patients with inadequate response to anti-TNF agents and other biologics. The upadacitinib package insert cautions that presence of upadacitinib residue or formed tablets in the stool or ileostomy output may be encountered, and more common in patients with altered anatomy associated with faster gastrointestinal transit times [23]. Interestingly, only four patients experienced this outcome; however, all four of these patients discontinued upadacitinib due to refractory symptoms related to CD. The recommended dosage of upadacitinib for patients with CD is 45 mg (mg) once daily for 12 weeks for induction followed by a maintenance dose of 15 mg once daily [23]. For patients with refractory, severe, or extensive disease, a maintenance dosage of 30 mg daily can be considered [23]. Adverse reactions that have been reported during induction or maintenance include upper respiratory tract infections, anemia, pyrexia, acne, herpes zoster, and headache [23].

Adverse events (AEs) associated with upadacitinib use in our cohort were similar to those reported in the phase 2 and 3 trials, with fewer than 10% of our patients experiencing AEs that led to discontinuation [8–11]. Specific AEs identified in our cohort were anemia, leukopenia, deep vein thrombosis, progression of skin malignancy, and headache.

Examining the pharmacokinetics of upadacitinib may provide insight into variations in absorption. Upadacitinib is 52% bound to plasma proteins and metabolized in vitro by cytochrome P450 enzyme 3A [24]. The extended release (ER) formulation used to treat IBD has a hydroxypropyl methyl cellulose polymer that creates a gel layer during dissolution that facilitates timed absorption through erosion of the polymer chains [25]. Peak plasma concentration of upadacitinib occurs within two hours of administration under fasting conditions and four hours under non-fasting conditions; and the average half-life is 8–14 h after administration [26]. Upadacitinib exhibits high permeability and solubility across the pH range 1 to 7.5, allowing uniformity in absorption throughout the gastrointestinal tract [26]. This may explain why patients with altered gastrointestinal anatomy still experience clinical response. Evans et al. used pH sensitive radiotelemetry capsules to quantify the gastrointestinal pH of 66 participants without IBD or intestinal surgeries and found the small intestine pH to range from 6.6 in the proximal small intestine to 7.5 in the terminal ileum [27]. This pH range has been reproduced across several studies [28, 29]. Fallingborg et al. found similar values in 11 patients with an ileostomy secondary to UC, with pH 6.3 in the proximal small intestine and 7.3 in the distal small intestine [30]. These studies suggest similar pH levels and consequently similar absorptive potential of the small intestine in both healthy patients and those with an ileostomy. According to Bhatnagar et al., none of the evaluated CD-specific patient characteristics, including prior gastrointestinal surgeries, had a meaningful impact on upadacitinib pharmacokinetics [31]. This suggests that upadacitinib is adequately absorbed and effective in patients with CD regardless of their surgical history, including those with an ileostomy.

In addition to the effects of the small intestine pH, the biologic availability of a medication is also affected by its temporal contact with the mucosa of the small intestine. Given the large absorptive area between 200 and 500 m^2 of the small intestine in comparison to the stomach and colon, the small intestine is consistently appreciated as the primary site of medication absorption [32, 33]. Therefore, the amount of exposure a medication has to the small intestinal mucosa is an important factor in determining its absorptive potential [34]. This variable is largely contingent on the transit time of a medication through the small intestine. Several studies have estimated the average small intestinal transit time of tablets using gamma-scintigraphy to be between 3 and 4 h regardless of whether administration was fasted or fed [35–40]. It should be noted that these studies were done in healthy individuals without surgically altered gastrointestinal anatomy. The effect of eating after medication administration was investigated by

Fadda et al. [41] in ten healthy volunteers. Similar to the previously cited studies, the small intestinal transit time was not significantly different between the fasted and fed participants.

There is a paucity of data on gastrointestinal transit times in patients with an ileostomy. Fallingborg et al. [30] studied eleven patients with an ileostomy secondary to UC and found the median small intestinal transit time of a capsule after at least 8 h of fasting to be 10.3 h. In comparison to 39 healthy participants without ileostomy in their previous study, small intestinal transit time was found to be 8 h, suggesting slower transport time in patients with an ileostomy [28]. Bechgaard et al. [27] studied 10 patients with an ileostomy secondary to IBD and found the average small intestinal transit time of a dummy tablet after 12 h of fasting to be 4.9 h, consistent with transit times appreciated in healthy subjects in the previously mentioned studies. This wide spectrum of data in such small patient populations gives little confidence in the generalizability of these results but does highlight the potential variability in small intestinal transit time that may impact medication absorption on an individual level.

Given the variability in results and small population of the studies evaluating small intestinal transit time, consideration should be given to the possibility of inadequate time for absorption in some patients with an ileostomy. Examination of treatment modalities of other conditions associated with malabsorption secondary to surgically altered intestinal anatomy may provide insight into methods of optimizing upadacitinib absorption in patients with an ileostomy.

The ileum is of particular importance with nutrient concentration with eating, as a meal will trigger a neurohormonal process that slows small intestinal transit time in addition to the ileocecal valve delaying emptying of the intestinal contents into the colon [15]. Pharmacologic management strategies focus on slowing intestinal transit time with mu receptor agonists including loperamide and diphenoxylate-atropine that act at the level of the myenteric plexus [42]. These medications should be timed with meals due to the increase in small bowel transit time appreciated immediately after eating [14, 43].

In summary, we report that upadacitinib use in patients with CD and ileostomy secondary to medically refractory CD was well tolerated and efficacious in two-thirds of our cohort. Further studies are needed to evaluate if altered gastrointestinal anatomy significantly impacts absorption and efficacy of upadacitinib in patients with CD.

Author Contributions LL was responsible for data collection, formal analysis, writing of the initial draft, and editing of the final draft. FAF, SC, EVL, CH, JAK, and MFP were responsible for the critical review of the article. JGH was responsible for the conceptualization, methodology, and supervision of the project and critically reviewed the article.

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Data Availability He data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest E.V.L. has consulted for AbbVie, Abivax, Amgen, Astellas, Avalo, Biocon, Boehringer Ingelheim, Bristol-Myers Squibb, Celltrion, Eli Lilly, Fresenius Kabi, Genentech, Gilead, Iota Biosciences, Iterative Scopes, Janssen, Morphic, Ono Pharma, Protagonist, Surrozen, Takeda, and TR1X Bio; has had research support from AbbVie, Genentech, Gilead, Janssen, and Takeda; and is a shareholder of Exact Sciences and Moderna. FAF received consulting fees from Astellas, Avalo Therapeutics, Bausch, BMS, Braintree Labs, Fresenius Kabi, GI Reviewers, GSK, IBD Educational Group, Iterative Health, Janssen, Pharmacosmos, Pfizer, Sandoz Immunology, and Viatris.

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