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CASE REPORT

Gastroenterology: Inflammatory Bowel Disease

Rescue therapy with upadacitinib in medically refractory pediatric ulcerative colitis

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Abstract

Approved options for advanced therapy in pediatric inflammatory bowel disease (IBD) are limited. Although Janus kinase (JAK) inhibitors are approved in adult IBD, their benefit in pediatric populations is not yet delineated. We present a 13-year-old female patient with ulcerative colitis (UC) refractory to numerous therapies and courses of prednisone that ultimately responded to a JAK inhibitor. Initial treatment consisted of 5-aminosalicylate and azathioprine. This was changed to adalimumab due to persistent symptoms. Repeat colonoscopy revealed pancolitis, thus she was transitioned to vedolizumab. She was hospitalized twice for uncontrolled symptoms on vedolizumab and subsequent scope showed continued pancolitis. As a result, she transitioned to ustekinumab without symptomatic relief after adjusting to monthly dosing. The family declined colectomy, opting to exhaust all medical therapies. Upadacitinib was started and her symptoms resolved within 1 week, and she remains in steroid-free remission. This case illustrates the possible role of JAK inhibitors in extensively refractory pediatric UC patients before colectomy.

KEYWORDS

inflammatory bowel disease, Janus kinase inhibitor, pediatrics

1 | BACKGROUND

There is a dearth of federal drug administration (US Food and Drug Admininstration [FDA])-approved advanced medical therapies for pediatric inflammatory bowel disease (IBD). Current antitumor necrosis factor medications approved are limited to infliximab and adalimumab.[1] Infliximab use in pediatric IBD was approved for use in pediatric Crohn's disease in 2006 and pediatric ulcerative colitis (UC) in 2011.[2] Adalimumab was approved for pediatric UC in 2021 based on the ENVISION TRIAL.[3]

Biologics with targets other than tumor necrosis factor include vedolizumab and ustekinumab. Vedolizumab is an anti-integrin therapy, which reduces lymphocyte migration in inflammatory pathways. It is FDA approved for adult IBD and has been shown to be safe and effective in a multicenter retrospective chart review of children with pediatric IBD, although it is not currently approved in pediatrics.[4] Ustekinumab is a monoclonal antibody that targets interleukin (IL)-12 and IL-23 through the shared p40. It is approved for use in adult IBD and although it is not approved for pediatric use, its utility in pediatrics has been illustrated via several studies.[5,6]

Janus kinase (JAK) inhibitors including tofacitinib and upadacitinib are small molecule drugs that have recently been approved for use in adult IBD. Upadacitinib has been approved for adult use in both Crohn's disease and UC, and tofacitinib is currently only approved for use in adult UC. Tofacitinib has activity against both JAK 1 and JAK 3.[7] It has been shown in recent reports to be an effective treatment for refractory pediatric IBD.[8,9] Upadacitinib is a narrow spectrum JAK inhibitor, which specifically targets JAK 1 and reduces inflammation by limiting immune cell migration, adhesion, and cytokine release.[10] A randomized

controlled trial highlighted both rapid symptomatic and endoscopic remission in adult UC patients treated with upadacitinib.[11] Its utility in pediatric populations remains largely unknown. Several case series and case reports on pediatric patients have shown its effectiveness in helping patients achieve clinical remission, thus making it a reasonable option to utilize in medically refractory pediatric UC patients before considering colectomy.[12,13]

2 | CASE DESCRIPTION

We report a 13-year-old female with UC (Paris classification E4, Mayo 2) refractory to five different medical therapies. As a result, she was placed on intermittent steroids, which led to temporary clinical improvement. Throughout her 6-year disease course, she received a total of eight 14-day courses of steroids, each followed by a 1-month taper. Initial treatment at diagnosis was with an oral 5-aminosalicylate (5-ASA) (4.8 g daily). Due to continued symptoms, azathioprine (75 mg daily) was added. After a trial of 30 months and adequate levels of 6-thioguanine metabolites (386 pmol/8×108 red blood cells), she required hospitalization due to persistent symptoms of abdominal pain and diarrhea. Adalimumab was initiated at this time at 160, 80, then 40 mg every 2 weeks according to dosing recommendations at the time of initiation. She was readmitted later that year and her adalimumab frequency was increased to weekly due to worsening symptoms. At the time of admission, she had received 11 months of adalimumab treatment and her drug levels were 11.4 μg/mL without antibodies (goal of level >7.5 μg/mL). Repeat colonoscopy was performed and revealed continued inflammation (Mayo 2). She continued to report intense periumbilical and postprandial pain, and was therefore placed on tacrolimus (0.1 mg/kg) to act as a bridge to vedolizumab after 12 months of adalimumab treatment. She was hospitalized an additional two more times over a 2-month period for uncontrolled abdominal pain, diarrhea, and anorexia. Her vedolizumab frequency was increased to every 4 weeks. A repeat colonoscopy revealed continued pancolitis (Mayo 2); thus, ustekinumab induction was initiated after a total of 3 months of vedolizumab. The patient remained symptomatic despite 10 months of treatment and increased frequency of ustekinumab to every 4 weeks. Her calprotectin at this time was 2180 μg/g. Levels of ustekinumab were found to be 1.9 μg/mL after 11 months. Although subtherapeutic, the decision to discontinue this therapy was due to maximal dosing and frequency.

There were multiple discussions about colectomy throughout the disease course, but the family was opposed and insisted that all medical therapy options be exhausted. After documented failure of ustekinumab, upadacitinib 45 mg daily was initiated for induction. The patient was symptom free within 1 week of starting upadacitinib therapy and her calprotectin level was normalized to 9.3 μg/g within 4 weeks of initiation. She was not rescoped following initiation to assess for mucosal healing. She is currently on a maintenance dose of 30 mg daily and remains in clinical steroid-free remission 9 months after the initial dose of upadacitinib.

3 | DISCUSSION

There are a limited number of medications that are FDA approved for use in pediatric IBD. Patients with refractory disease may require multiple courses of corticosteroids to improve symptoms and are at risk of developing the numerous adverse effects associated with long-term steroid use. The time and diligence required to gain authorization to use nonapproved therapies is an additional barrier to effective treatment of refractory disease. The patient discussed here completed eight courses of prednisone and failed 5-ASA, immunomodulator therapy, and three biologics. She ultimately responded rapidly to upadacitinib and remains in remission.

Due to the relatively limited research on use of biologics in pediatric IBD as compared to their use in adults, definitions of drug failure and ideal trough levels are based on guidelines rather than firmly established levels. Studies on ideal adalimumab troughs during the maintenance phase of IBD treatment have shown that levels should be >5.85 μg/mL, and that higher levels should be considered in more severe or refractory disease.[14] The institution in the current study aims for trough levels >10 μg/mL. Despite having trough levels of 11.4 μg/mL, our patient continued to have significant clinical disease with abdominal pain as the most prominent feature. Repeat colonoscopy at this time showed continued inflammation which confirmed the lack of response to adalimumab and further supported the decision to begin vedolizumab therapy.

The decision to stop ustekinumab was based on the lack of evidence to support dose escalation greater than 90 mg q4 weeks. Although studies have shown success in shortening dose intervals from 8 weeks to 4 weeks, no evidence exists for further decreasing time between doses.[15] When our patient's ustekinumab levels remained low at 1.9 μg/mL despite being given the recommended dose, the decision was thus made to change therapy to upadacitinib rather than further increase the ustekinumab dose.

The decision to initiate upadacitinib was also based on its effectiveness in adult UC populations who experienced improved Mayo scores and endoscopic improvement following treatment with upadacitinib.[11]

Our patient had outcomes similar to those cited in adult studies. Her rapid response to treatment with upadacitinib,

which is not yet approved in pediatrics, illustrates the need for further investigation regarding the drug's safety and effectiveness in refractory pediatric IBD patients including those with acute or severe colitis. JAK inhibitors have the potential to reduce the need for prolonged steroid use in this population and may eliminate the need for eventual colectomy due to refractory disease.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The patient and her family consented to the presentation and publication of this case.

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