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Original Article

The Role of Tofacitinib in the Treatment of Acute Severe Colitis in Children

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Abstract

Objectives: Acute severe colitis (ASC) occurs in up to 15 percent of children with ulcerative colitis, with a high index of morbidity and mortality. Treatment includes high-dose steroids, infliximab, and salvage therapies. Unfortunately, up to 20 percent of patients may need an urgent colectomy due to treatment failure. We report our experience using tofacitinib for the treatment of six patients.

Methods: A retrospective review of our medical electronic records was conducted. We included every patient with ASC and treatment failure, in whom tofacitinib was used as a salvage therapy. Response, complications, and disease course were noted.

Results: Six patients were included with Pediatric Ulcerative Colitis Activity Index (PUCAI) scores ranging from 65 to 85 on admission, and 35 to 85 before tofacitinib was started (*P* 0.07). Median response time was 72 h. A median decrease of 40 points in PUCAI was noted (*P* 0.00001). Mean length of stay was 18 days with discharge 9 days after tofacitinib introduction. Haemoglobin, albumin, fecal calprotectin, and CRP improved after tofacitinib (*P* 0.02, *P* 0.02, *P* 0.025, and *P* 0.01, respectively). The mean follow-up was 8.5 months, four patients achieved complete remission and only one had a recrudescence of symptoms (*P* 0.01). One patient had a systemic Epstein-Barr virus infection prior to tofacitinib therapy, which resolved with rituximab treatment. No other complications were noted.

Conclusions: Tofacitinib response is rapid and impressive in children suffering from ASC, and the safety profile appears comparable to or better than other available treatments. In the future, tofacitinib should be integrated into pediatric protocols.

Key words: tofacitinib; acute severe colitis; pediatrics

Introduction

The incidence of pediatric inflammatory bowel disease has increased in the last decade, with ulcerative colitis (UC) at 6 per 100,000 person-years in Canada. Acute severe colitis (ASC) has been defined as a Pediatric Ulcerative Colitis Activity Index (PUCAI) ≥65 points and usually develops in the first 3 months after diagnosis. It may be the initial presentation in up to 15 percent of patients. Moreover, its prevalence is approximately 25 percent during the disease course.[1–5]

Standard of care consists of high-dose intravenous corticosteroids (IVCS) with infliximab introduced by day 5. Salvage therapies include accelerated infliximab induction, calcineurin inhibitors, and other biologics. These therapies have decreased the need for urgent colectomy from up to 70 percent of patients to 10–20 percent. Unfortunately, regardless of initial treatment response, it remains approximately 50 percent 5 years after an ASC.[6–8]

Tofacitinib is a rapidly acting small molecule that inhibits Janus kinases (JAK) types 1, 2, and 3, which play a pivotal role in triggering and maintaining immune responses as they are responsible for pro-inflammatory cytokine transcription. JAK inhibitors have been approved for immune-related disorders like rheumatoid arthritis, psoriasis, and UC in the adult population.[9–12] Tofacitinib has proven effective in adult ASC.[13–15] Different characteristics make it an attractive option. It is absorbed rapidly, and response may be noted as early as day 3. Drug loss secondary to hypoalbuminemia and intestinal losses is non-existent. Moreover, its short half-life makes immunosuppression reversible after drug cessation. Finally, its non-immunogenicity allows for a possible recapture of response, even in previously treated patients.[16–22]

To date, the data regarding the use in the pediatric setting is lacking, with our group reporting the first case.[23] Since then, we have treated thirteen patients with tofacitinib, six of whom received it for an ASC.

Material and methods

We conducted a retrospective review from January 2021 to December 2022 of patients treated for an episode of ASC as defined by current guidelines. Patients were included if tofacitinib was used as a salvage therapy during an ASC. It was started at 10 mg twice a day and decreased to 5 mg twice a day after 8 weeks if remission was achieved.

Testing for tuberculosis was done by PPD and chest radiography. Serologies for hepatitis A, B, C, and E, rubella, measles, parotiditis, and varicella-zoster virus were performed at diagnosis. Prothrombin time, fibrinogen, activated partial thromboplastin time, HDL and LDL cholesterol, and triglycerides were measured before tofacitinib and repeated after 72 h. Duration of disease, previous treatments, indication for tofacitinib, and follow-up were noted. Haemoglobin, C-reactive protein (CRP), albumin, and PUCAI were documented at admission, on days 3 and 5, the day tofacitinib was started, 72 h later, at discharge, and at the last follow-up. Fecal calprotectin (FC) was measured during the episode and 8–12 weeks after tofacitinib introduction. Relapses were recorded. Clinical response was considered when a PUCAI decrease of ≥20 points was observed, and clinical remission with a PUCAI <10. Complete remission was clinical remission with normal FC and colonoscopy (no zone with a Mayo score >1).[7]

Data were analyzed using GraphPad Prism 8.0. Normality of distribution was determined using Kolgoromov–Smirnov Test. Friedman's Test was used if normally distributed and ANOVA when not. Fisher's Exact Test was used for categorical variables. Significance was established as $P < 0.05$.

Ethic's committee approval was not necessary, but an authorization for the review of medical charts and results publication was obtained.

Results

During the 24 month study period, 331 patients were diagnosed with IBD, of which 69 had a UC. Six ASC treated with tofacitinib were identified, ages ranging from 10.9 to 17 years old. Median length of stay was 18 days (7–58, $\sigma^2 = 281$) with no ICU admissions. Discharge occurred at a median of 9 days (2–13, $\sigma^2 = 15$) after starting tofacitinib. Median follow-up was 11.2 months (8–20 months, $\sigma^2 = 40.7$). Table 1 presents patients' characteristics before tofacitinib therapy was initiated, while Table 2 shows their outcomes. PUCAI changes are shown in Figure 1. A median decrease of 25 points after 72 h ($P < 0.001$) was observed. Four patients were in clinical remission at discharge. Haemoglobin, albumin, CRP, and FC all improved (Fig. 2) Neutrophiles and lymphocytes were above the lower limits of normal in all patients before the start of tofacitinib. Clinical variables before and after are shown in Figure 3.

Regarding adverse events, one patient had a positive blood polymerase chain reaction (PCR) for Epstein-Barr virus (EBV) with negative colonic biopsies. She was treated with rituximab given reports of tofacitinib-induced EBV colitis and symptoms resolved. Tofacitinib was restarted without further complications. Risk factors for thromboembolism included disease severity and inmobilization in all patients. Four patients had a PICC inserted, and four patients were adolescents. One patient was being treated for a thrombosis before the introduction of tofacitnib, and a resolution was achieved nonetheless. No thrombosis was registered after tofacitinib was started. Although thromboprophylaxis in IBD is part of our current practice, it was not implemented in 2021, and no patient received it at the time. One patient showed a mild and transitory hypertriglyceridemia that resolved without treatment. Renal function (blood urea and creatinine) was normal before and after starting tofacitinib. No patient developed hypertension. Cholesterol (HDL and LDL) was normal in all patients.

Patients' descriptions

The first patient was diagnosed 3 years prior, and treated with infliximab but switched to adalimumab due to antibodies development. He was non-adherent and had a severe relapse requiring hospitalization. IVCS were started without response (PUCAI 65 at day 3), and Mayo 3 pancolitis. Tofacitinib was introduced with response at day 5 and clinical remission at day 7. Haemoglobin increased from 106 g/L to 127 g/L at the last follow-up. No transfusions were required. CRP decreased from 45 to 5 mg/L. Albumine increased from 31 to 41 g/L at the last follow-up. He had not relapsed, but he did not tolerate the dose tapering. No adverse events were noted.

The second case presented as an ASC, with a PUCAI of 75 and a Mayo 3 pancolitis. He showed no response to IVCS and received six weekly infliximab doses. Vedolizumab was added after the fourth dose, without much improvement.

Table 1. Patients' characteristics.

Characteristics	ASC 1	ASC 2	ASC 3	ASC 4	ASC 5	ASC 6
Age	17 years	15 years	16 years	16 years	13 years	11 years
Sex	Male	Male	Male	Male	Female	Female
Disease duration before Tofa	46 months	3 months	5 months	14 months	4 months	2 months
Treatments before Tofa	IV steroids Infliximab (ATI) Adalimumab (non adherence) Azathioprine	IV steroids Infliximab Methotrexate Vedolizumab	IV steroids Infliximab Azathioprine	IV steroids Infliximab Ustekinumab Vedolizumab	IV steroids Infliximab	IV steroids Infliximab 5-ASA Azathioprine
Reason for Tofa	Relapse with anti-TNF failure	Steroid resistance IFX non responder Vedolizumab failure	IFX loss of response	Steroid resistant IFX non-responder	Steroid resistant IFX non responder	Steroid dependent IFX loss of response Relapse with biologics
Concomitant treatment	PO steroids (tapering)	PO steroids (tapering) Vedolizumab (3 doses)	PO steoids (tapering)	PO steroids (tapering)	PO steoids (tapering)	PO steroids (tapering)

Tofa, tofacitinib; PO, per os; IFX, infliximab; ADA, adalimumab; ATI, antibodies toward infliximab.

Table 2. Patients' outcomes.

Outcomes	ASC 1	ASC 2	ASC 3	ASC 4	ASC 5	ASC 6
Time to response (days)	5	5	5	3	7	3
LOS (days)	17	58	18	7	30	13
Discharge after Tofa (days)	11	10	13	2	8	4
Time to clinical remission (days)	7	9	30	3	N/A	5
Complete remission	Yes	Yes	Yes	Yes	No	N/A***
Colectomy	No	No	No	No	No	No
Medication at last F/U	Tofa + steroids	Tofa	Tofa	Tofa	Usteki	Tofa
F/U after Tofa (months)	6	14	20	8	2	8
Hospitalizations after Tofa	No	No	No	No	No	No
Infections after Tofa	No	No	No	No	Yes*	No
Relapse	No	No	No	No	Yes**	No
Blood transfusion after Tofa	No	No	No	No	Yes	No

TOFA, Tofacitinib,;LOS, length of stay; F/U, follow-up; Usteki, ustekinumab.
[a]Infectious mononucleosis, refer to body article.
[b]The patient had a mild recrudescence of symptoms while on 10 mg twice daily, and combination therapy with ustekinumab was not approved by the insurance company, therefore tofacitinib was stopped.
[c]Control colonoscopy has no yet been performed.

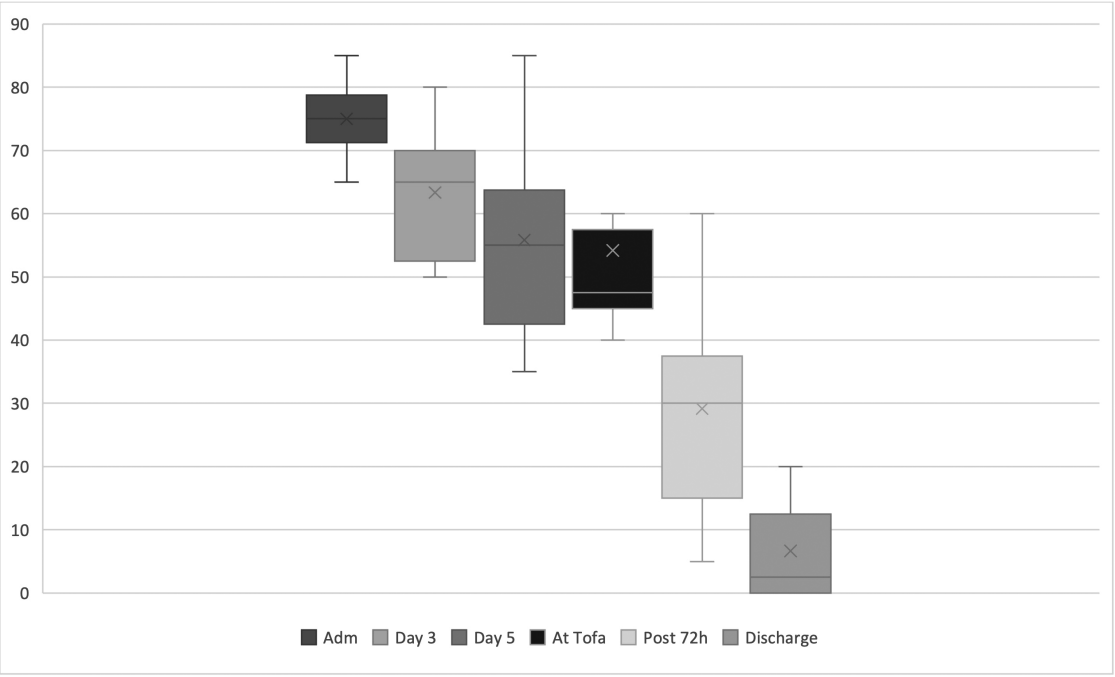

Figure 1. PUCAI between admission and discharge.

Tofacitinib was started and a response was noted after 5 days. Haemoglobin improved from 77 g/L (despite receiving weekly doses of IV iron and blood transfusions) to 138 g/L at the last follow-up. Albumin increased from 31 to 41 g/L. Calprotectin decreased from 530 to 55 ug/g, and complete remission was observed after 8 weeks. Vedolizumab was stopped after the third dose. Mild symptoms reappeared when tofacitinib was decreased, so treatment was continued at 10 mg twice daily. No adverse effects were registered.

The third patient was admitted for ASC despite being on infliximab and oral steroids. IVCS were started but PUCAI remained unchanged after 5 days, so tofacitinib was added. Response was noted after 72 h. Clinical remission was recorded after 3 weeks. Haemoglobin improved from 80 (having received blood transfusions) to 134 g/L at the last follow-up, without further transfusions. Albumin increased from 26 to 44 g/L, while CRP decreased from 104 to 5 mg/L. Complete remission was noted after 8 weeks. He developed a mild hypertriglyceridemia (1.49 mmol/L) that normalized after 4 days. No other complications were noted, but tofacitinib's tapering dose was not tolerated.

The fourth patient had a refractory ASC having failed treatment with infliximab, ustekinumab, and vedolizumab. Colonoscopy showed a Mayo 3 pancolitis and persistently elevated after five doses of IVCS. Response was fast after tofacitinib introduction, with PUCAI decreasing to 5 after

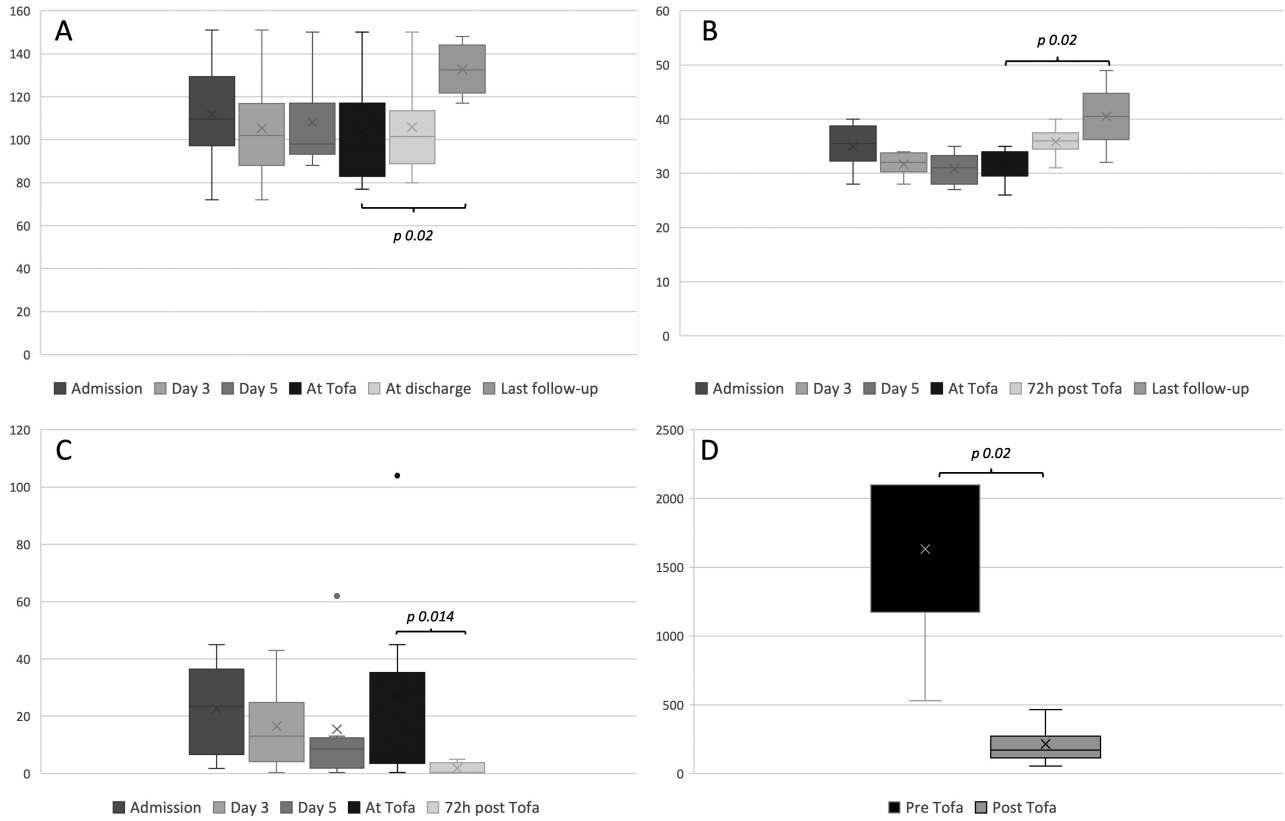

Figure 2. Biochemical parameters before and after tofacitinib. (A) Haemoglobin in g/L. (B) Albumin g/L. (C) C-reactive protein in mg/L. (D) Fecal calprotectin in µg/g.

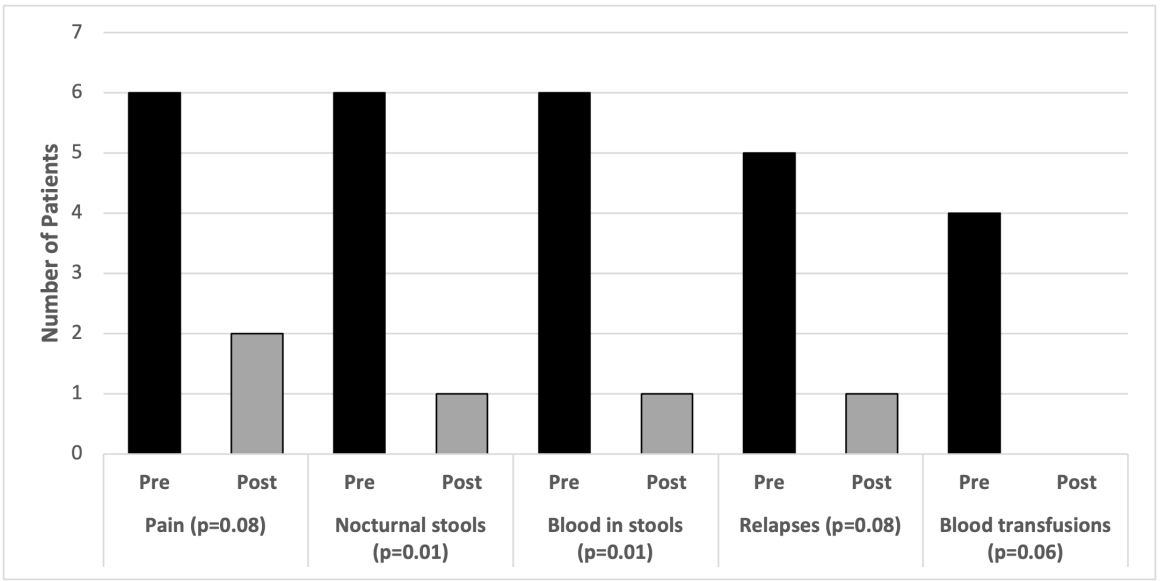

Figure 3. Clinical variables before tofacitinib treatment and at last follow-up.

3 days and to 0 at the time of discharge. Colonoscopy was normal 3 months later. Albumin improved from 34 to 45 g/L. No complications were registered and the patient remains in complete remission.

Patient number five had been diagnosed with UC 4 months prior to admission, having to go through an infliximab reinduction protocol due to insufficient response. She was readmitted with a PUCAI of 85 to start IVCS, but tofacitinib was introduced since no response was noted. She developed infectious mononucleosis symptoms, and blood PCR was positive for EBV so treatment with rituximab was started and tofacitinib was held. Complete resolution of symptoms followed. Tofacitinib was restarted without further complications, with clinical response after 3 days, and already in clinical remission

at discharge. She experienced a mild flare-up 2 months later and ustekinumab was added. However, insurance refused to cover both, and tofacitinib was stopped.

The last patient had an ASC treated with IVCS and infliximab, needing a reinduction protocol given the poor response. She developed a PICC-related deep venous thrombosis (DVT), Coagulation studies including prothrombin time, Factor V Leiden, antiphospholipid syndrome, factor VIII, and homocystein were normal. Treatment with enoxaparin was started. She was readmitted one month later due to relapse, showing no response to IVCS nor to infliximab, so tofacitinib was introduced. PUCAI decreased from 45 to 10 by day 3. The patient's haemoglobin, which had always been between 72 and 92 g/L despite multiple transfusions and IV iron, had increased to 117 g/L at the last follow-up. Albumin increased also from 29 to 37 g/L. The patient remains in clinical and biochemical remission after 8 months of treatment.

Discussion

Given the increasing incidence and prevalence of UC in the pediatric population, ASC may unfortunately become more frequent.[1] Various scientific societies have proposed different protocols for its treatment, but they vary mainly regarding second- and third-line treatments, probably owing to differential access to biologics.[7,24] Nonetheless, initial treatment for any patient with a PUCAI score of ≥65 is admission for IVCS. The joint societal statement from the European Crohn's and Colitis Organisation and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ECCO-ESPGHAN) recommends revaluation at the third and fifth day, and second-line treatment should be started if PUCAI score is ≥65 at day 5.[7] However, as many as 30 percent may not respond to IVCS alone and infliximab is regarded as the best option in those patients.[25] Unfortunately, young age, severity of colonic mucosal inflammation, and hypoalbuminemia, all normally present in ASC, increase drug clearance, frequently necessitating intensified induction regimens.[16–18,26–29] If these treatments fail, some guidelines suggest the utilization of calcineurin inhibitors but ECCO-ESPGHAN 2018 guidelines for ASC still recommend an urgent colectomy when second-line treatment fails.[7] Recent guidelines for UC treatment recommend induction therapy with either ustekinumab, vedolizumab, or tofacitinib, for those failing infliximab induction, but none in the setting of ASC.[30]

To our knowledge, there is only one published series of 11 pediatric patients treated with tofacitinib as salvage therapy for refractory UC, of which eight had ASC.[31] They suggest that tofacitinib may be used as a bridge therapy allowing for nutritional rehabilitation before colectomy. We believe that it may have a role in two scenarios. One would be its use instead of steroids, before infliximab re-induction in biologic-experienced patients with low trough levels. The other scenario is to use in combination with vedolizumab, which is effective for UC, but its delay of action makes it unattractive during an ASC. Data on tofacitinib use are mainly limited to adult cohorts with most centres favouring an induction protocol of 10 mg twice daily for 8 weeks, and a dose reduction to 5 mg during maintenance, but evidence-based guidelines are still lacking.[32–38] The first published data came from the OCTAVE trials in 2017 and their post hoc analysis thereafter, where they found that tofacitinib was better for inducing and maintaining remission at 52 weeks when compared to placebo in patients with failure to first- and second-line treatment (34.3 percent with 5 mg and 40.6 percent with 10 mg vs. 11.1 percent with placebo).[39,40] Further reports, particularly those from the GETAID-TALC Study Group showed that tofacitinib was effective in achieving steroid-free remission and lessening the need for colectomy in the acute setting.[41] In 2019, Berinstein et al.[13] published the first series of four adult patients with ASC who received tofacitinib as salvage therapy and reported remission in three of them, with a need for colectomy in the fourth patient. Similar findings were reported by Honap et al.[14] in a series of seven steroid-refractory patients treated for up to a year with tofacitinib and achieving remission in five of them. However, colectomy was eventually performed in four patients, two because of non-response and in two for relapse after a symptom-free period of 12 and 26 weeks.

In 2019, Dolinger et al.[42] published the first five children treated with tofacitinib for UC (none with ASC) and reported clinical remission in four, with no need for colectomy. Our results are similar with all patients showing a clinical response, and tofacitinib being discontinued in one patient, despite an initial clinical response, as dual therapy with ustekinumab was not approved by the insurance company. Unlike other reports, our tofacitinib-treated patients have not required additional medication for the duration of follow-up. We also found that biochemical parameters of inflammatory activity such as haemoglobin, albumin, CRP, and FC normalized after tofacitinib treatment, although statistical significance was only achieved for CRP and FC, probably owing to our small sample size. A weakness of our cohort is the absence of clear criteria for beginning treatment as it is not yet approved for its use in pediatrics; however, the decision was made after a case-by-case consensus during our weekly IBD multidisciplinary meetings. It must be noted that all our patients had previously received a combination of IVCS, intensified infliximab induction, and either ustekinumab, vedolizumab, or immunomodulators prior to starting tofacitinib. Therefore, response cannot be exclusively attributed to tofacitinib, but the fact that patients ceased all other therapies after starting it is noteworthy.

Furthermore, response to tofacitinib therapy was rapid, with evidence of symptom improvement after 3 days, compatible with findings published in the adult population.[19,32] This finding makes the use of tofacitinib as a third-line treatment in the context of ASC attractive, especially in a patient who previously failed biologics, in order to avoid urgent colectomy.

Side effects associated with tofacitinib, as reported by the OCTAVE trial, are infections, risk of malignancy, followed by DVT, and possible pulmonary embolism.[43] DVT is an especially worrisome complication in the adult population, as adults have more risk factors for severe embolism, but more information regarding the true risk is needed, as ASC is a known independent risk factor for thromboembolism. Importantly, none of our patients developed a thrombotic complication after treatment with tofacitinib was introduced. There was one patient who was being treated for a PICC-related thrombosis from a previous hospitalization, and the resolution was achieved despite tofacitinib introduction. Currently, all of our patients with ASC receive thromboprophylaxis, but at the time of this report, protocols did not include it in the absence of other risk factors, so none of the patients in this study received thromboprophylaxis.

Some authors report an increased risk of infection with tofacitinib; however, mild upper respiratory tract infections were most commonly found with no increase in mortality.[34] In our cohort, we found one patient with a symptomatic EBV infection 5 days after starting tofacitinib, but causality is difficult to analyze as she had previously received high-dose IVCS and two doses of infliximab 1 week apart. Furthermore, blood PCR tested positive in a blood sample from before tofactinib was started. Moreover, colon biopsies were negative so a diagnosis of EBV colitis could not be made. Nonetheless, given a deterioration in symptoms treatment with rituximab was started as per rheumathology consultation. Some infections appear to be more prevalent with Tofacitinib such as EBV and herpes zoster reactivation, the latter being four times more frequent when compared to placebo[44–46] and COVID infection remains a concern in current times. In the SECURE-IBD Registry only seventy-two patients received treatment with tofacitinib, and no difference in fatal outcomes was noted when compared to other medications.[46]

Another reported side-effect is the development of dyslipidemia with increases of up to 19 percent in serum cholesterol. These findings seem to be more important during the first weeks of treatment, possibly normalizing during the maintenance phase as long-term reports place the absolute change between 0.2 percent and 4.3 percent.[19,34,44] In our cohort, one patient developed mild and transitory hypercholesterolaemia with no further complications.

The ease of administration and the lack of immunogenicity make tofacitinib a theoretically viable option as part of combination therapy with other biologics and may be used as a drug capable of recapturing response after treatment interruption. Dolinger et al.[33] reported that six of nine patients were in steroid-free remission after 6 months, with only one of those patients having an adverse side effect. Recapture of response has only been studied to date by Panés et al.,[47] where patients who achieved remission with tofacitinib induction were randomized to receive a placebo as maintenance. When re-induced with tofacitinib, 75 percent of patients had a clinical response after 2 months, which was sustained for up to a year.

ASC is a worrisome presentation in pediatric UC, and although treatment response has improved since the advent of biologic therapy, results are still far from ideal, with colectomy rates up to 50 percent regardless of initial treatment response. Tofacitinib may very well have a role in pediatric ASC protocols, owing to the ease of administration, its short half-life, the apparent safety profile, and the speed of response. Furthermore, initial findings seem to show that, unlike biologics, it could be used for recapturing response in patients previously treated, behaving in a similar way to steroids. One scenario where tofacitinib could prove useful is remission induction in ASC in biologic-experienced patients with poor or no response after initial IV steroid treatment. Another possibility is its use during an ASC as a bridge therapy in combination with ustekinumab or vedolizumab, considering that these medications start acting after some weeks. However, further investigations and multicentric studies are necessary to clearly define these indications.

Author contributions

All authors made substantial contribution to the conception of the work, acquisition, data analysis and interpretation, and drafting of the work. They revised it critically and gave the final approval for the manuscript. They are all accountable for all aspects of the work.

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Conflict of interest

C. Deslandres served as an advisory board member and speaker for AbbVie, Jansen, and Organon. The rest of the authors have no conflict of interest to declare.

Data availability

The data that support the findings of this study are available on request from the corresponding author, G.A.C. The data cannot be made publicly available due to the nature of the article: it contains few cases and it is, therefore, impossible to ensure that no more than three minor identifiers are not present. All the data utilized in the making of this work will be made available in an online repository for further examination and for reproducibility purposes.

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