OPEN

Outcomes of Tofacitinib Use in an Irish Pediatric Cohort

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ABSTRACT

Background: Pediatric ulcerative colitis (UC) is typically more extensive and severe at diagnosis compared with adult disease. Tofacitinib, a Janus kinase inhibitor, has been used since 2018 to induce and maintain remission in UC. There are limited pediatric data regarding its use, either as a monotherapy or in combination with other treatments.

Objectives: To determine the real-world experience and outcomes of tofacitinib therapy in the Irish national cohort with pediatric UC.

Methods: A retrospective study of tofacitinib outcomes was undertaken at Ireland's single national center for pediatric inflammatory bowel disease. All patients commenced on tofacitinib since its availability in 2019 were included. Baseline and follow-up clinical characteristics, phenotype, Pediatric Ulcerative Colitis Activity Index (PUCAI) scores, and treatments before and after tofacitinib commenced were recorded. The primary outcome was remission by 8 weeks, with other clinical outcomes being recorded to maximal available follow-up.

Results: Between November 1, 2019 and June 30, 2022, 15 children (M:F 1:2) were prescribed tofacitinib, 5 as monotherapy. Thirteen had baseline pancolitis at diagnosis and all patients had prior infliximab exposure. The mean time from diagnosis to starting tofacitinib was 381 days (±SD 265). Dual therapy included 5 with infliximab, 4 with vedolizumab, and 1 with adalimumab. The average length of treatment on tofacitinib was 232 days (±SD 170) with 2 patients transitioning to adult services while in remission on tofacitinib therapy. The mean PUCAI score was 48.7 (±SD 14.1) pre-tofacitinib, 16.7 (±SD 15.6) at week 8, and 22.5 (±SD 29.6) by week 16, with a significant reduction in PUCAI by week 16 ($P = 0.0004$). Eight patients (3 monotherapy) achieved clinical remission, with 4 of the 5 dual therapy patients on infliximab. There were no significant outcome differences between those on mono- or dual therapy. Three patients with combined vedolizumab therapy did not achieve remission, 2 of whom required colectomy by week 24. There were no malignancies, 1 patient developed shingles and another developed herpangina post-tofacitinib. Failure to achieve clinical remission by week 16 was seen in all children who progressed to colectomy (n = 4).

Conclusion: Combining tofacitinib with other biologics is effective in select children with refractory UC. Early responders were more likely to achieve a sustained response at week 16. Failure to achieve remission by week 16 of tofacitinib therapy was strongly associated with progression to colectomy.

What Is Known

Pediatric refractory inflammatory bowel disease poses ongoing therapeutic challenges. Tofacitinib used as monotherapy has shown promising results.

What Is New

In our cohort, dual Tofacitinib therapy was no more likely to induce remission than monotherapy using tofacitinib alone. This suggests that tofacitinib can be used as sole therapy, thus avoiding any potential drug-drug interactions of using it in combination with a biologic agent. PUCAI scores at week 8 are indicative of remission at week 16 and further long-term remission.

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INTRODUCTION

Tofacitinib is a pan-Janus kinase inhibitor and since 2018 has been licensed for adults with inflammatory bowel disease (IBD) who have had inadequate responses to treatment or who are intolerant of TNF inhibitors where it has demonstrated superior efficacy to placebo for induction of clinical and endoscopic remission. Tofacitinib offers a welcome alternative, particularly when other biologic agents have failed to induce clinical response or remission. Tofacitinib has a relatively short half-life and is orally administered, which is more

convenient and favored by pediatric patients in particular (1). Limited literature exists on its use in combination with biologic treatments. Herein we present our national cohort experience of using tofacitinib, as a mono- or combined therapy, in pediatric ulcerative colitis (UC) over a 2-year period.

METHODS

All Irish children with pediatric IBD attend a single national referral center at Children's Health Ireland at Crumlin (CHI-Crumlin). Ethical approval was obtained from the hospital ethics committee for a retrospective chart review of all children who had been commenced on tofacitinib for IBD in CHI-Crumlin since its licensing and availability for usage in Ireland, from November 1, 2019 to June 30, 2022. All children with a confirmed diagnosis of IBD who were commenced on tofacitinib either as monotherapy or in combination with another biologic agent were included. Children who first commenced tofacitinib after colectomy were excluded. Variables collected included sex, age at diagnosis, endoscopic score, and Paris phenotype at diagnosis; treatments used before tofacitinib, mono- or dual tofacitinib therapy, Pediatric Ulcerative Colitis Activity Index (PUCAI) score, C-reactive protein, erythrocyte sedimentation rates and albumin pre- and during tofacitinib therapy, and the number of hospitalizations and infections or malignancies post-tofacitinib introduction. The PUCAI score was used to define clinical remission (<10), clinical response (change of 20 points), severe (>65), moderate (35–64), or mild (10–34) activity (2). Continuous data are presented as the mean and standard deviation and categorical data as frequency and percentage. Statistical analyses were performed using Jamovi Version 2.3.21.0 (The Jamovi Project, 2020).

RESULTS

Patient Characteristics

Sixteen children commenced tofacitinib therapy between November 2019 and June 2022. One was excluded as they first commenced it post-colectomy. The remaining fifteen were included for analysis. Ages ranged from 6.8 to 16.3 years (mean age 12.9 years [±SD 2.3] and 66% [n = 10]) were female. Eight patients had a Paris phenotype of E4, S1 at diagnosis, 5 had E4, S0, 1 had E3, S1 and 1 was E2, S1. The mean PUCAI at diagnosis was 62 (±SD 16.8) and the mean Ulcerative Colitis Endoscopic Index of Severity score was 6.5 (±SD 1.1) (3). One patient had a PUCAI >65 at time of starting tofacitinib. Additional characteristics are summarized in Table 1 and individual analysis is in Supplemental Digital Content Table 1 http://links.lww.com/PG9/A118. No patients were prescribed azathioprine, tacrolimus, or ciclosporin during their treatment course. All patients had prior infliximab exposure. Three patients were on steroids at time of starting tofacitinib. Ten children received adjunctive tofacitinib combined with a biologic, whereby patients had shown a partial response to the biologic agent, rather than primary non-response.

Tofacitinib Therapy

The mean time to treatment with tofacitinib from diagnosis was 381 days (±SD 265 days). The standard dosing of tofacitinib was 10mg BD for 8 weeks and then a reduction to 5 mg BD maintenance dose. Four patients remained on 10 mg BD maintenance due to increased symptoms on reducing to maintenance doses of 5 mg BD, an additional 3 patients continued on 10 mg BD for 16 weeks before reducing to 5 mg BD. One patient with very early-onset IBD was started on 5 mg BD. The mean tofacitinib dose was 0.39 mg/kg

TABLE 1. Patient characteristics of tofacitinib cohort

Patients included	**n = 15**		
Mean age at diagnosis	12.9 years (±SD 2.3)		
Female	n = 10		
Biologic exposure pre-tofacitinib			
Adalimumab	n = 5		
Vedolizumab	n = 5		
Ustekinumab	n = 2		
Infliximab	n = 15		
Mean lab values	Pre-tofacitinib	Week 8	Week 16
ESR (n = 14)	30.1 mm/h (±SD 25)	30.5 mm/h (±SD 14.2)	20.7 mm/h (±SD 12.2)
CRP (n = 15)	10.4 mg/L(±SD 11)	10.1 mg/L (±SD 10.7)	13.3 mg/L (±SD 15.4)
Albumin (n = 15)	37.5 g/dL (±SD 4.0)	41.3 g/dL (±SD 1.8)	40.3 g/dL (±SD 3.8)
Fecal calprotectin (n = 5)	4296 (±SD 2569)	2727 (±SD 447)	22.5 (±SD 29.6)
Mean PUCAI			
PUCAI (n = 15)	48.7 (±SD 14.1)	16.7 (±SD 15.6)	
Tofacitinib therapy stopped			
By week 8	n = 1		
By week 16	n = 2		
By week 21	n = 4		
By 1 year	n = 3		
Tofacitinib therapy continued until end of study period	n = 5		
Progression to surgery post-tofacitinib	n = 4		
Time to colectomy post-tofacitinib	110 days (+SD 60.5)		
Parenteral antibiotics during tofacitinib course	n = 2		

CRP = C Reactive Protein; ESR = Erythrocyte Sedimentation Rate; PUCAI = Pediatric Ulcerative Colitis Activity Index.

and the mean length of treatment on tofacitinib to maximal available follow-up was 232 days (±SD 170 days), with 2 patients transitioning to adult services while in remission on tofacitinib therapy.

Induction of Remission

Clinical response to tofacitinib was seen in ten patients (66%) by week 16. The overall mean PUCAI score pre-tofacitinib was 48.7 (±SD 14.1) with a mean of week 8 and week 16 post-tofacitinib PUCAI of 16.7 (±SD 15.6) and 22.5 (±SD 29.6), respectively. Eight patients in total achieved clinical remission. Seven of these patients achieved steroid-free/normal CRP remission by week 16. The pre-tofacitinib PUCAI score of patients achieving remission was 56 (±SD 12.4), reducing to 2.5 (±SD 3.5) by week 8 and 3 (±SD 2.74) by week 16 post-introduction of tofacitinib. Clinical remission was achieved by 5 patients on dual therapy, 4 of whom were treated with dual infliximab and tofacitinib. There was no significant difference in week 8 or week 16 PUCAI scores between those on tofacitinib as a monotherapy or a combination therapy (Fisher's exact test $P > 0.99$). Three patients on monotherapy achieved clinical remission, with a pre-tofacitinib PUCAI of 33 (±SD 10.4) reducing to 8.3 (±SD 14.4) at week 8 and 3.3 (±SD 5.7) by week 24.

Four of the 8 patients in remission had a mean PUCAI of 2.5 (±SD 5) recorded between weeks 41 and 52. The week 16 PUCAI was significantly different between those who did and did not achieve remission (2.5 versus 52.5, $P < 0.0005$). Three patients who did not achieve remission on dual therapy were on a combination of vedolizumab and tofacitinib, and 2 of these patients proceeded to colectomy by week 24 post-tofacitinib.

There were no new safety signals observed in our cohort with no malignancies identified, 1 patient developed shingles and another developed herpangina.

DISCUSSION

This is the first report on the early outcomes of tofacitinib use in the national cohort of Irish children with UC. The OCTAVE trial in adult patients demonstrated that tofacitinib was more effective than placebo as an induction and maintenance therapy and this has been replicated in subsequent studies (4). Comparable trial data are not available for children, and the pediatric literature relies upon case series such as this to provide real-world data for clinicians. Whereas our study included only patients with UC primarily aged under 16 years, many of the pediatric case series to date have included patients with all subtypes of IBD, with patient ages often straddling older adolescence to adulthood. Consensus has yet to be established regarding the optimal position and timing of tofacitinib in the therapeutic paradigm of IBD.

In our experience, children who promptly responded and attained remission by week 8 were more likely to show a sustained response at week 16 and week 52. A previous study including 14 patients with UC also noted early responses to therapy in 50% of their cohort, with a median PUCAI of 15 by week 6 and 20 at week 12, many of whom had previously failed multiple biologics (5). That study included all IBD subtypes, and 20% had discontinued tofacitinib by week 12. Another pediatric study described an 88-day median time to steroid-free remission following tofacitinib introduction, although this study pooled outcomes for patients with UC and Crohn's disease (6). Patients who attained early remission in our study were also less likely to proceed to colectomy. None of the 4 patients requiring a colectomy in our study achieved clinical remission with tofacitinib by week 8 or week 16, for example. A recent study of hospitalized patients with steroid- and biologic-refractory UC reported a 90-day colectomy-free survival in 6 of 11 pediatric patients (7). That study included some patients who received thrice-daily dosing, whereas in our study all received twice-daily tofacitinib. The Predicting Responses to Standardized Pediatric Colitis Therapy study has previously shown that early response correlates with better medium-term clinical outcomes in UC (3). While the current context is different from the Predicting Responses to Standardized Pediatric Colitis Therapy study, it is tempting to speculate that slow response to induction therapy forebodes ultimate treatment failure in UC.

Our study was not powered to demonstrate the superiority of either treatment approach, but there were no clear signals favoring monotherapy or dual therapy with tofacitinib in terms of the clinical outcomes examined. This questions whether and when any merit exists to continue current biologic therapies once tofacitinib is started in pediatric patients, especially given the potential additive infectious risk profile.

Tofacitinib monotherapy outcomes in pediatric IBD are encouraging, with clear evidence of clinical response and remission success (5,7,8). The rates of early clinical remission and PUCAI values were comparable in our study between those on mono- or dual-therapy with tofacitinib. The current predominant use of tofacitinib in refractory disease does not render dual therapy inevitable in most patients. Patients in our cohort with a partial clinical response to their existing biologic therapy received dual therapy when tofacitinib was started as an adjunctive agent. No patient was commenced on "up-front" dual therapy, for example. The largest study of dual therapy in pediatric IBD to date had previously shown steroid-free remission at 6 months in 7 of 9 patients with UC (6). As with our study, various dual therapy combinations were described. Four patients in our series had dual therapy with infliximab, a combination not widely reported to date. We also found no apparent correlation between either tofacitinib monotherapy or combination therapy and progression to colectomy, but our patient numbers were limited. It is futile to continue biologics following primary non-response, or complete secondary loss of response. However, in select cases and under careful supervision, using concomitant JAK inhibitor therapy is an alternative induction approach to consider, especially given the prompt onset of action and short half-life in cases where it must be stopped quickly.

Our duration of follow-up was limited given the relatively recent availability of tofacitinib to our patients and our cohort size. Long-term follow-up data on mono- or dual-therapy with tofacitinib in pediatrics is scarce. None of the patients who achieved remission in our study required a subsequent colectomy by maximal available follow-up. In the recent series from Philadelphia, 9 of 14 patients with UC remained on tofacitinib by week 52, with a median PUCAI score of 5 (5). Their week 52 steroid-free remission rate was 41%, but all IBD cases were pooled and it was not clear how many patients with UC were in remission but on steroids. In the study of acute severe UC, only 4 of 11 patients were colectomy-free at maximal follow-up (7). Data from the same group demonstrated remission rates peaking at 12–16 weeks but decreasing by 6 months (7). Dolinger et al reported clinical outcomes of dual therapy to 6 months, with 75% demonstrating steroid-free remission in their combined IBD cohort. Data from the OCTAVE trials on the durability of response to tofacitinib has shown an association between week 52 remission and milder baseline endoscopic severity and higher induction dosing, whereas baseline steroid use and higher CRP were associated with a lower likelihood of remission (9). Ultimately, further studies are needed to explore the durability of response to tofacitinib in pediatric IBD and to identify the therapeutic window for its optimal use.

Our description of the outcomes of tofacitinib therapy use in our patient population adds to the limited literature in the field and provides additional information for clinicians. We temper our findings in the context of our study's limitations that preclude broad

extrapolation to patient populations. Our cohort was derived from the national patient cohort, but its size was limited, and meaningful statistical analysis was not possible for most outcomes of clinical interest. Our study was retrospective in nature, and although our single center status ensures full patient capture not all data of interest were available on retrospective chart review. Our cases were not matched with comparator "control" cases without tofacitinib. Another limitation of this study is the lack of objective endoscopic data before and after tofacitinib commencement, or calprotectin correlates of mucosal activity as an alternative. Larger, multicentre studies are needed to further evaluate the long-term safety and efficacy of tofacitinib either as a single agent or in combination with other immunomodulatory treatments, given the limited patient numbers in our national cohort alone.

CONCLUSION

Tofacitinib has a role in treating refractory pediatric UC, either alone or in combination with other biologics. Patients who rapidly respond and attain remission are more likely to sustain their response and avoid colectomy. There were no clear advantages of combining tofacitinib with other biologics in our case series, but additional larger studies may clarify this and identify where and when tofacitinib best fits in contemporary IBD treatment pathways.

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