



Original Article

Efficacy and Safety of Tofacitinib in Pediatric Ulcerative Colitis Patients: A Systematic Review

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ABSTRACT

Introduction: Ulcerative colitis (UC), an inflammatory Bowel Disease (IBD), is a chronic illness of unknown mechanism affecting the colonic mucosa, mainly causing diarrhea and bleeding. It can potentially disrupt the quality of life. Tofacitinib, a Janus Kinase inhibitor, showed a promising effect in inducing remission in IBD patients. In this study, we aim to assess the efficacy and safety of Tofacitinib in treating children with ulcerative colitis.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA), we searched four electronic databases (PubMed, Scopus, Cochrane Library, Embase, and Web of Science) to identify eligible studies reported up to July 2024. We reported outcomes as frequencies and proportions in our study.

Results: We identified five studies encompassing 83 children diagnosed with IBD, of which 57 children had ulcerative colitis. The proportion of patients achieving a clinical response across one included study was 66.67%. The proportion of patients achieving clinical remission was 38.46%. Also, the proportion of patients achieving steroid-free remission across the three studies was 48.57%. The rate for serious adverse events was 25.53% across the three included studies.

Conclusion: Tofacitinib could be useful in achieving clinical remission in children with UC and reducing colectomy rates. Also, a low infection rate and the incidence of serious adverse events were observed. Future randomized controlled trials with larger samples and longer follow-up periods are needed to support these findings.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by inflammation of the colonic mucosa, leading to symptoms such as abdominal pain, diarrhea, and rectal bleeding that have a negative impact on the quality of life of affected individuals, including children. Management of UC in pediatric patients presents special challenges, as patients' growth, development, psychological health, and physical health [1, 2]. Numerous treatments, such as steroids, 5-aminosalicylic acid (5-ASA), azathioprine, and biologic therapy using anti-tumor necrosis factor (TNF) inhibitors, are currently authorized for use in juvenile UC patients. Many individuals have severe refractory illness, meaning that they do

not respond to therapy and may need surgery, even with their effectiveness. Individuals with moderate-to-severe UC who don't respond to biological treatment can now use Tofacitinib [3].

Tofacitinib, an oral Janus kinase (JAK) inhibitor, has become a viable UC therapeutic option. It functions by specifically blocking JAK enzymes, which mediate immune response-related signaling pathways and are essential to the inflammatory process. Initially approved for the treatment of rheumatoid arthritis, Tofacitinib has demonstrated efficacy in adults with moderate to severe UC, providing rapid symptom relief and sustained remission in many cases. This success has prompted interest in its potential use for pediatric patients, who often have limited treatment options and may experience significant side effects from conventional therapies such as corticosteroids and immunomodulators [4].

Clinical trials and studies are increasingly focusing on the safety and efficacy of Tofacitinib in children and adolescents with UC. Early findings suggest that Tofacitinib may offer a well-tolerated and effective alternative, capable of inducing and maintaining remission with a favorable safety profile. As the understanding of JAK inhibitors in pediatric inflammatory diseases grows, Tofacitinib represents a beacon of hope for children with UC, offering a

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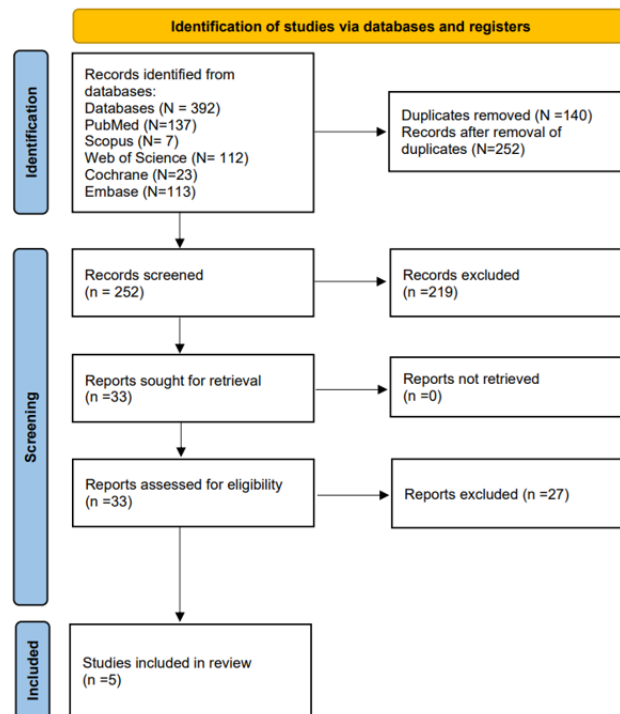


Figure 1: PRISMA flow chart diagram for our literature review results.

potential new avenue for management that could significantly improve their quality of life and long-term health outcomes [5, 6, 7]. Consequently, the goal of this study is to evaluate the effectiveness and safety of tofacitinib in pediatric patients.

2. Methods

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were adhered to in this systematic review and meta-analysis [8]. The Cochrane Handbook for Systematic Reviews of Interventions served as the primary reference for all steps of the study [9]. This study was registered with PROSPERO.

2.1. Data source and search terms

We searched PubMed, Web of Science (WOS), Scopus, Cochrane Library, and Embase databases until July 2024 for studies using Tofacitinib to treat children with ulcerative colitis. The applied search strategy is available in the supplementary file. Additionally, we reinforced our search by reviewing the references of our final included studies to include other relevant studies.

2.2. Eligibility criteria and study selection

We included observation studies evaluating the safety and efficacy of Tofacitinib, conducted on participants under 18 years old and published in English. The primary outcome was the clinical response, defined as a ≥ 20 -point decrease in the Pediatric Ulcerative Colitis Activity Index. Secondary outcomes included clinical remission, steroid-free remission, colectomy rate, and adverse events. Animal studies and Studies published in other languages were excluded. After searching the mentioned databases, we imported the search results into Rayyan. Two researchers independently screened the titles and abstracts of all identified studies. Full-text articles of potentially eligible studies were sorted out and assessed

for inclusion. Conflicts were resolved by discussion or by a third reviewer.

2.3. Data extraction

Data were extracted from each paper of the final included studies by two independent researchers into Microsoft Excel spreadsheets to ensure the accuracy of our data. Any conflicts were resolved by discussion or by a third reviewer. Extracted data included the following: (a) Summary of the included studies, (b) Baseline characteristics, and (c) Outcomes. Clinical response was our primary outcome. Our secondary outcomes included clinical remission, colectomy, and safety outcomes.

2.4. Risk of bias and quality assessment

We used the Newcastle Ottawa Scale (NOS) to assess the risk of bias for our observational included studies [10]. Two independent researchers assessed the quality using these NOS domains (Selection, Comparability, and Outcome). Any disagreements were resolved by consensus.

3. Results

3.1. Literature results

As shown in (Figure 1), the systematic search identified 392 records from databases including PubMed, WOS, Scopus, Cochrane, and Embase. After removing 140 duplicates, 252 records were screened based on titles and abstracts. A total of 219 records were excluded as they did not meet the inclusion criteria. The remaining 33 full-text articles were assessed for eligibility. After further exclusions, 5 studies with a total of 83 participants with IBD met the inclusion criteria and were included in this review [5, 11, 12, 13, 6, 7].

Table 1: Summary of included studies

Study ID	Country	Study design	Total of Participants	Study duration	Main inclusion criteria	Outcomes	Conclusion
Ryan 2023 [7]	Ireland	Retrospective cohort study	15	November 1, 2019, and June 30, 2022	All children with a confirmed diagnosis of IBD who were commenced on Tofacitinib either as monotherapy or in combination with another biological agent	The primary outcome was remission by 8 weeks, with other clinical outcomes being recorded to the maximum available follow-up.	Combining Tofacitinib with other biologics is effective in selecting children with refractory UC. Early responders were more likely to achieve a sustained response in week 16. Failure to achieve remission by week 16 of Tofacitinib therapy was strongly associated with progression to colectomy.
Constant 2022 [5]	USA	Retrospective cohort study	11	2018 to 2021	Patients were identified from departmental lists of patients initiating Tofacitinib and were eligible for inclusion if they were diagnosed with UC (per clinical, endoscopic, and histologic findings)	The primary outcome was 90-day colectomy-free survival. Secondary outcomes included colectomy-free clinical remission, corticosteroid independence, colectomy-free Tofacitinib drug persistence, Tofacitinib-related adverse events, and postoperative complications.	Tofacitinib may represent a new treatment option for hospitalized pediatric patients with corticosteroid- and anti-TNF-nonresponsive ulcerative colitis. Future research is essential in determining the optimal positioning of these therapies.
Moore 2021 [6]	USA	Retrospective cohort study	21	52 weeks	All patients 21 years and younger initiated on Tofacitinib because of active IBD despite biologic therapy being included.	The primary outcome measures were a clinical response to Tofacitinib at week 12, a time point corresponding to the end of the induction period, and at week 52. Secondary outcomes measured were clinical response at weeks 6 and 24 as well as adverse events (AEs). Specific AEs of interest included the development of thrombi, hyperlipidemia, and opportunistic infections.	There is limited experience with Tofacitinib in pediatric IBD. In this cohort, Tofacitinib induced a rapid clinical response with sustained efficacy in nearly half of the subjects. This study provides encouraging evidence for the efficacy and safety of Tofacitinib as part of the treatment paradigm for young individuals with moderate-to-severe IBD. Larger, well-powered, prospective studies are warranted.
Koubek 2023 [12]	USA	Retrospective cohort study	20	September 1, 2019, to September 30, 2021	Patients aged 0 to 18 years admitted to our institution for 2 years from September 1, 2019, to September 30, 2021, who received infliximab, adalimumab, Tofacitinib, Ustekinumab, and/or vedolizumab for the treatment of CD or UC	Outcomes are Readmission within 6 months, Colectomy, Biologic acceleration >7 days, Patients with new therapy, Infusion reaction, and Time to biologic administration.	The diversity of practice observed within our institution supports the need for guidelines to define the standard of therapy or guide the selection of second-line therapies based on patient-specific factors.
Dolinger 2021 [11]	USA	Retrospective cohort study	16	Part of an ongoing, single-center, pediatric IBD observational registry, initiated in October 2014	All patients under the age of 18 years starting dual therapy were identified prospectively.	The primary outcome was steroid-free remission at 6 months, defined as a wPCDAI ≤ 12.5 for CD or pMS <2 for UC/IBD-U, and no form of corticosteroids for at least 4 weeks. Secondary outcomes included time to steroid-free remission, change in serum biomarkers (CRP and ESR) and albumin between baseline and 6 months, and adverse events. Safety reporting included infusion and injection reactions, in addition to any serious adverse events.	Our data suggest that dual therapy may be an option for patients with limited therapeutic options remaining. Safety concerns should always be at the forefront of decision-making, and larger studies are needed to help confirm the preliminary safety data observed.

UC, Ulcerative Colitis; IBD, Inflammatory Bowel Disease; CD, Crohn's disease; IBD-U, Indeterminate Inflammatory Bowel Disease; AEs, Adverse Events; TNF, Tumor Necrosis Factor; Retro., Retrospective; wPCDAI, Weighted Pediatric Crohn's Disease Activity Index; pMS, Pediatric Mayo Score; CRP, C-reactive Protein; ESR, Erythrocyte Sedimentation Rate

Table 2: Baseline characteristics of participants in included studies

Study ID	Age (Years), Mean (SD)	Gender (Female), N (%)	Diagnosis	Previous therapies							
				Infliximab	Adalimumab	Vedolizumab	Ustekinumab	5-ASA	Corticosteroids	Tofacitinib	Tacrolimus
Ryan 2023 [7]	12 (2.3)	10 (66.7)	UC = 15	15	5	5	2	-	-	-	-
Constant 2022 [5]	16 (1.8)	3 (27)	UC = 11	8	2	3	-	8	11	-	-
Moore 2021 [6]	17 (3.8)	7 (33.3)	UC = 14	20	9	13	2	-	-	-	-
			IBD-U = 4								
			CD = 3								
Koubek 2023 [12]	15 (1.6)	10 (50)	UC = 9	15	3	1	1	-	-	4	-
			CD = 11								
Dolinger 2021 [11]	15.4 (2.8)	8 (50)	UC = 8	16	3	8	10	-	10	4	-
			CD = 7								
			IBD-U = 1								

UC, Ulcerative Colitis; CD, Crohn's Disease; IBD-U, Inflammatory Bowel Disease-Unclassified; 5-ASA, 5-Aminosalicylic acid

Table 3: Summary of outcomes in included studies

Outcome	Number of studies	Event	Total	Proportion (%)
Clinical Response	1	10	15	66.67
Clinical Remission	2	10	26	38.46
Steroid-free remission	3	17	35	48.57
Colectomy	3	12	35	34.28
Infections	3	11	47	23.4
Serious adverse events	3	12	47	25.53

3.2. Characteristics of the included studies

A total of five studies encompassed 83 children diagnosed with IBD, of which 57 children had ulcerative colitis. Twenty-one patients (25.3%) were on corticosteroids before receiving Tofacitinib. Only eight patients (9.63%) were previously treated with 5-aminosalicylic acid. The summary and baseline characteristics of the included studies are shown in (Table 1) and (Table 2), respectively.

3.3. Quality assessment of the included studies

We used the Newcastle Ottawa Scale to assess the risk of bias for included studies. All of the included cohort studies were of good overall quality [5, 11, 12, 13, 6, 7]. The detailed quality assessment is available in the supplementary material (Supplementary Table 1).

3.4. Outcomes

One of our included studies reported a clinical response with a total of 15 from the total population. The proportion of patients achieving a clinical response was 66.67% (n=10) (Table 3). We reported Clinical remission, steroid-free remission, colectomy, infections,

allergies, and serious adverse events (Table 3). Clinical remission was reported in two studies with a total population of 26 and a proportion of 38.46% (n=10). Steroid-free remission was reported in three studies with a total population of 35 and a proportion of 48.57% (n=17). Colectomy was reported in three studies, involving a total population of 35 and a proportion of 34.28% (n = 12). Infections were reported in three studies with a total population of 47 and a proportion of 32.4% (n=11). Serious adverse events were reported in three studies with a total population of 47 and a proportion of 25.53% (n=12).

4. Discussion

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that primarily affects the colon. In children, UC causes the inner lining of the colon to become inflamed and develop ulcers. Symptoms commonly include abdominal cramping, bloody diarrhea, fatigue, weight loss, loss of appetite, rectal bleeding, and an urgency to have a bowel movement. These symptoms can vary in severity and duration depending on the extent and duration of the disease. The exact cause of UC in children is not fully understood, but it is believed to involve a combination of genetic, environmental, and immune system

factors. The condition can significantly impact a child's growth, development, and overall quality of life. Treatment aims to reduce inflammation, manage symptoms, and induce and maintain remission. This can include medications such as aminosalicylates, corticosteroids, immunomodulators, and biologics, including tofacitinib, vedolizumab, and Ustekinumab. In some cases, surgery may be necessary [14].

Janus kinase inhibitors have gained growing popularity among gastrologists for several inflammatory conditions, especially when most other therapeutic options are exhausted [15]. Tofacitinib is an oral Janus kinase (JAK) inhibitor that targets JAK1 and JAK3 enzymes. Its mechanism of action involves inhibiting the JAK-STAT signaling pathway, which is crucial in the inflammatory

response. By blocking these kinases, Tofacitinib disrupts the downstream signaling that leads to inflammation; this inhibition reduces the activity of pro-inflammatory cytokines, thereby decreasing inflammation and halting the progression of the disease.

Tofacitinib has been studied for its pharmacokinetic profile in pediatric patients. The pharmacokinetics (PK) of the drug in children and adolescents with JIA have shown that it is well-absorbed orally, and its safety profile is consistent with that observed in adults. The PK parameters, such as absorption rate and plasma concentration, vary depending on the age and weight of the pediatric patients. These studies are crucial for determining appropriate dosing regimens to ensure both efficacy and safety in younger populations [16, 17, 18]. In this systematic review, we investigated the efficacy of Tofacitinib in Pediatric Inflammatory Bowel Disease in terms of clinical response. The primary efficacy outcome in our study. The results showed a clinical response proportion of 66.67% (10 out of 15), Ryan et al. 2023 [7]. For clinical remission, the proportion was 38.46% (10 out of 26). Regarding allergy, Koubek 2023 reported zero events, with a proportion of 0% (0 out of 20) [12].

Moving to serious adverse events, real-world safety data have associated Tofacitinib with higher incidences of venous thromboembolic events, herpes zoster reactivation, and serious infections. In our study, 15 % of children treated with Tofacitinib got an infection. However, these risks appear to be lower in the pediatric population [19]. Constant et al. 2021 stated that no serious adverse events were linked to Tofacitinib during follow-up [5]. On the other hand, the FDA has reported that adult patients with comorbidities who are taking higher doses of Tofacitinib face risks of pulmonary embolism and death, as well as cardiovascular events and cancers. Moore et al. 2021 declared that the majority of their subjects were on 10 mg BID for most of the study period, and there were no occurrences of thrombi, clinically significant hyperlipidemia, or other cardiovascular or oncologic adverse events [6]. Tofacitinib has shown benefits when used sequentially with or concomitantly to anti-TNF therapy. In the study, 4 out of 6 patients who received Tofacitinib after inpatient anti-TNF therapy remained colectomy-free at the last follow-up [15, 20]. Shimizu et al. 2021 used infliximab alone. Six patients (30%) underwent colectomy during the study period [21]. The colectomy rate was 3(21.5%) in Rohani et al. 2021 who used adalimumab and infliximab in the treatment of very early-onset ulcerative colitis.

Additionally, emerging research supports the use of Tofacitinib in combination with biological therapies like Ustekinumab or vedolizumab to achieve corticosteroid-free remission in medically refractory UC cases [22]. In the study of 16 biologically refractory pediatric IBD patients treated with dual biologics or biologics in combination with Tofacitinib, 75% (12 out of 16) achieved and maintained steroid-free remission after a median of 88 days. These children had previously failed to achieve steroid-free remission with at least 2 biological therapies and had a median disease duration of 3 years. The combination therapy allowed them to be safely weaned off steroids [11]. It can be considered as an add-on therapy as clinical and remission rates are < 50 %, which is low.

Although Tofacitinib has emerged as an adjunctive treatment in patients with refractory UC, the data in pediatric patients are limited, particularly regarding the effect of this agent in combination with TNF- inhibitors. In pediatrics, use of the lowest effective dose is advised given a boxed warning noting an increased risk of pulmonary embolism observed in adult rheumatoid arthritis patients with additional risk factors. Further safety considerations should include dose-dependent herpes zoster infection rates and

lipid abnormalities, as well as CYP3A4 drug interactions that may require empiric dose adjustment [23].

Overall, while the study demonstrates the efficacy of Tofacitinib, the five included studies provided data on a total of 83 participants and exhibited variations in design, sample size, and interventions. Despite the merits and strengths of our synthesis, there are important limitations. First, the lack of a comparator group and biases associated with retrospective studies. Second, the observed variability in the studies and outcomes highlights the need for further research to refine treatment protocols and understand the factors contributing to outcome differences. Third, the observational nature of the included studies and their small numbers of patients, lack of objective endoscopic data there was a lack of objective endoscopic data before and after Tofacitinib commencement, as well as a lack of calprotectin correlates of mucosal activity. Also, the study does not assess long-term outcomes, preventing conclusions about the efficacy and safety of specialty therapies over time. Additional studies with stronger evidence, extended follow-up periods, and more comprehensive data are necessary to reach more conclusive results.

5. Conclusions

In conclusion, our study may demonstrate the efficacy of Tofacitinib in inducing clinical response and remission. Still, due to the variability observed among included studies, the need for more robust, well-designed trials with more efficacy data is essential to confirm our findings. Additionally, while the safety profile of Tofacitinib was observed in the pediatric population, the small sample sizes and limited long-term data necessitate cautious interpretation. Further research is crucial to establish optimal dosing regimens, understand the long-term safety, and evaluate the potential of combining Tofacitinib with other therapies.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Large-Language Model

The manuscript was language-edited using an LLM strictly to refine clarity, grammar, and readability. No new content was created or collected during this process, ensuring that the original scientific content remains unchanged.

Authors' Contribution

AAA: conceptualization and methodology. AAA, MA: investigation and data curation. AAA: formal analysis. AAA, SA, MA, NE,

AA, and ALY: Writing - Original Draft. HA: Supervision. AAA: Project administration. AAA and MA: Writing - Review & Editing. All authors read and approved the final content.

Data Availability

All data generated or analyzed during this study are included in this published article

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