ISSN Print: 2664-8350
ISSN Online: 2664-8369
Impact Factor: RJIF 5.26
IJPN 2023; 5(2): 36-40
www.pediatricsjournal.net
Received: 05-06-2023
Accepted: 09-07-2023

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Anti-TNF therapy in pediatric inflammatory bowel disease: Systematic review

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DOI: https://doi.org/10.33545/26648350.2023.v5.i2a.49

Abstract
Introduction: Anti-TNF drugs have transformed IBD treatment since their introduction over two decades ago. Anti-TNF drugs like infliximab (IFX) and adalimumab (ADA) can elicit and maintain corticosteroid-free remission in adults and adolescents with Crohn's disease (CD) and ulcerative colitis. For decades, corticosteroid (CS) has been the main treatment for IBD, despite its substantial side effects, especially on growth and development.
The aim: This article demonstrated study on anti-TNF therapy in pediatric IBD (inflammatory bowel disease).
Methods: This study demonstrated that it met all of the requirements by comparing itself to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. As a result, the specialists were able to ensure that the study was as up to date as possible. Publications published between 2013 and 2023 were considered for this search strategy. This was accomplished using a variety of online reference sources, including Pubmed and SagePub. It was chosen not to include review pieces, previously published works, or works that were just partially completed.
Result: In the PubMed database, the results of our search brought up 46 articles and SagePub 52 articles. The results of the search conducted for the last year of 2013 yielded a total 11 articles for PubMed and 9 articles from SagePub. In the end, we compiled a total of four papers.
Conclusion: Early anti-TNF treatment is becoming more common in juvenile inflammatory bowel disease, notably Crohn's. Targeting higher dosages (> 5 µg/mL) with proactive TDM has been proven to increase disease remission rates and anti-TNF biologic durability in real-world and clinical investigations in children.

Keywords: Anti-TNF therapy, gatrointestine, inflammatory bowel disease

Introduction
Inflammatory bowel diseases (IBDs) are characterized as chronic conditions that include immune-mediated processes, encompassing both Crohn's disease and ulcerative colitis [1]. The straight referral for endoscopic evaluation is warranted in cases of Inflammatory Bowel illness (IBD) where there is a clinical presentation with rectal hemorrhage or perianal illness. When red-flag symptoms are not present, the utilization of patient history along with blood and fecal biomarkers can aid in differentiating suspected inflammatory bowel disease (IBD) from other etiologies of abdominal pain or diarrhea [2, 3].
Approximately 10% of all patients exhibit a juvenile beginning of illness. The therapeutic management of pediatric inflammatory bowel disease (IBD) has seen significant advancements by considering factors that indicate a negative prognosis [2]. This supports the rationale for initiating anti-tumor necrosis factor therapy as an initial treatment for patients who are at a heightened risk of developing severe disease. The therapeutic objective in managing patients with inflammatory bowel disease (IBD) is to achieve biochemical or endoscopic remission, rather than clinical remission [4, 5].
This is due to the fact that intestinal inflammation frequently continues even after the cure of abdominal symptoms. Pediatric IBD presents distinct supplementary difficulties, including growth retardation, delayed onset of puberty, the psychological aspects of adolescence, and the formation of body image [3]. Following the attainment of remission, a considerable number of individuals diagnosed with IBD persistently encounter non-specific symptoms such as abdominal pain and fatigue.

The shift from pediatric to adult care is widely acknowledged as a significant factor contributing to the potential relapse of diseases [4].

This emphasizes the fragility of patients and underscores the necessity of a transition program that is seamlessly carried out by the adult-focused IBD team. The role of the general pediatrician is crucial in effectively addressing these problems within the context of clinical treatment for patients with IBD and enhancing their overall outcomes [3]. The objective of this comprehensive review is to furnish general pediatricians with the latest information on pediatric IBD, thereby enhancing their ability to engage in meaningful discussions with pediatric gastrointestinal specialists [6, 7].

Anti–tumor necrosis factor alpha (anti–TNF) agents have revolutionized the treatment of inflammatory bowel disease (IBD) since their introduction more than two decades ago [8]. Several anti-TNF agents, including infliximab (IFX) and adalimumab (ADA), have been shown to induce and maintain corticosteroid-free remission in both adults and adolescents with Crohn's disease (CD) and ulcerative colitis (UC) [9, 10]. Corticosteroid (CS) has been the primary agent for inducing remission in individuals with IBD for decades, despite their multiple serious adverse effects, particularly on growth and development [11].

The present research offers a comprehensive analysis of a study that specifically examines the efficacy of anti-TNF medication in pediatric patients diagnosed with inflammatory bowel disease.

Methods

The principal investigator of the study ensured strict adherence to the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 protocol. The objective of this methodology is to ensure the accuracy of the findings obtained from the investigation. The primary objective of this study was to investigate the efficacy of anti-tumor necrosis factor (anti-TNF) medication in the treatment of pediatric inflammatory bowel disease (IBD). The primary objective of this study is to demonstrate the significance of the aforementioned themes that have been explored in the literature. In order to participate in the study, researchers were required to meet specific criteria and adhere to predetermined norms.

One of the stipulations entailed composing the manuscript in the English language and primarily focusing on anti-TNF medication in the context of pediatric inflammatory bowel disease (IBD). In order for the document to be issued, it is necessary for both of these conditions to be satisfied. Several publications under consideration were published in 2018, falling within the selected time frame deemed pertinent to the objectives of this systematic review. In an academic context, it is not permissible to submit editorials, manuscripts lacking a Digital Object Identifier (DOI), already published review articles, or duplicate submissions of journal articles that have already been published.

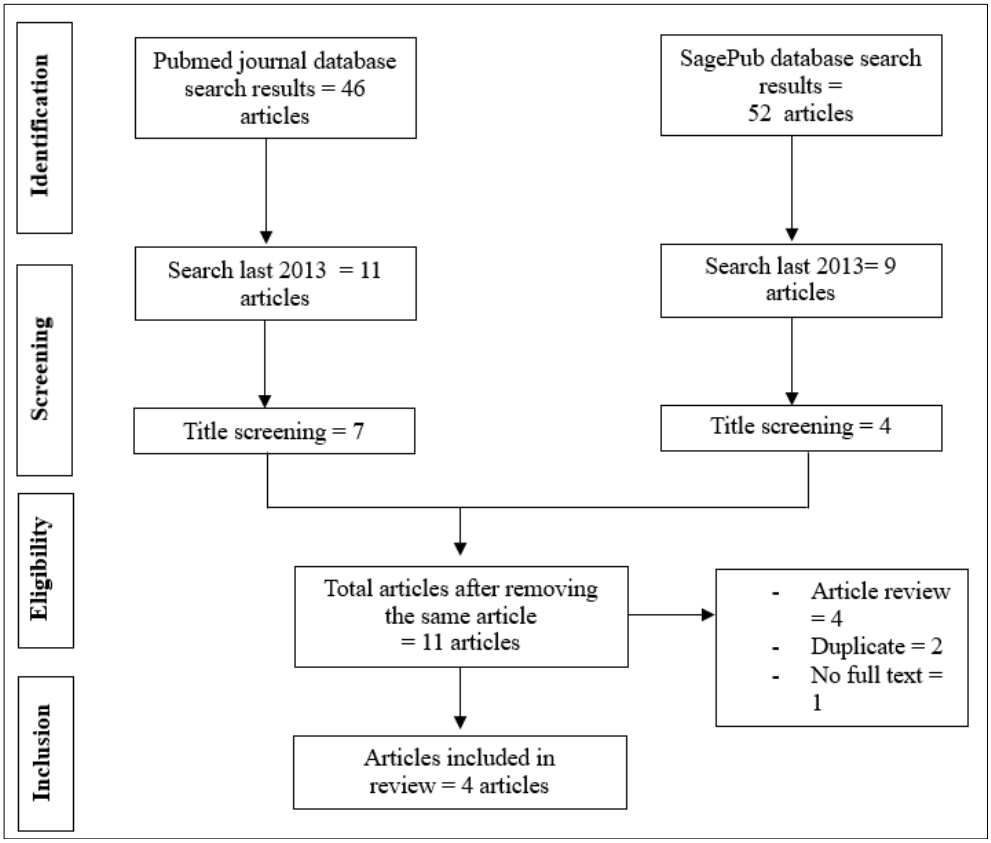

Fig 1: Article search flowchart

We used “anti-TNF therapy”; “pediatric”; and “inflammatory bowel disease” as keywords. The search for studies to be included in the systematic review was carried out from September, 23th 2023 using the PubMed and SagePub databases by inputting the words: ("anti-TNF"[All Fields] AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]) AND ("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND ("inflammatory bowel

diseases"[MeSH Terms] OR ("inflammatory"[All Fields] AND "bowel"[All Fields] AND "diseases"[All Fields]) OR "inflammatory bowel diseases"[All Fields] OR ("inflammatory"[All Fields] AND "bowel"[All Fields] AND "disease"[All Fields]) OR "inflammatory bowel disease"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter])) used in searching the literature.

The researchers ensured that each study's abstract and title were included. The essayists then selected pertinent research from the literature. This was discovered by analyzing numerous studies that all followed the same pattern. All submissions must be written in English and have never been published before. The systematic review was limited to studies that satisfied all inclusion criteria. This ensures that the search results only pertain to what the user requested. We disregard studies that do not meet our requirements. The results of the investigation will be thoroughly examined. This study's investigation uncovered names, authors, publication dates, locations, study activities, and parameters. Everyone who wrote the paper looked at the research in the title and abstract of every paper before choosing which ones to read more deeply. The next step is to choose which articles to include from all the ones that meet the review's requirements. Then we'll choose which stories to include in the review based on what we find. This is how papers that need to be looked at more closely are chosen. So it's as simple as possible to pick works to review. This part talks about the studies that have already been done and why they were added to the review.

Result

In the PubMed database, the results of our search brought up 46 articles and SagePub 52 articles. The results of the search conducted for the last year of 2013 yielded a total 11 articles for PubMed and 9 articles from SagePub. In the end, we compiled a total of four papers.

Table 1: The literature include in this study

Author	Origin	Method	Participant	Agent	Result
El-Matary, 2020 [12]	Canada	Retrospective study	291 persons diagnosed with IBD	No describe	Over an 11-year timeframe, there has been a notable trend of administering anti-TNFs at earlier stages in the progression of juvenile inflammatory bowel disease (IBD), accompanied by a corresponding decrease in the cumulative dosage of corticosteroids (CS).
Aloi, 2018 [10]	United State of America	Retrospective study	Thirty-two children with ulcerative colitis (UC) previously treated with infliximab (IFX)	Adalimumab and infliximab	The efficacy of ADA in children with UC has been observed, since it has demonstrated the ability to facilitate recovery in a substantial proportion of kids who are either intolerant or unresponsive to IFX. The safety profile exhibited favorable characteristics.
Singh, 2016 [13]	United State of America	Prospective study	1400 new users of anti-TNF agents	Adalimumab and infliximab	In a large retrospective cohort of ulcerative colitis (UC) patients who started anti-TNF treatment, infliximab (IFX) was found to reduce corticosteroid use compared to Adalimumab. Both therapy groups had equal hospitalization and severe infection rates.
Christine, 2014 [19]	Norway	Prospective study	Thirty-six pediatric patients	Infliximab	When infliximab treatment started, there were high amounts of inflammatory markers and lesions in the upper GI tract. A big part of the patients still had unclear lesions in their upper GI system even after treatment. More research needs to be done to figure out what role chronic upper GI involvement plays in predicting outcome even when mucosal healing occurs in the ileocolon.

El-Matary, *et al* (2020) [12] showed 42.5% of CD and 28.4% of UC patients had been prescribed an anti-TNF antagonist within 12 months of IBD diagnosis for those diagnosed after 2012. Initiating an anti-TNF without prior exposure to an immunosuppressive agent increased over time (before 2008: 0%; 2008-2012: 18.2%; 2012-2016: 42.8%; $p<0.001$). There was a significant reduction in median cumulative dose of corticosteroids (CS) in the year before anti-TNF initiation (2005-2008: 4360 mg; 2008-2012: 2010 mg; 2012-2016: 1395 mg prednisone equivalents; $p<0.001$).

Aloi, *et al* (2018) [10] showed thirty-two children received ADA (median age 10±4 years). Before ADA therapy, median illness duration was 27 months. All patients had IFX (43% intolerant, 50% nonresponders [37.5% primary, 42.5% secondary], 6.7% positive anti-IFX antibodies). 13 patients (41%) achieved corticosteroid-free remission 52 weeks after ADA beginning. Nine patients (28%) healed at 52 weeks. The cumulative likelihood of clinical relapse-free course was 69%, 59%, and 53% at 12, 30, and 52 weeks. Ten (31%) initially failed and five (15%) lost ADA response. ADA was maintained by 19 patients (59%) at 52 weeks. Seven patients (22%) had adverse events, none reported significant side effects or ADA discontinuation.

Singh, *et al* (2016) [13] showed there was no significant difference in the risk of UC-related hospitalisation (IFX vs. ADA; adjusted hazard ratio [aHR] = 1.04; 95% confidence interval [CI] = 0.71-1.51), corticosteroid use (aHR = 0.85; 95% CI = 0.68-1.06) and serious infections (aHR = 0.62; 95% CI = 0.29-1.34) between IFX- and ADA-treated patients; the number of surgical events was very small. On IPTW analysis, risk of corticosteroid use was significantly lower in IFX - as compared to ADA - treated patients (aHR = 0.82; 95% CI = 0.68-0.99). Results were stable on multiple sensitivity analyses.

Patients who were given infliximab had shorter disease duration, more upper GI involvement (p = 0.03), and higher median levels of CRP (28 vs. 7.5 mg/l, p = 0.02), ESR (32 vs. 18 mm/h, p = 0.01), and calprotectin in their feces (1506 vs. 501 mg/kg, p = 0.01). The treatment with infliximab was well accepted, and 15/18 of the patients reached clinical remission. At the follow-up, 11/17 people in the infliximab group had healed ileocolonic mucosa and 8/13 people in the non-infliximab group had. Most of the people in the infliximab group had a big drop in CD-specific upper GI ulcers, but they still had general upper GI inflammation at the follow-up [14].

Discussion

Multiple empirical investigations and a single controlled experiment including pediatric subjects have shown evidence that proactive therapeutic drug monitoring (TDM), specifically focusing on attaining higher concentrations of over 5 µg/mL, can effectively enhance the rates of illness remission and prolong the efficacy of anti-tumor necrosis factor (anti-TNF) biologic treatments. The analysis of recent data obtained from individuals with both adult and juvenile inflammatory bowel disease (IBD) has provided evidence of a correlation between a specific genetic variation (HLA-DQA1*05) and the emergence of auto-drug antibodies [15].

The inquiry into the influence of this link on clinical outcomes, particularly in relation to the more frequent implementation of proactive therapeutic drug monitoring (TDM) and dose optimization in pediatric patients, is still ongoing. Moreover, recent research has revealed possible indicators of inflammation and biomarkers that could potentially be used as companion diagnostics for anti-tumor necrosis factor (anti-TNF) biologics. Evidence-based precision dosing techniques, such as frequent therapeutic drug monitoring (TDM) and proactive pharmacodynamic assessments, are crucial for the efficient management of anti-TNF treatments in pediatric patients with inflammatory bowel disease (IBD) [15].

The reasons for the increased utilization of anti-TNF medications in the juvenile population compared to adults remain unclear. The characteristics of pediatric inflammatory bowel disease (IBD) may manifest as increased disease severity, more involvement of the gastrointestinal tract, and heightened acuity. However, a recent study has demonstrated that while Crohn's disease (CD) in adolescents and young adults may exhibit a greater range of symptoms, it does not display a higher level of aggressiveness when compared to CD that develops in adults [16].

Another potential explanation is to the appeal of anti-TNF medicines as a substitute for CS, given the potential detrimental impact of CS on children who are still in the process of active growth, in contrast to adults who have already reached their ultimate growth status. The study demonstrated a notable decrease in the cumulative dose of CS over the course of time. In a previous study, our research team demonstrated a consistent utilization of CS among individuals aged 0-25 years diagnosed with IBD. Specifically, study showed that 56% of this population were exposed to CS within one year of their IBD diagnosis. Furthermore, study revealed no statistically significant decline in CS usage over the period of observation spanning from 2002 to 2010 [17].

There has been a noticeable shift in recent times, characterized by a substantial decline in the utilization of CS from 2010 to 2016. The findings of our study suggest that pediatric gastroenterologists demonstrate a propensity to employ anti-TNF medications at an earlier stage of the illness trajectory, with the aim of mitigating the deleterious effects associated with corticosteroid exposure. The impact of Crohn's disease on growth is more pronounced in comparison to ulcerative colitis (UC), potentially leading to a higher prevalence of anti-tumor necrosis factor (anti-TNF) therapy utilization in children diagnosed with Crohn's disease as opposed to those diagnosed with UC [18].

Conclusion

Anti-TNF medicines are increasingly used early in juvenile inflammatory bowel illness, especially Crohn's disease. It was encouraging to see cumulative CS use drop in recent years, especially in children with Crohn's disease, suggesting that increased anti-TNF treatment will minimize CS harm. Proactive TDM, targeting greater exposure doses (> 5 µg/mL), has been shown to improve illness remission rates and anti-TNF biologic durability in real-world studies and a clinical study in children.

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Sundana DP. Anti-TNF therapy in pediatric inflammatory bowel disease: Systematic review. International Journal of Pediatrics and Neonatology. 2023;5(2):36-40.