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Early Versus Late Initiation of Biological Therapy for The Treatment of Paediatric Inflammatory Bowel disease, A Single Center Experience

*Mai M. Emam[1], Ayman E. Eskander[1], Nouran N. Moemen[2], Hala. H. Mansour[1]**

[1]*Faculty of Medicine, Cairo University, Pediatrics- Egypt.*

[2]*Faculty of Medicine, Cairo University, clinical and chemical pathology- Egypt.*

Abstract

The incidence and prevalence of pediatric inflammatory bowel disease (IBD) are rising, and the lines of management had clearly changed with the emergence of tumor necrosis factor (TNF) antagonists. We aimed to compare early and late initiators of anti-TNF in pediatric IBD patients, with trial to validate non-invasive predictors of clinical and endoscopic response. A Cohort longitudinal study enrolled pediatric patients with inflammatory bowel disease on biological therapy attending the Gastroenterology outpatient clinic of Children University Hospital (Abo-Elreesh), Cairo University and fitting the inclusion criteria divided into two main groups, early initiators and late initiators of biological therapy and both groups were assessed for clinical, demographic, hematological, and endoscopic response at baseline, 3, 6, and 12 months. Of 91 patients assessed for eligibility, only 76 ones were included in the study with further classification into 2 groups with the ratio 1:1, and only one patient in the early group has family history of IBD and 9 in the late group. Only 1 patient in the late group didn`t does not receive steroids unlike 9 patients in the early group and 6 ones received steroid once in the early group. Nearly equal impact on growth parameters, clinical and endoscopic response was observed among both groups with PUCAI/PCDAI at the baseline of significant prognostic value on clinical response. Using anti-TNF for the treatment of pediatric IBD is crucial, and either starts early or late within time of diagnosis, it has a great impact on growth of children, clinical and endoscopic response.

Keywords: IBD, Biological therapy, Anti-TNF, Infliximab, Adalimumab.

Full length article **Corresponding Author*, e-mail: halahussienmansour@yahoo.com; hala.h.monsoor@kasralainy.edu.eg

1. Introduction

Chronic recurrent intestinal inflammation is a hallmark of inflammatory bowel disorders (IBD). IBD-unclassified (IBD-U), Crohn's disease (CD), and ulcerative colitis are the three primary subgroups of pediatric IBD. In children under the age of five, the incidence and prevalence of pediatric inflammatory bowel disease (IBD) are clearly on the rise. Pediatric IBD has different consequences, most notably growth impairment, and a more severe, aggressive phenotype than adult IBD [1]. The pathogenesis of IBD is not clear but is thought to a result of dysregulated mucosal immune response, microbial dysbiosis, genetic and environmental factors [2]. There are more than 200 genes that are associated with development of IBD. These genes, involved in innate and adaptive immunity or epithelial function, and are important for immunological homeostasis. Chronic inflammation may be brought on by a genetically predisposed, dysregulated immune response to the intestinal microbiome. Multiple environmental risk factors have been identified in the pathogenesis of IBD as diet, antibiotic use, and lack of breastfeeding [3]. It is also confirmed that dysbiosis is closely linked to initiation or progression of IBD; however, it is whether dysbiosis is a primary or a secondary event [4]. There are variable presentations of IBD, especially in children and adolescents. Manifestations of the disease include both gastrointestinal and extra-intestinal symptoms. The symptoms are consistent and result inflammation in the gastrointestinal tract [5]. Despite differences in clinical manifestation, histopathology and pathogenesis, the treatment is similar in both diseases. After diagnosis, steroids, and exclusive enteral nutrition (EEN) are basically started first, to induce remission, together with thiopurines or methotrexate (MTX) to maintain remission. Anti-tumor necrosis factor-a (anti-TNF-a) antibodies have been documented to be very effective in induction and maintenance of remission in refractory pediatric CD patients [6]. Anti-TNF medication not only results in the disappearance of clinical symptoms but also in the endoscopic remission of mucosal tissue integrity [7].

Anti-TNF medicine causes the endoscopic remission of mucosal tissue integrity in addition to the absence of clinical symptoms. Intestinal healing, reaching growth potential, and enhancing quality of life are all treatment objectives. The prospect of achieving

these objectives has considerably increased recently with the development of anti-TNF agents. The optimum timing to start anti-TNFs for the treatment of pediatric IBD is still controversial till now.

2. Patients and methods

2.1. Data source

This Cohort longitudinal study included pediatric patients with inflammatory bowel disease on biological therapy attending the Gastroenterology outpatient clinic of Children University Hospital (Abo-Elreesh), Cairo University for follow up. The study protocol was approved by Research and Ethical Committee of Pediatric Department, Faculty of Medicine at Cairo University and coded as MD-35-2022. Informed consent was obtained from patient's legal guardians before enrollment.

2.2. Patients

The data were collected by direct patients interviewing with inclusion of patients age equals or less than 18 years, of both sexes and children diagnosed as IBD and on biological therapy either alone or in combination with immunomodulators or corticosteroids. IBD patients with a history of cardiovascular disease, hemopathy, malignant tumor, connective tissue disease was excluded.

2.3. Interventions

The data were collected by reviewing of patients' medical records as well as direct patients' interviewing, and pediatric patients diagnosed as IBD and on biological therapy were divided into two main groups:

- Early initiators of biological therapy (<1 year of diagnosis) [8].
- Late initiators of biological therapy (>1 year after diagnosis).

Initial assessment at the time of initiation of biological therapy (without any affection of their protocol of treatment) was done for both groups for:

2.3.1. History with special emphasis on

(Gender, age, family history, consanguinity, age of onset of symptoms, age of diagnosis, age at starting biological therapy, disease subtype (infantile IBD (I-IBD), VEO-IBD, early IBD (E-IBD,) or P-IBD), disease phenotype (CD, UC, or IBD-U), anti-TNF type, extra-intestinal manifestations as arthritis, hepatobiliary manifestations.

2.3.2. Clinical assessment

Clinical assessment using Pediatric Crohn's Disease Activity Index (PCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI) [9-10].

2.3.3. Examination

Thorough physical examination of all body systems with special emphasis on:

2.3.3.1. Anthropometric measurements

Anthropometric measurements include weight for age, height for age, weight for height and body mass index according to the Z- score and percentile curves using weight scale, stadiometer.

2.3.3.2. Interpretation of growth parameters

World health organization (WHO) Z score values were calculated for children below 2 years and Centers for Disease Control and prevention (CDC) Z score values for children more than 2 years for weight-for-age, weight -for-length or height, length or height- for-age, body mass index (BMI)-for-age, using Growth calculator app version April, 2021 (**https://play.google.com/store/apps/details?id=anassheikhibrahim.growthcalc**)

2.3.4. Endoscopic activity index assessment

Endoscopic activity index assessment according to simple endoscopic score for Crohn`s disease (SES-CD) 11 and Ulcerative colitis endoscopic index of severity score (UCEIS) 12 in ulcerative colitis patients.

2.3.5. Follow up assessment

Follow up assessment was done for both groups at 3, 6, 12 months of initiating biological therapy regarding: weight, height, BMI, time to start showing signs of clinical remission from initiating biological therapy, frequency of relapse and the need for corticosteroids, needs for hospitalization, serious infections and associated mortality, surgical complications and endoscopic remission (ER) and mucosal healing (MH) at 1 year from starting anti-TNFs according to SES-CD& UCEIS scores [11-12].

2.3.6. Statistical analysis:

The socio-demographic and clinical characteristics will be described using descriptive and comparative statistics. Continuous variables will be summarized as means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on the distribution of the data. Categorical variables will be summarized as frequencies and percentages. Analysis of

normality was performed using the Kolmogorov-Smirnov test. Comparisons between two parallel groups with continuous data were performed using an independent t test, while similar non- parametric categorical data were performed using the chi-square test, and non- parametric continuous data were performed using the Mann Whitney test. Area under the receiver operating characteristics (AUROC) curve, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV value were used to predict clinical response at the end of 12-month treatment period.All analyses were performed based on per protocol to treat and at a significance level of P < .05. Statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM Corp., Armonk, NY).

3. Results and Discussion

Clinical and demographic characteristics were shown to be comparable between early and late initiators of Anti-TNF therapy at baseline. While there were more males in the late initiation group (76.32% versus 55.26% in the early initiation group), this difference was not statistically significant (p=0.053). Both age at diagnosis and the onset of symptoms were slightly higher in the late initiation group; however, these differences were also not statistically significant (p=0.2 and p=0.3, respectively). The time to diagnosis was also comparable between both groups (p=0.7). Alternatively, there was a significant difference in the age at treatment start, with the late initiation group starting treatment at a higher age (mean 138.37±49.2 months) compared to the early initiation group (mean 92.29±56.08 months), p<0.001. In terms of classification, no significant difference was found (p=0.052). The distribution of IBD subtypes did not differ significantly between groups (p=0.4), nor did the consanguinity factor (p=0.4). Notably, there was a significantly higher prevalence of a family history of IBD in the late initiation group (23.68%) compared to the early initiation group (2.63%), p=0.007 (

). Clinical presentations were comparable between patients who initiated anti-TNF treatment early and those who started it late (each group, n=38). No significant differences were identified across the reported clinical presentations.

Bleeding per rectum and diarrhea were the most common presentations in both groups, with slightly higher rates in the late initiation group (86.84% and 63.16% respectively) than in the early initiation group (81.58% and 60.53% respectively), but these differences were not statistically significant (p=0.5 and p=0.8 respectively). In terms of abdominal pain, 78.95% of patients in the late initiation group experienced it, compared to 68.42% in the early initiation group; however, this difference was also not significant (p=0.3). Oral ulcers, perineal disease, fever, failure to thrive, arthritis, and dermatitis were all more prevalent in the late initiation group, although these differences did not reach statistical significance (P>0.5). There were no reported hepatobiliary disorders in either group. In terms of associated diseases, familial Mediterranean fever (FMF) was found more frequently in the late initiation group (10.53%) compared to the early initiation group (2.63%), but the difference was not statistically significant (p=0.3). Other associated conditions were rare or absent in both groups**.** In terms of the specific anti-TNF therapy used, Adalimumab was the most used in both groups, although a higher percentage was seen in the early initiation group (63.16%) compared to the late initiation group (55.26%). However, this difference was not statistically significant (p=0.5). Infliximab was used equally in both groups (31.58%), while Ustekinumab was used more in the late initiation group (13.16%) compared to the early initiation group (5.26%), but again this was not a significant difference (p=0.5). Nearly all patients in both groups used amino salicylates at baseline (97.37% in the early initiation group and 100.00% in the late initiation group; p>0.9), while Azathioprine was used more in the late initiation group (97.37%) compared to the early initiation group (86.49%), although this difference approached but did not reach statistical significance (p=0.11). Importantly, there was a significant difference in the use of steroids. A much higher proportion of patients in the late initiation group frequently used steroids (92.11%) compared to the early initiation group (60.53%) (p=0.003). A minimal number of patients in the late initiation group reported no use of steroids (2.63%), in contrast to the early initiation group (23.68%). Significant improvements in anthropometric parameters were shown over the course of treatment in the early anti-TNF treatment group (n=38). Statistically significant increases over time were observed in weight (p<0.001), height (p<0.001), and body mass index (BMI) (p<0.001). The mean weight increased from a baseline of 25.25kg to 29.26kg at 12 months. The standard deviation of weight also showed a significant change over time (p<0.001). Mean height followed a similar trend, with a statistically significant increase from a baseline of 112.77cm to 119.50 cm at 12 months. The standard deviation of height over the study period, however, did not show a significant change (p=0.2). The mean BMI at baseline was 17.90 kg/m^2, and it increased significantly to 18.89 kg/m^2 by 12 months. In addition, the standard deviation of BMI changed significantly over the time points (p<0.001). There were statistically significant changes in weight (p < 0.001), body mass index (BMI) (p < 0.001), and height (p < 0.001) over time in the late initiation group when it came to the late initiation of biologic treatment. In terms of weight, there was a significant increase from baseline (mean: 25.25kg) to 12 months (mean: 29.26 kg). The standard deviation of weight also showed a significant change over time (p < 0.001). Similar trends were observed for BMI, with a significant increase from baseline (mean: 17.90 kg/m^2) to 12 months (mean: 18.89 kg/m^2). The standard deviation of BMI also showed a significant change over time (p < 0.001). In terms of height, there was a significant increase from baseline (mean: 112.77cm) to 12 months (mean: 119.50 cm). However, the standard deviation of height did not show a significant change (p = 0.2). Comparing early- vs. late-initiation groups at each follow-up time, there was consistently higher mean body weight (p<0.01) and height (p<0.01) in the late initiation group from baseline to the end

of treatment. Alternatively, BMI, standard deviation of weight, and standard deviation of BMI showed non-significant differences between both groups at different follow-up points (p>0.05). The standard deviation of height showed non-significant differences over different time points, except for at 3 months were early initiators demonstrated significantly higher values (p<0.05). (

3)

3.1. Impact on hematological parameters: early initiation of biologic treatment

The data shows that early initiation of biologic treatment had a significant impact on the hematological parameters of the patients (N=38) over the course of 12 months. Starting with hematocrit levels, an increasing trend was observed. The baseline hematocrit mean was 28.78%, which increased significantly to 33.29% at 12 months (p<0.001). Hemoglobin concentration also showed a significant increase over the course of the treatment. The mean baseline hemoglobin concentration was 9.38 g/dL and increased to 11.10 g/dL by the end of 12 months (p<0.001). Lastly, the White Blood Cell (WBC) Count showed a significant decrease over the treatment period. The mean baseline WBC count was 11.30 *10^3/mm^3 which decreased to 7.12 *10^3/mm^3 by 12 months (p<0.001)**.**

3.2. Late initiation of biologic parameters

The hematocrit levels increased over time, with a mean of 32.55% at baseline and 35.43% at the 12-month (p < 0.001). Hemoglobin concentration likewise showed a significant rise from a mean baseline value of 10.44 g/dL to 11.91g/dL at the 12-month follow-up (p<0.001). Furthermore, there was a significant reduction in the mean White Blood Cell (WBC) Count, from a baseline mean of 8.59 *10^3/mm^3 to 6.98 *10^3/mm^3 at 12 months (p = 0.002). These results demonstrate that, even with late initiation, biologic treatment significantly affects hematological parameters, improving hematocrit and hemoglobin levels while reducing white blood cell count**.** Comparing early- vs. late-initiation groups at each follow-up time, there were statistically significant higher mean WBC at baseline (p<0.05), and at 3 months (p<0.001); however, WBC count declined to a comparable level at both 6 and 12 months of follow up (p>0.05**)**. Hemoglobin levels were significantly higher at baseline in the late initiation arm (p<0.001); however, after 3 months of treatment, both groups demonstrated comparable, statistically non-significant levels (p>0.05). Hemoglobin levels returned to higher values for the late initiation arm at 6 months (p<0.05) and 12 months (p<0.01) of anti-TNF therapy. Hematocrit was significantly higher in the late initiation group at baseline (p<0.05) and after 12 months of treatment (p<0.01). However, statistically non-significant differences in hematocrit between the two groups were attained at both 3 and 6 months of treatment (p>0.05).

3.3. Comparing the clinical outcomes at the end of Anti-TNF treatment

Both early and late initiation of anti-TNF therapy was associated with comparable clinical and endoscopic outcomes after 12 months of treatment in this cohort of patients. After 12 months of Anti-TNF therapy, there was no significant difference between the groups in PUCAI/PCDAI score (measures of disease activity) with a mean score of 17.76 for the early initiation group and 16.12 for the late initiation group (p = 0.3). Similarly, the SES-CD/UCEIS score (endoscopic indices for disease activity) showed no significant difference between the groups, with a mean score of 5.16 in the early initiation group and 5.42 in the late initiation group (p = 0.4). Regarding clinical response, all patients in the early initiation group (100%) and 35 patients (92.11%) in the late initiation group responded to the therapy, but this difference was not statistically significant (p = 0.2). Only 1 patient (2.63%) in the late initiation group achieved endoscopic response, and none in the early initiation group, with this difference not being statistically significant (p > 0.9). As for clinical remission, 10 patients (26.32%) in the early initiation group and 11 patients (28.95%) in the late initiation group achieved remission, and again, this difference was not significant (p = 0.8). In terms of hospitalization at the end of 12 months therapy, a larger proportion of patients in the late initiation group (94.74%) were not hospitalized compared to the early initiation group (84.21%), but this difference was not significant (p = 0.3). Azathioprine and 5-Aminosalicylate were used by all the patients in both groups (Table 1: Comparing baseline demographics and clinical characteristics in early vs. late initiation of anti-TNF (N=76).

Characteristic	**Early initiation**, N = 38[1]	**Late initiation**, N = 38[1]	**p-value**[2]
Gender			
Female	17 (44.74%)	9 (23.68%)	0.053
Male	21 (55.26%)	29 (76.32%)	
Age at Diagnosis (months)			
Mean (SD)	85.97 (56.95)	102.11 (46.85)	0.2
Median (IQR)	60.00 (39.75, 146.00)	110.00 (65.25, 139.25)	

Range	8.00, 183.00	16.00, 180.00	
Age at Start of symptoms (months)			
Mean (SD)	77.11 (59.72)	93.54 (47.34)	0.3
Median (IQR)	52.50 (19.75, 140.00)	108.00 (60.00, 126.00)	
Range	2.00, 175.00	4.00, 178.00	
Time to Diagnosis (months)			
Mean (SD)	8.87 (9.55)	7.16 (6.41)	0.7
Median (IQR)	6.00 (3.25, 12.00)	6.00 (3.00, 8.00)	
Range	1.00, 48.00	1.00, 36.00	
Age at Treatment Start (months)			
Mean (SD)	92.29 (56.08)	138.37 (49.20)	**<0.001**
Median (IQR)	71.50 (42.75, 151.25)	144.00 (112.00, 178.25)	
Range	13.00, 189.00	30.00, 216.00	
Classification			
I-IBD (0-2)	10 (26.32%)	5 (13.16%)	0.052
VEO-IBD (<6)	10 (26.32%)	6(15.79%)	
E-IBD (<10)	5 (13.16%)	15 (39.47%)	
P-IBD (<17)	13 (34.21%)	12 (3.58%)	
IBD Subtype			
IBD-CD	14 (36.84%)	15 (39.47%)	0.4
IBD-U	11 (28.95%)	6 (15.79%)	
IBD-UC	13 (34.21%)	17 (44.74%)	
Consanguineous			
Consanguineous	6 (15.79%)	9 (23.68%)	0.4
Non- consanguineous	32 (84.21%)	29 (76.32%)	
Family History of IBD	1 (2.63%)	9 (23.68%)	**0.007**
[1]n (%)			
[2]Pearson's Chi-squared test; Wilcoxon rank sum test			

Table). Despite no significant differences between the early- and late-initiation groups, both groups demonstrated a statistically significant reduction of SES-CD/UCEIS (Figure 2), as well as PUCAI/PCDAI scores (Figure 3) after 12 months of treatment ($p<0.001$ for both scores). Anti-TNF agents are usually prescribed when IBD patients fail to respond to conventional medical therapies such as amino salicylic acids, immune-suppressants, and corticosteroids [13]. The main rationale for this "step-up" treatment approach is the effective treatment of symptoms, while attempting to avoid over-treating and/or exposing patients to the more side effects associated with more potent therapies. Nonetheless, an increasingly common approach to IBD management involves offering certain selected patients a more effective therapy earlier in the disease course, trying to avoid the irreversible, structural changes to the bowel that occurs with disease progression. In our study, we enrolled pediatric patients who were diagnosed as IBD and on anti-TNF therapy for ≥ 1 year and sub-classified them into two groups according starting anti-TNF therapy in relation to time of diagnosis. When we compared both groups we found significant improvements in anthropometric parameters over the course of treatment in the early anti-TNF treatment group regarding weight, height, and BMI. The mean weight increased from a baseline of 25.25kg to 29.26kg at 12 months. Mean height followed a similar trend, with a statistically significant increase from a

baseline of 112.77 cm to 119.50cm at 12 months. The mean BMI at baseline was 17.90 kg/m^2, and it increased significantly to 18.89kg/m^2. Similarly, this coincides with the results of the study performed by Church et al., (2014) who reported that the mean height z-score improved significantly for children who were Tanner 1/2 at induction during the 2 years after infliximab initiation within 18 months from diagnosis of CD [14]. But unlikely this does not match with what Walters et al., proved in (2015) that the overall linear growth patterns had not changed significantly at 1 year form starting ant-TNF therapy (early group defined as starting ant-TNF within 3 months of diagnosis) [15]. But both weight and BMI significantly improved (D z-score, 0.64; P <.001; and 0.89; P <.001, respectively). However the REACH study (2007) reported an improvement of height z-score of 0.5 after 54 weeks of treatment in 112 children with moderate to severe CD, while Diamanti et al., (2009) found no improvement of linear growth despite an increase in weight and BMI in a small sample of 14 subjects [16-17]. Moreover, Pfefferkorn et al., (2009) reported an increase in height velocity z score after 2 years [18]. But Olbjørn et al., (2014) reported that all patients except one non-responder in the infliximab group had normalized and improved pubertal development and growth, demonstrating higher Tanner scores, regardless of therapy received [19]. While comparing our early & late-initiation groups at each follow-up time, there were great impact on hemoglobin and hematocrit levels at the end of 12 months duration, but without any statistically significant difference between the two groups, matches with what Lucendo et al., (2020) found in the adult study that the 2 groups showed significant response to iron therapy and increase of HB level [20]. Unfortunately, studies on anemia and hematological parameters in pediatric IBD patients on biological therapy are lacking, especially the ones which compare early and late initiation of anti-TNF, but Buczy (2022) found that anemia at the onset of starting anti-TNF can be considered as a prognostic factor of response [34]. In our study we found that after 12 months of Anti-TNF therapy, there was no significant difference between the two groups in PUCAI/PCDAI score (measures of disease activity) with a mean score of 17.76 for the early initiation group and 16.12 for the late initiation group (p = 0.3) unlike what Lionetti et al., (2003) proved in the stud performed that mean PCDAI at 18 weeks in children with early Crohn's disease and late Crohn's disease was 5.5 and 18.1, respectively (P < 0.05) [21]. Also Walters et al., (2014) has mention that 58 of 68 (85%) patients treated with early anti-TNFa alone, 152 of 248(61%) patients, and 129 of 236 (55%) patients who were not treated with either anti-TNF nor immunomodulators within the first 3 months all attained PCDAI scores of 10 or below at 1year (P.0001) [15]. Regarding the SES-CD/UCEIS score we found no significant difference between the two groups, with a mean score of 5.16 in the early initiation group and 5.42 in the late initiation group (p = 0.4) and that goes with what was proofed by Olbjørn et al., (2014) that at the follow up point of 1 year of treatment that the proportions of CD patients who had ileocolonic mucosal healing were similar in both groups [19]. Walters et al., (2014) who showed that the in the early anti-TNFa group the percentage of patients who achieved or did not achieve remission at 1 year is like the findings were noted in the early IM group (61% vs 59%) and the no early immunotherapy group (59% vs 61%) [15]. (

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Unlikely it doesn`t go with that the longer time interval between the disease onset and initiation of biologics remained significant the more the incidence of bowel damage [23]. Regarding clinical response, all patients in the early initiation group (100%) and 35 patients (92.11%) in the late initiation group responded to the therapy (according to our definition of clinical response as decrease from baseline in the PCDAI score ≥15 points; total score ≤30), but this difference was not statistically significant (p = 0.2) and that matches with the finding of that the overall outcome was good in the both who achieved a clinical remission rate of above 80% with normalized PCDAI scores [19]. For both therapy groups, the rate of ileocolonic mucosal repair was high and comparable in Markowitz and coworkers (2000) demonstrating that standard care can lead to endoscopic remission (defined as SES-CD 0-2 and UCEIS 3), which is similar to what was found in our study that only 1 patient (2.63%) in the late initiation group achieved endoscopic response, and none in the early initiation group, with this difference not being statistically significant (p > 0.9) [24]. Regarding clinical remission (defined PCDAI score ≤10 points), 10 patients (26.32%) in the early initiation group and 11 patients (28.95%) in the late initiation group achieved remission. Despite non-significant differences between the early- and late-initiation groups, both groups demonstrated a statistically significant reduction of SES-CD/UCEIS, as well as PUCAI/PCDAI scores after 12 months of treatment (p<0.001 for both scores) and that`s fits what was found in [25]. The 2nd question we tried to answer in our study was the type of anti-TNF influences clinical, hematological outcomes? So, the 76 enrolled patients were stratified into 24 patient receiving Adalimumab in the early group and 21 in the late one, and 12 patient received infliximab in both groups, and 2 biological naïve patients received Ustekinumab in the early group and 5 biological experiences in the late one. When we compared the patients at the start and end of period of follow up, there was no statistically significant difference despite being different in onset of initiation or biological therapy previous exposure, but these results can be explained by the small sample size and possibility of need for longer period of follow up. Likely there was no significant difference between the different ant-TNFs regarding the body mass index either at the baseline or at the end of 12 months period, unless that of significantly greater standard deviation of BMI at 12 months at the infliximab arm. Unfortunately, there are no current head-to-head trials to compare efficacy of the different anti-TNF agents. Moreover, the selection of anti-TNF medication is influenced by several factors that should be considered, including country-specific availability and labeling, efficacy and safety profiles, administration routes, patient and caregiver preferences, adherence to therapy, and cost-effectiveness [26]. But the height showed statistically significant difference at the baseline and at 12 month point for the different arm, otherwise the standard deviation of the height didn`t show the same difference.

However, infliximab and Adalimumab showed higher BMI at 6 ($p<0.05$) and 12 months ($p<0.001$) compared to Ustekinumab and that can be attributed to decision to start Ustekinumab depends mainly unresponsiveness the biological experience group. The same findings were observed when we compared the three groups regarding hemoglobin, hematocrit and WBCs at the baseline and 12 months. When we had a look on the PUCAI/PCDAI Score the SES-CD/UCEIS the mean values across all three groups: Adalimumab (16.33 ± 6.58) (5.11 ± 1.21), Infliximab (18.33 ± 11.07) (5.62 ± 1.95), and Ustekinumab (16.07 ± 7.62) (5.29 ± 1.8), respectively were similar with no statistically significant difference. Despite that the clinical remission rates were variable, with the Ustekinumab group showing the highest percentage (42.86%), followed by Infliximab (33.33%), and Adalimumab (22.22%), but this variation did not reach statistical significance ($p=0.4$). The number of hospitalizations at the end of the 12-month therapy showed no significant difference among the groups ($p>0.9$), with most patients in each group not requiring any hospitalization. Few studies on different anti-TNF agents in different class of pediatric IBD are present and all of them relied on studying the safety and efficacy of each different agent in different class, and to compare these agents by each other [27]. It is still debatable whether immunomodulators should be used in addition to anti-TNF therapy or not. Adult IBD patients have participated in most combination therapy trials, and some of these studies have demonstrated that combination therapy is more effective than IFX alone, whereas others reported no differences in terms of efficacy [28-29]. In a large group of moderate-to-severe CD pediatric patients revealed no differences between patients treated with combination therapy and patients treated with IFX monotherapy in terms of PCDAI and SES-CD improvement following maintenance after 54 weeks [30]. Similarly, in a cohort of anti-TNF treated CD pediatric patients done by Nuti and coworkers and Meij with his collegues have shown no significant differences in patient outcomes between anti-TNF monotherapy and combination therapy [29-30]. And that is consistent with what we saw in our trial, which showed that the use of azathioprine was uncommon across the groups and had no bearing on the clinical result. On the contrary, Grover et al., and Church et al., have demonstrated that combination therapy with MTX or thiopurines, started during IFX induction and continued for at least 30 weeks, significantly better clinical response [14,31]. To continue or discontinue 5-aminosalicylic acid after starting anti-TNF is still doubtable and few studies have focused on this issue like Choi et al., who found that continuation of 5-ASA after initiation of anti-TNF-alpha agents did not improve prognosis in Korean IBD patients when compared with those who discontinued 5-ASA during maintenance treatment [32]. And also Shaffer et al., reported that in fact biological monotherapy is both cheaper and not less effective suggesting that once biologic is initiated for UC discontinuing 5-ASA therapy is cost-effective [33]. Till now the studies on this point are scarce and detected one demonstrates upper hand for continuing 5-aminosaloicilates after initiating anti-TNF and that similar to our study results of no significant difference between using or not using 5-aminosalicilates on the clinical outcome in the three groups despite the fact of the usage of 5-Aminosalicylate across the three groups ($p=0.024$) was statistically significant, with its use being most common in the Adalimumab group (86.67%), followed by Ustekinumab (71.43%), and infliximab (58.33%). Trying to validate predictors of clinical response is a main issue that was concerning during our study.

Among the baseline characteristics, only the PUCAI/PCDAI score, the height and the hematocrit showed significant associations with clinical response which is similar to Buczy which reported that high PCDAI at diagnosis affects significantly the clinical response but unlikely the significance of hypoalbuminemia and high CRP [34]. Other baseline characteristics did not reach statistical significance. At the 3&6 months, the standard deviation of the height showed significant association with clinical response as well as hemoglobin level at 6 months. In contrast, this study discovered that the only factors that potentially predict an improvement in endoscopic response at 12 months are the baseline SES-CD/UCEIS score and the 6-month height standard deviation [35].

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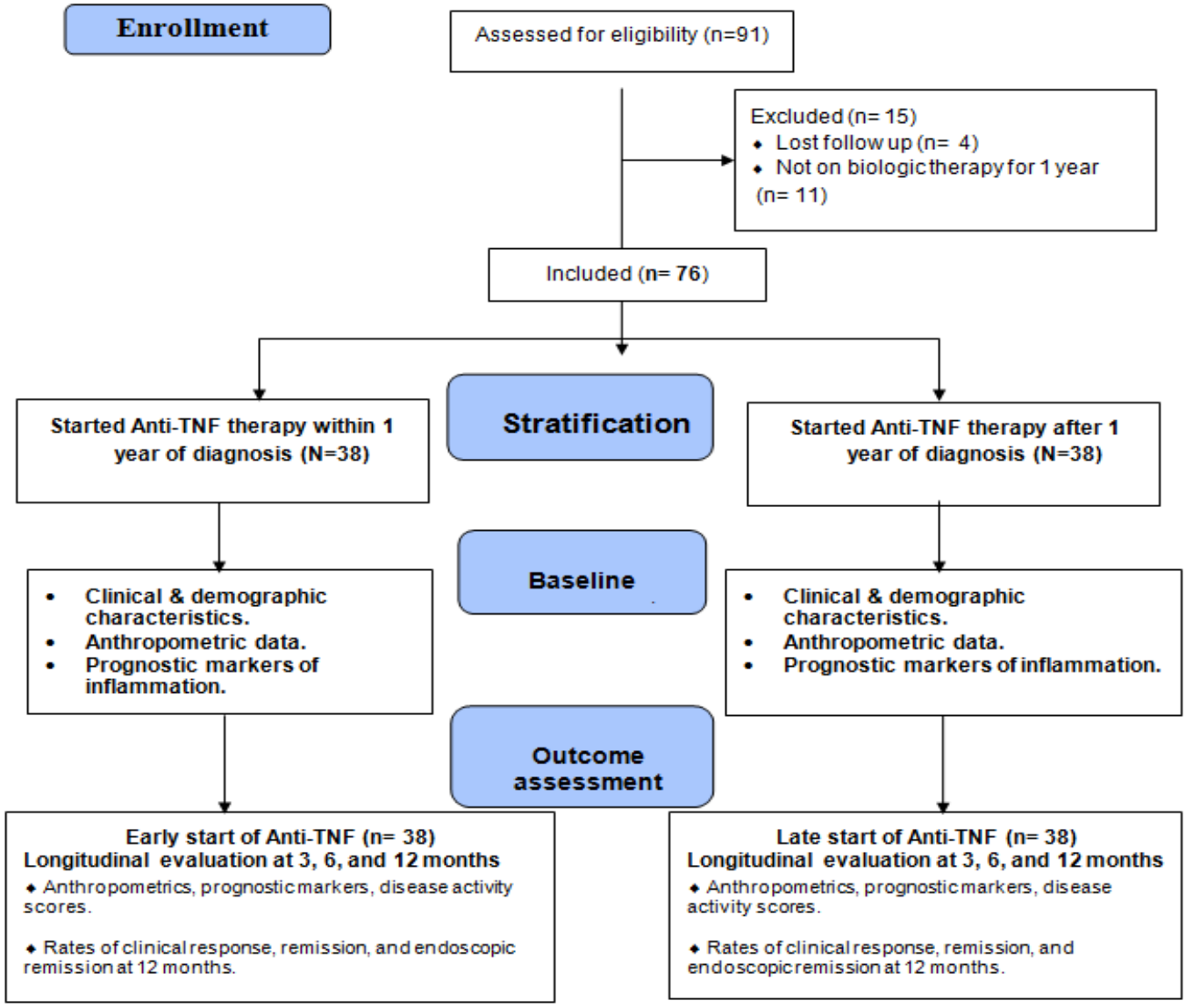

Figure 1: Study flow chart.

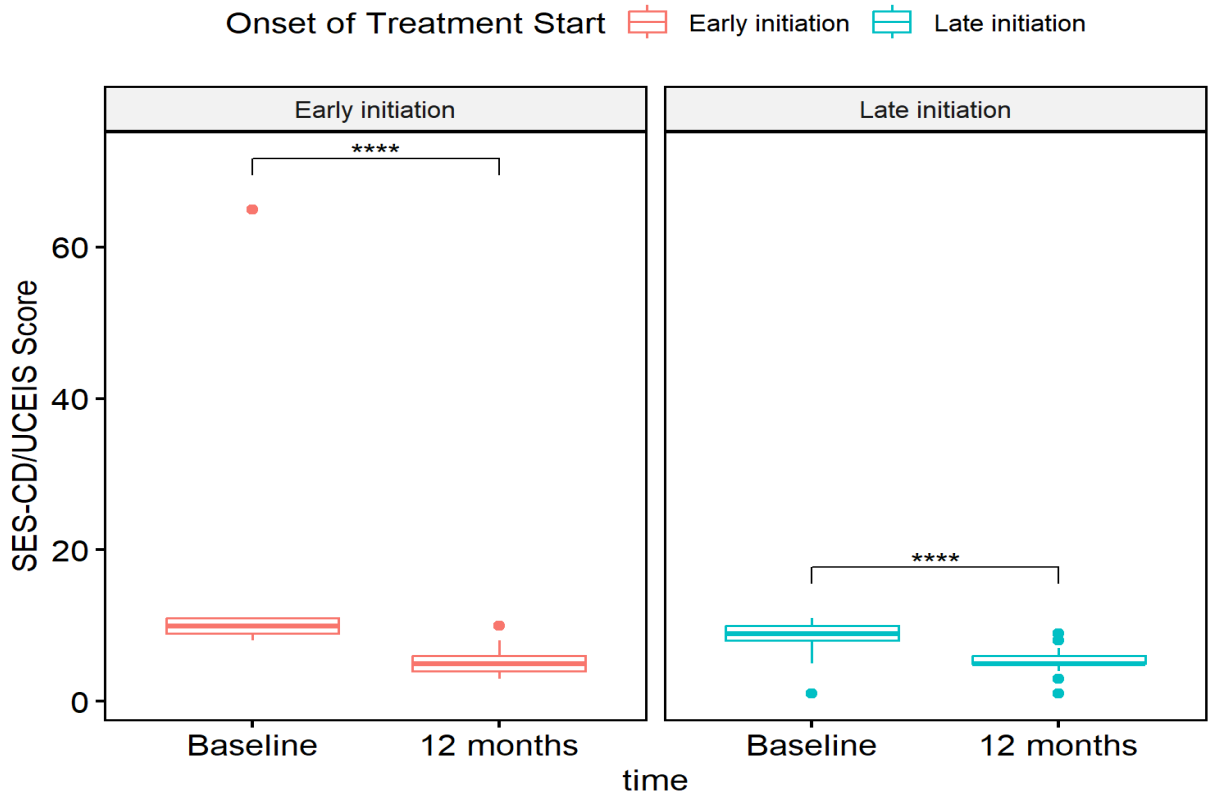

Figure 2: Box-Whisker plot demonstrating the differences in SES-CD/UCEIS scores before anti-TNF and after 12-months of treatment stratified by the onset of treatment start. ***: p<0.001 using Wilcoxon sign rank test.

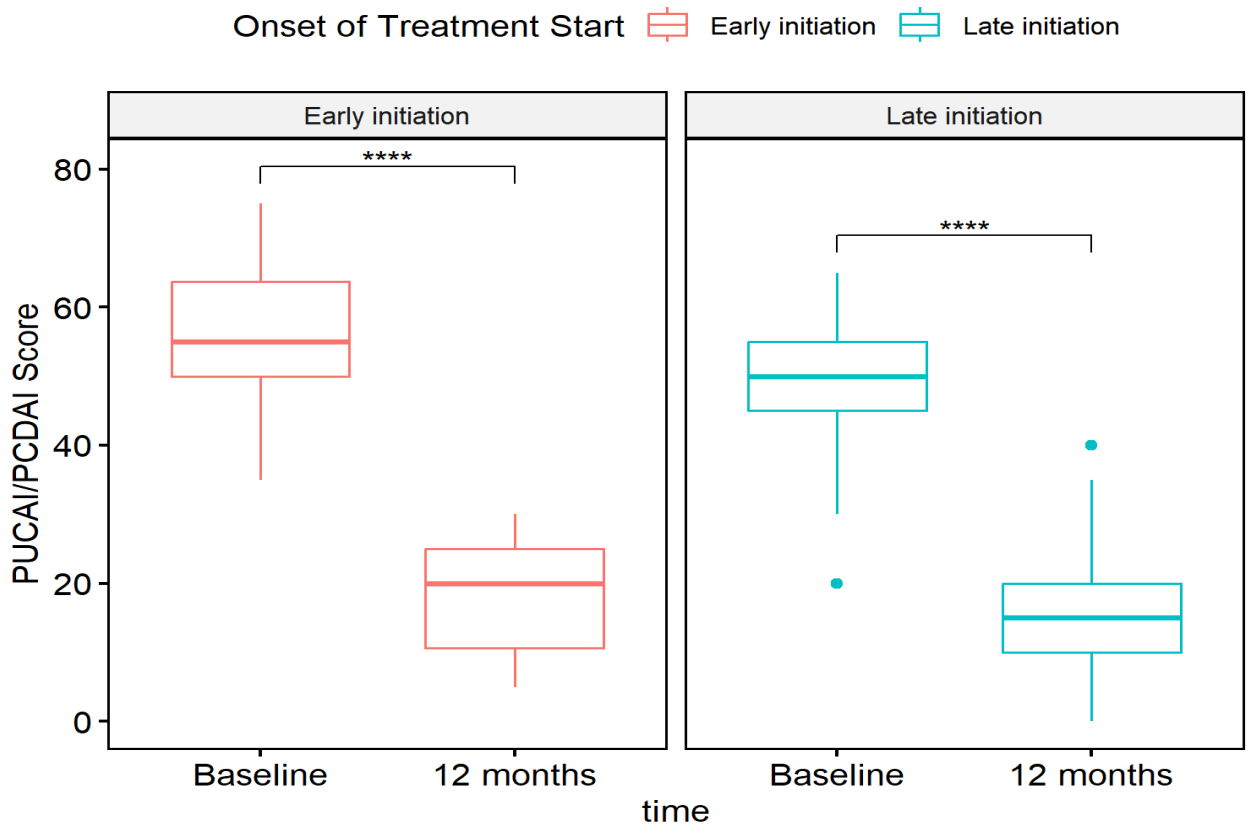

Figure 3: Box-Whisker plot demonstrating the differences in PUCAI/PCDAI scores before anti-TNF and after 12-months of treatment stratified by the onset of treatment start. ***: p<0.001 using Wilcoxon sign rank test.

Table 1: Comparing baseline demographics and clinical characteristics in early vs. late initiation of anti-TNF (N=76).

Characteristic	Early initiation, N = 38[1]	Late initiation, N = 38[1]	p-value[2]
Gender			
Female	17 (44.74%)	9 (23.68%)	0.053
Male	21 (55.26%)	29 (76.32%)	
Age at Diagnosis (months)			
Mean (SD)	85.97 (56.95)	102.11 (46.85)	0.2
Median (IQR)	60.00 (39.75, 146.00)	110.00 (65.25, 139.25)	
Range	8.00, 183.00	16.00, 180.00	
Age at Start of symptoms (months)			
Mean (SD)	77.11 (59.72)	93.54 (47.34)	0.3
Median (IQR)	52.50 (19.75, 140.00)	108.00 (60.00, 126.00)	
Range	2.00, 175.00	4.00, 178.00	
Time to Diagnosis (months)			
Mean (SD)	8.87 (9.55)	7.16 (6.41)	0.7
Median (IQR)	6.00 (3.25, 12.00)	6.00 (3.00, 8.00)	
Range	1.00, 48.00	1.00, 36.00	
Age at Treatment Start (months)			
Mean (SD)	92.29 (56.08)	138.37 (49.20)	**<0.001**
Median (IQR)	71.50 (42.75, 151.25)	144.00 (112.00, 178.25)	
Range	13.00, 189.00	30.00, 216.00	
Classification			
I-IBD (0-2)	10 (26.32%)	5 (13.16%)	0.052
VEO-IBD (<6)	10 (26.32%)	6(15.79%)	
E-IBD (<10)	5 (13.16%)	15 (39.47%)	
P-IBD (<17)	13 (34.21%)	12 (3.58%)	
IBD Subtype			
IBD-CD	14 (36.84%)	15 (39.47%)	0.4
IBD-U	11 (28.95%)	6 (15.79%)	
IBD-UC	13 (34.21%)	17 (44.74%)	
Consanguineous			
Consanguineous	6 (15.79%)	9 (23.68%)	0.4
Non- consanguineous	32 (84.21%)	29 (76.32%)	
Family History of IBD	1 (2.63%)	9 (23.68%)	**0.007**

[1]n (%)

[2]Pearson's Chi-squared test; Wilcoxon rank sum test

Table 2: Comparing the clinical outcomes at the end of 12-month treatment period between early vs. late initiation of anti-TNF (N=76).

Characteristics	**Early initiation**, N = 38[1]	**Late initiation**, N = 38[1]	**p-value**[2]
PUCAI/PCDAI Score			
Mean (SD)	17.76 (7.71)	16.12 (8.85)	0.3
Median (IQR)	20.00 (10.62, 25.00)	15.00 (10.00, 20.00)	
Range	5.00, 30.00	0.00, 40.00	
SES-CD/UCEIS Score			
Mean (SD)	5.16 (1.37)	5.42 (1.62)	0.4
Median (IQR)	5.00 (4.00, 6.00)	5.00 (5.00, 6.00)	
Range	3.00, 10.00	1.00, 9.00	
Clinical response	38 (100.00%)	35 (92.11%)	0.2
endoscopic response	0 (0.00%)	1 (2.63%)	>0.9
Clinical remission	10 (26.32%)	11 (28.95%)	0.8
Hospitalization at the end of 12 months therapy			
0	32 (84.21%)	36 (94.74%)	0.3
1	5 (13.16%)	2 (5.26%)	
2	1 (2.63%)	0 (0.00%)	
Azathioprine	37 (100.00%)	38 (100.00%)	
5-Aminosalicylate	38 (100.00%)	38 (100.00%)	
[1]n (%)			
[2]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test			

Table 3: Comparing anthropometric data among different follow up time points in early treatment arm (N=38)

Characteristic	Baseline, N = 38	3 months, N = 38	6 months, N = 38	12 months, N = 38	p-value[1]
Weight (Kg)					<0.001
Mean (SD)	25.25 (19.95)	26.31 (19.10)	27.01 (18.36)	29.26 (17.93)	
Median (IQR)	18.25 (13.62, 31.75)	19.50 (14.50, 32.75)	20.25 (15.50, 33.75)	22.50 (17.00, 38.00)	
Range	8.00, 115.00	9.00, 110.00	10.00, 105.00	11.00, 102.00	
Standard Deviation of Weight (Kg)					<0.001
Mean (SD)	-1.38 (1.98)	-1.10 (1.75)	-0.96 (1.57)	-0.60 (1.53)	
Median (IQR)	-1.46 (-2.38, -0.19)	-1.24 (-1.84, -0.05)	-0.94 (-1.72, 0.11)	-0.70 (-1.25, 0.63)	
Range	-6.00, 3.57	-4.48, 3.31	-4.45, 3.03	-5.20, 2.83	
Height (cm)					<0.001
Mean (SD)	112.77 (25.10)	114.16 (24.81)	115.85 (24.69)	119.50 (24.45)	
Median (IQR)	110.00 (92.38, 134.25)	111.00 (95.88, 135.25)	112.00 (97.10, 136.50)	115.50 (100.00, 140.00)	
Range	70.00, 150.00	73.00, 152.00	75.00, 155.00	80.00, 160.00	
Standard Deviation of Height (cm)					0.2
Mean (SD)	-2.00 (1.39)	-1.53 (1.88)	-1.99 (1.28)	-3.86 (12.90)	
Median (IQR)	-1.94 (-2.46, -1.32)	-1.76 (-2.45, -1.20)	-1.99 (-2.50, -1.43)	-1.72 (-2.48, -1.24)	

Table 3: Comparing anthropometric data among different follow up time points in early treatment arm (N=38)

Characteristic	Baseline, N = 38	3 months, N = 38	6 months, N = 38	12 months, N = 38	p-value[1]
Range	-6.30, 1.54	-4.95, 5.50	-5.30, 1.08	-81.00, 0.93	
Body mass index (Kg/m2)					<0.001
Mean (SD)	17.90 (7.04)	18.24 (6.06)	18.37 (5.21)	18.89 (4.51)	
Median (IQR)	17.04 (13.91, 20.41)	17.31 (14.92, 20.02)	17.50 (15.87, 19.75)	17.98 (16.38, 20.05)	
Range	6.19, 51.11	10.94, 47.61	11.56, 44.27	12.25, 39.84	
Standard Deviation of Body mass index (Kg/m2)					<0.001
Mean (SD)	-0.22 (2.03)	0.15 (1.84)	0.37 (1.54)	0.59 (1.49)	
Median (IQR)	-0.19 (-1.08, 0.99)	0.03 (-0.64, 1.15)	0.27 (-0.20, 1.41)	0.55 (0.05, 1.34)	
Range	**-4.69, 3.57**	**-4.69, 4.19**	**-4.21, 4.47**	**-3.76, 4.35**	

[1]**Friedman rank sum test**

Table 4: Comparing the clinical outcomes at the end of 12-month treatment period between early vs. late initiation of anti-TNF (N=76)

Characteristic	**Early initiation**, N = 38[1]	**Late initiation**, N = 38[1]	**p-value**[2]
PUCAI/PCDAI Score			0.3
Mean (SD)	17.76 (7.71)	16.12 (8.85)	
Median (IQR)	20.00 (10.62, 25.00)	15.00 (10.00, 20.00)	
Range	5.00, 30.00	0.00, 40.00	
SES-CD/UCEIS Score			0.4
Mean (SD)	5.16 (1.37)	5.42 (1.62)	
Median (IQR)	5.00 (4.00, 6.00)	5.00 (5.00, 6.00)	
Range	3.00, 10.00	1.00, 9.00	
Clinical response	38 (100.00%)	35 (92.11%)	0.2
endoscopic response	0 (0.00%)	1 (2.63%)	>0.9
Clinical remission	10 (26.32%)	11 (28.95%)	0.8
Hospitalization at the end of 12 months therapy			0.3
0	32 (84.21%)	36 (94.74%)	
1	5 (13.16%)	2 (5.26%)	
2	1 (2.63%)	0 (0.00%)	
Azathioprine	37 (100.00%)	38 (100.00%)	
5-Aminosalicylate	38 (100.00%)	38 (100.00%)	

[1]n (%)

[2]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

4. Recommendations

This study suggests considering a top-down strategy and utilizing biologics as soon as required. Anthropometric measurements of patients with IBD are frequently assessed to detect early growth problems. To stop additional affection, early biological therapy should be considered in cases where follow-up data indicates a growth slowing. The selection of the biological agent thought to be based on the IBD subtype, the existence of extraintestinal symptoms, and tolerance.

5. Limitations

There aren't many pediatric patients receiving biological treatment because of problems with availability, expense, and side effect fear. The study's follow-up period was too short, as longer follow-up times might have revealed differences in the two groups' exposure to the various biological agents. Some patients and their caregivers fail to adhere to rigorous follow-up protocols. There were a Few research on response prognostic indicators.

6. Conclusion

Using anti-TNF for the treatment of pediatric IBD is crucial, and either starts early or late within time of diagnosis, it has a great impact on growth of children, clinical and endoscopic response.

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