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The Impact of Concomitant Enteral Nutrition Therapy with Anti-Tumor Necrosis Factor-Alpha Therapy in Active Pediatric Crohn's Disease

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1. Abstract

1.1. Background: In pediatric Crohn's disease (CD), anti-TNF-α medications remain a mainstay of therapy, but primary nonresponse and secondary loss of response remain significant concerns. Enteral nutritional therapy is also an effective therapy in pediatric CD. The aim of this study was to assess the impact of concomitant enteral nutrition (EN) with anti-TNF-α therapy compared to anti-TNF-α monotherapy on outcomes in pediatric CD.

1.2. Methods: A retrospective chart review of children with CD seen at Seattle Children's Hospital from 2005 to 2021 who received anti-TNF-α therapy and had a minimum of 52 weeks of follow-up was initiated. Participants were separated into 2 groups: anti-TNF-α therapy alone or in conjunction with a 4-week course of enteral nutrition.

1.3. Results: This study included 36 participants with CD, with 6 receiving anti-TNF-α and concomitant EN and 30 receiving an anti-TNF-α alone. The number of flares were similar between the two groups with 6(16%) subjects experiencing a flare(p=1.00). No differences were seen in required hospitalizations(p=1.00), surgeries(p=1.00), or anti-TNF related adverse events(p=1.00). The number of dose escalations was similar between the two groups (p=1.00).

1.4. Conclusion: Concomitant anti-TNF-α therapy with EN in pediatric CD may not impact efficacy of anti-TNF-α therapy or loss of response to anti-TNF-α therapy overtime.

2. Introduction

Crohn's disease (CD) is an immune-mediated inflammatory disorder that affects the gastrointestinal tract. The precise etiology of CD is unknown, but both genetics and environmental triggers are thought to play a role in immune dysregulation, leading to a cycle of chronic intestinal inflammation [1]. The primary focus for CD therapies has been to suppress the immune system's ability to instigate an inflammatory reaction. Anti-TNF-α therapies, including infliximab and adalimumab, are some of the most effective and commonly used therapies for IBD [2]. Despite advances, many patients do not respond to anti-TNF-α therapy, have partial response, or lose response after initially achieving remission. Patients who are non-responsive to anti-TNF-αs may require increased dose and/or frequency of anti-TNF-α, switching to other classes of biologic medications, steroid bursts, and/or concomitant immunomodulators [3]. Patients who are non-responsive to anti-TNF-α therapy also experience continued physical and psychosocial strain of active disease [4]. Several studies of adults with CD demonstrate concomitant enteral nutrition may improve the short- and long-term efficacy of infliximab and adalimumab [5-7]. Concomitant enteral nutrition with anti-TNF-α therapy is therefore an appealing option in pediatric CD to improve outcomes.

As a monotherapy, enteral nutrition shows benefit in pediatric CD. Exclusive enteral nutrition (EEN), or receiving 100% of daily caloric intake from elemental or polymeric formulas, is a common and highly effective induction therapy for pediatric CD, and works through different mechanisms than immunosuppressive therapies, altering the fecal microbiome and improving mucosal integrity to produce anti-inflammatory effects [8]. As a primary therapy, EEN is unique in its efficacy at inducing remission without immunosuppressive drugs and is recommended as first-line therapy for pediatric CD by both the North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN and ESPGHAN) [3,8]. EEN has been shown to be as effective as corticosteroids in inducing remission in pediatric CD, [9] and rates of endoscopic mucosal healing are higher in patients who receive EEN compared to corticosteroids as induction therapy, highlighting the importance of dietary exposures in CD [10].

Long-term adhere to EEN therapy presents a challenge because of the restrictive nature of the diet regimen, so the option of less restrictive partial enteral nutrition (PEN) therapy is appealing. The definition of PEN varies but in general involves receiving 50-80% of daily calorie goals from elemental or polymeric formulas. While the efficacy of PEN is less than that of EEN, it has been shown to induce clinical and biochemical remission in CD as well [11]. Concomitant EEN or PEN are compelling options to improve response to anti-TNF-α therapy in pediatric patients given their impact on intestinal inflammatory pathogenesis. While some data exists in the adult IBD literature, there is no data available to assess the potential efficacy of EEN or PEN in combination with anti-TNF-α therapy in pediatrics.

The incomplete efficacy of anti-TNF-α medications is a significant issue in pediatric IBD. There are potential benefits to combining therapeutic approaches that target various components of IBD pathogenesis–microbial dysbiosis, mucosal integrity, and immune dysregulation. With studies in adults showing the combination of PEN improves long and short-term efficacy of infliximab, the combination of enteral nutrition and anti-TNF-α therapies is a potential way to optimize pediatric CD therapy and improve pediatric CD remission rates [5,6,12,13]. The goal of this study is therefore to determine whether concomitant EEN or PEN with anti-TNF-α therapy can improve remission rates in pediatric CD. Specifically, we explore the use of concomitant EEN or PEN for 4 weeks in conjunction with anti-TNF therapy on clinical remission rates and secondary loss of response to anti-TNF-α therapy in pediatric patients with CD.

3. Methods

We initiated a retrospective chart review of children with CD seen at Seattle Children's Hospital from January 1, 2005 to December 31, 2021 who received anti-TNF-α therapy. Participant information was evaluated from prior to the start of anti-TNF-α therapy and followed for 12 months after initiation of anti-TNF-α therapy. The protocol was approved by the Seattle Children's Hospital Institutional Review Board. All data were extracted from electronic medical records. The diagnosis of CD was based on conventional criteria, including clinical, radiologic, endoscopic, and histologic findings. Exclusion criteria included clinical follow-up after anti-TNF-α medication < 52 weeks or insufficient follow up for data collection. Assessment of disease activity was evaluated with the abbreviated Pediatric Crohn's Disease activity index (PCDAI); remission was defined as a PCDAI score below 10 [14]. Laboratory data used to assess IBD-related inflammatory activity included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, hematocrit, and fecal calprotectin. Nutritional and growth status were evaluated with anthropometric measures including BMI and height velocities. The use of EEN was defined as patient taking 80-100% of calorie needs via enteral nutrition. PEN was defined as patients getting between 50-80% of caloric needs via enteral nutrition. EEN/PEN was initiated at 1 – 4 weeks prior to starting anti-TNF therapy and continued for a total of 4 weeks.

4. Statistical Methods

SAS 9.4 (Cary, NC) was used for all analyses. Categorical variables were summarized as counts and percentages for both the anti-TNF-α monotherapy and anti-TNF-α in combination with enteral nutrition groups and compared using Fisher's Exact tests. Continuous variables were assessed for normality using histograms and QQ-plots. If normally distributed, they were summarized as means and standard deviations and compared using independent samples t-tests. If not normally distributed, they were summarized as medians and interquartile ranges and compared using Wilcoxon Rank Sums tests. A p-value of 0.05 was considered statistically significant. Given the exploratory nature of this study, analyses were not adjusted for multiple comparisons. Laboratory results below a cutoff threshold were recoded as half of the cutoff value.

5. Results

Study inclusion criteria were met by 36 patients with CD, with 6 participants receiving an anti- TNF-α and an EEN or PEN diet (diet group) for 4 weeks and 30 participants receiving an anti-TNF-α without dietary intervention (anti-TNF-α only). The mean age for all patients was 12.9 ± 2.7 years, with no significant differences in age between the diet group and anti-TNF-α only group (Table 1). The sex distribution was similar in both groups, with approximately 70% male (Table 1). Race and ethnicity did not significantly differ between the two groups, although a higher percentage identified as white in the anti-TNF-α only group compared to the diet group (p=0.15, Table 1).

The median days from diagnosis to first anti-TNF-α and anti-TNF-α type were similar for both groups (p=0.47 & p=0.64, respectively). More patients in the diet group were on concomitant

steroids compared to the anti-TNF-α only group (p=0.05, Table 1). There were no differences in concomitant immunomodulator therapy, mesalamines, or antibiotics (Table 1). Most patients in both groups stayed on a single anti-TNF-α one year after initiation, however, the diet group had one patient who moved onto a second anti-TNF-α therapy (Table 1) secondary to non-response.

CRP values appeared to be higher in the diet group than the anti-TNF-α only group prior to starting anti-TNF-α therapy, nearing statistical significance (Median: 3.4 vs. 1.4, p=0.07, Table 2). At initiation of the anti-TNF-α and at 6 months, the CRP levels did not differ between the two groups, however, CRP levels were significantly lower in diet group at 12 months after anti-TNF initiation compared to the anti-TNF-α only group (Median: 0.8 vs. 1.0, p=0.002, Table 1). Drug and antibody levels for adalimumab and infliximab did not differ between the groups at any timepoint; however, most patients did not have drug trough levels checked (Table 2). The number of flares were similar between the two groups, with 16.7% of the diet group vs 16.6% of anti-TNF- α only group experiencing a flare (p=1.00). No differences were seen in required hospitalizations (p=1.00), surgeries (p=1.00), or anti-TNF related issues (p=1.00). The number of dose escalations was similar between the two groups (p=0.79). At the start of the anti-TNF-α, the diet group had a significantly lower BMI z-score than the anti-TNF-α only group (-1.4 vs. -0.2, p=0.04). While not statistically significant, the difference in BMI z-score at baseline was attenuated over the course of 12 months (Table 3).

Table 1: Demographics of Pediatric Crohn's disease patients on anti-TNF-a Only or with Concomitant Enteral nutrition

Characteristic	Category	Statistic	All n(%)	EEN or pEN with anti-TNF-a n(%)	Anti-TNF-a Only n(%)	P-Value
Age at Diagnosis, Years		Mean (SD)	12.91 (2.71)	12.18 (2.64)	13.06 (2.74)	0.48
Sex	Female		11 (30.6)	2 (33.3)	9 (30)	1.00
	Male		25 (69.4)	4 (66.7)	21 (70)	.
Race	American Indian or Alaska Native		1 (2.8)		1 (3.3)	0.15
	Black		1 (2.8)	1 (16.7)		.
	Other		2 (5.6)	1 (16.7)	1 (3.3)	.
	Refused		3 (8.3)		3 (10)	.
	White		29 (80.6)	4 (66.7)	25 (83.3)	.
Ethnicity	Hispanic		2 (5.6)		2 (6.7)	0.75
	Non-Hispanic		27 (75)	6 (100)	21 (70)	.
	Refused		6 (16.7)		6 (20)	.
	Unknown		1 (2.8)		1 (3.3)	.
Days to First Biologic		Median (IQR)	112.00 (60.5-425.5)	99.00 (44-193)	112.00 (64-433)	0.47
Biologic Type 1	Adalimumab		15 (41.7)	4 (66.7)	11 (36.7)	0.64
	Humira		2 (5.6)		2 (6.7)	.
	Inflectra		1 (2.8)		1 (3.3)	.
	Infliximab		18 (50)	2 (33.3)	16 (53.3)	.
Concomitant Steroids	Budesonide		1 (2.8)		1 (3.3)	0.05
	None		32 (88.9)	4 (66.7)	28 (93.3)	.
	Prednisone		1 (2.8)		1 (3.3)	.
	Unknown Steroid		2 (5.6)	2 (33.3)		.
Immunomodulators	Azathioprine		13 (36.1)	2 (33.3)	11 (36.7)	0.46
	Methotrexate		13 (36.1)	1 (16.7)	12 (40)	.
	None		10 (27.8)	3 (50)	7 (23.3)	.
Mesalamine	No		35 (97.2)	6 (100)	29 (96.7)	1.00
	Yes		1 (2.8)		1 (3.3)	.
Additional Concomitant	Antibiotics		3 (8.3)		3 (10)	1.00
	Methotrexate		3 (8.3)		3 (10)	.
	None		30 (83.3)	6 (100)	24 (80)	.
Number of Biologics in First Year	1		35 (97.2)	5 (83.3)	30 (100)	0.17
	2		1 (2.8)	1 (16.7)		.

Table 2: Laboratory evaluation of Pediatric Crohn's disease patients on anti-TNF-a Only or with Concomitant Enteral nutrition

Characteristic	All Median (IQR)	EEN or pEN with anti-TNF-a Median (IQR)	Anti-TNF-a Only Median (IQR)	P-Value	N
CRP Prior	1.80 (0.8-4)	3.40 (3.4-5)	1.40 (0.8-3.5)	0.07	35
CRP 1	0.80 (0.8-1)	0.80 (0.8-0.8)	0.80 (0.8-1)	0.7	36
CRP 2	0.80 (0.8-0.8)	0.80 (0.8-0.8)	0.80 (0.8-0.8)	0.77	36
CRP_3	1.00 (1-1)	0.80 (0.8-0.8)	1.00 (1-1)	0.01	30
Drug Level Adalimumab 1	13.80 (9.3-14.4)	7.70 (6.1-9.3)	14.40 (13.8-17.7)	0.15	6
Drug Level Adalimumab 2	13.90 (8.8-19)	8.80 (8.8-8.8)	19.00 (19-19)	0.05	3
Drug Level Adalimumab 3	8.15 (2.9-13.4)	8.15 (2.9-13.4)	. (.-.)	0.79	3
Antibodies Adalimumab 1	5.00 (5-5)	5.00 (5-5)	. (.-.)	0.04	2
Antibodies Adalimumab 3	54.90 (54.9-54.9)	54.90 (54.9-54.9)	. (.-.)	0.09	2
Drug Level Infliximab 1	8.95 (3.4-18)	7.70 (3.4-12)	11.95 (4-25)	0.69	11
Drug Level Infliximab 2	2.00 (0.75-3.5)	0.50 (0.5-0.5)	3.00 (1-4)	0.37	5
Drug Level Infliximab 3	6.00 (6-6)	. (.-.)	6.00 (6-6)	0.35	2
Antibodies Infliximab 1	20.00 (15-21)	10.00 (10-10)	20.00 (20-22)	0.35	5
Antibodies Infliximab 2	48.00 (10-86)	86.00 (86-86)	10.00 (10-10)	.	3

Table 3: Clinical course of Pediatric Crohn's disease patients on anti-TNF-a Only or with Concomitant Enteral nutrition over 52 weeks

Characteristic	Category	Statistic	All n(%)	EEN or pEN with anti-TNF-a n(%)	Anti-TNF-a Only n(%)	P-Value
Number of Flares	0		30 (83.3)	5 (83.3)	25 (83.3)	1.00
	1		5 (13.9)	1 (16.7)	4 (13.3)	.
	2		1 (2.8)		1 (3.3)	.
Hospitalization Required	No		32 (88.9)	6 (100)	26 (86.7)	1.00
	Yes		4 (11.1)		4 (13.3)	.
Surgery	No		33 (91.7)	6 (100)	27 (90)	1.00
	Yes		3 (8.3)		3 (10)	.
Anti TNF Related Issues	Anti TNF Psoriasis		1 (2.8)		1 (3.3)	1.00
	None		35 (97.2)	6 (100)	29 (96.7)	.
Biologics Change First Year	No		33 (97.1)	4 (80)	29 (100)	0.15
	Yes		1 (2.9)	1 (20)		.
Number of Biologics till Present		Median (IQR)	1.00 (1-1)	1.50 (1-2)	1.00 (1-1)	0.05
Number of Dose Escalations		Median (IQR)	0.00 (0-1)	0.50 (0-1)	0.00 (0-1)	0.8
BMI Z Score Biologic Start		Mean (SD)	-0.38 (1.29)	-1.35 (0.77)	-0.18 (1.30)	0.04
BMI Z Score 6 Months		Mean (SD)	0.08 (1.18)	-0.66 (0.66)	0.23 (1.21)	0.09
BMI Z Score 12 Months		Mean (SD)	0.25 (1.19)	-0.48 (0.72)	0.39 (1.22)	0.10

6. Discussion

Anti-tumor necrosis factor-alpha (TNF-α) therapies, including infliximab (IFX), and adalimumab (ADA) are a mainstay for pediatric CD therapy. Despite their efficacy, concerns including non-response and loss of response remain significant issues. Improving the short term and long-term effectiveness of these anti-TNF-α therapies is important to optimizing likelihood of sustained remission in patients with pediatric CD. As such, we explored the potential benefits of adding nutritional therapy with EEN or PEN for 4 weeks during initiation of immunosuppressive therapy with IFX or ADA. While this study did not show improved efficacy of anti-TNF-α therapy in conjunction with short-term treatment (4 weeks) with EEN/PEN in active CD, it does not rule out the potential positive effects of its use and highlights the need for further research into interventions, which may improve outcomes.

TNF-α therapies have changed both the treatment paradigm and outcomes for patients with CD, significantly impacting the natural history of the disease [15]. While effective, significant concern over primary non-response and secondary loss of response after achieving remission exists with anti-TNF-α therapy [4,16-18]. Annual loss of response can occur in up to 20% of CD patients treated with anti-TNF-α agents who have achieved remission [19]. The main mechanism of the decreased efficacy is secondary to low serum drug levels coupled with anti-drug antibodies. [4,20-22] Therefore, it is crucial to identify strategies to reduce the occurrence of loss of response for CD patients treated with anti-TNFs.

Prior research on concomitant use of PEN in combination with anti-TNF-α therapy has solely been in adult CD patients. A meta-analysis of four adult studies comparing the remission rates of concomitant PEN and IFX versus IFX alone found significantly improved long-term clinical remission rates with concomitant therapy [23]. While three of the studies included were retrospective and showed a positive effect of adding PEN to infliximab therapy in adult CD on both short term induction of remission as well as reduction of disease recurrence and loss-of-response [5,6,12] the one prospective randomized control trial did not show added benefit of PEN with anti-TNF-α therapy. This study defined PEN as ≥900 kcal/day, equal to half of the nutritional intake for maintaining remission [13].

There is also data to support the use of concomitant PEN with other anti-TNF-α agents to reduce secondary loss of response to therapy. Specifically, one study showed that use of PEN in combination with ADA compared to adalimumab therapy alone reduced the rates of loss of response to ADA in adult patients with CD who were IFX intolerant or refractory [7]. Interestingly, serum ADA levels were not significantly different between the PEN + ADA and ADA alone groups, so the use of concomitant PEN appears to reduce loss of response independent of any direct effect on serum drug levels [5]. Additionally, concomitant PEN did not reduce loss of response to ADA in CD patients who were anti-TNF-α naïve [5].

While the results of this study do not show a benefit of concomitant short-term EEN or PEN on anti-TNF-α therapy for pediatric patients with CD, this study does not offset the possibility that EEN, PEN, or other dietary interventions for longer periods of time might be beneficial in pediatric CD. In addition, this study has several limitations including its retrospective nature as well as an inability to capture potential benefits in short term clinical response rates given lack of standardized follow-up. Further, a potential for selection bias exists, as patients selected for concomitant EEN/PEN had significantly higher CRP levels and lower BMI z-scores at the start of therapy. These considerations, plus the location at only a single center, limits the ability to make broad and generalizable conclusions. Importantly, while objective markers of inflammation were found to decline over the course of the study, mucosal healing was not assessed directly with ileocolonoscopy and biopsy.

The shorter duration of EEN/PEN in this study may have affected results as well, as prior studies have evaluated EEN at 8- and 10-week durations, compared to the 4-week duration in this study. It would provide additional insight for future studies to have a full 8-week duration to assess for further changes. Additionally, our conclusions regarding the impact of enteral nutritional therapy on pediatric CD outcomes are limited by our small sample size of patients who were on either EEN or PEN (n=6), and by including individuals on EEN and PEN in the same group. EEN has more data to support its efficacy in pediatric CD compared to PEN, so our data may have been stronger if we included patients only on concomitant EEN.

Finally, dietary compliance is challenging to ascertain in patients, which has the potential to bias study results towards the null. Further studies of concomitant EEN with anti-TNF-α therapies as a potential therapeutic option are required to better define marginal benefit. As research in dietary intervention expands, it is imperative for researchers and clinicians to understand the complexity of dietary interventions. Offering patients and families adjunctive dietary therapies to help optimize the efficacy of immunosuppressive medications may be of unique value, particularly in pediatric patients who have challenging and refractory CD.

7. Conclusion

While the combination of EEN/PEN for 4 weeks with anti-TNF-α therapy did not show additive benefit in our patient cohort, further research is needed to determine the optimal duration of EEN/PEN in combination with anti-TNF-α therapy and to establish the safety and efficacy of the combination therapy in a broader patient population. Clinicians should consider the potential benefits of the combination therapy when treating patients with CD, particularly if there is delay in initiating anti-TNF-α therapy.

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