Long-term outcome of tumor necrosis factor alpha antagonist’s treatment in pediatric Crohn’s disease

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Abstract

Background: Anti tumor necrosis factor alpha (TNFα) agents have become widely used in pediatric inflammatory bowel disease (IBD). So far, only few studies examined the long-term results of anti-TNFα treatment in children with IBD.

Methods: The long-term outcome of pediatric patients with IBD was assessed retrospectively in a multicenter cohort of children treated with anti-TNFα beyond induction treatment. Short- and long-term response rates, predictors for loss of response, data on growth and laboratory parameters were assessed.

Results: 120 patients [101 crohn’s disease (CD), 19 ulcerative colitis (UC) or indeterminate colitis (IC)] received either infliximab or adalimumab. The mean age at initiation of anti-TNFα was 13.4 ± 3.9 years and the median duration of anti-TNFα treatment was 15 months (range: 2–90). Overall, 89% of the cohort experienced short-term response following induction. Response was associated with improvement in weight and BMI Z-scores (p < 0.001) but not with linear growth. Responders experienced a significant decrease in erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) during treatment (p < 0.001). Albumin and hemoglobin both improved but only albumin increased significantly (p < 0.001).

The cumulative probability of losing response to anti-TNFα treatment was 17%, 38%, and 49% after 1, 3, and 5 years, respectively. Responders had a significantly lower weight and BMI Z-
scores at initiation of anti-TNFα treatment in compared to non-responders (p=0.04 and 0.02 respectively).

Conclusions: Our long term cohort supports the current evidence on the effectiveness and safety of anti-TNFα treatment in children with IBD. Response to treatment was interestingly associated with lower weight and BMI.
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1. Introduction

Anti tumor necrosis factor alpha (TNFα) agents have become widely used in the management of pediatric inflammatory bowel diseases (IBD). Biologic agents were launched in 1998 with the approval of infliximab, the first commercially available agent, initially for the treatment of moderate-to-severe Crohn's disease (CD) in adults, and more recently in children. The efficacy of infliximab treatment for induction and maintenance of remission in both adults and children with moderate-to-severe CD has been demonstrated in several clinical trials.1–8 Only few studies, however, have examined the long-term outcome of infliximab therapy in children with CD.9–13 Long-term response rates to infliximab of pediatric CD patients vary from 50% to 80%. Infliximab is currently the only anti-TNFα agent approved for pediatric IBD, however, clinical trials using adalimumab and certolizumab in pediatric CD were recently published with encouraging results.14–16 The British Society of Pediatric Gastroenterology, Hepatology and Nutrition survey reported a 41% remission rate at 1 year in children with CD treated with adalimumab.17 In addition, the recent RESEAT study showed short-term efficacy of adalimumab rescue therapy in pediatric CD patients previously treated with infliximab.18 Much has been learned about these agents over the last decade; however, questions concerning the use of anti-TNFα for the treatment of pediatric IBD are yet to be answered. While episodic infliximab therapy was demonstrated to be associated with higher relapse rates compared with scheduled maintenance administration,19,20 other risk factors for anti-TNFα failure have not been delineated in children. An exception comes from two studies which reported better outcome for infliximab when treatment was initiated early in disease course.21,22

Weight and body mass index (BMI) have been shown to improve during anti-TNFα treatment,6,23–25 yet, controversy still remains regarding the influence on linear growth. Some studies demonstrated increase in height velocity during 6–26 months of infliximab treatment6,23,26 while others21,24,27 showed no significant change during similar follow-up time.

Beyond data on efficacy, long term follow-up studies of children treated with anti-TNFα are important as they provide information on long-term safety of these agents in children, especially regarding long-term risk of infections and malignancy, such as hepatosplenic T cell lymphoma.28 Such information is, again, limited. Thus, the purpose of this retrospective cohort study was to examine the long term efficacy and safety of anti-TNFα induction and maintenance treatment in children with CD. In addition we evaluated which features or markers were associated with short- and long-term remission and investigated treatment's influence on anthropometric indices.

2. Materials and methods

2.1. Patients and data collection

This retrospective cohort included all cases of pediatric CD listed in the databases of three medical centers in Israel (Schneider Children's Medical Center, Petah Tikva, Safra Children's Hospital, Tel-Hashomer, and Assaf Harohef Medical Center—Zerifin, all affiliated with the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel) since 1999 who were treated with infliximab or adalimumab. The medical files of patients who initiated first line anti-TNFα treatment prior to 17.5 years of age and completed at least 3 induction doses of infliximab or 2 induction doses of adalimumab were evaluated. Patients who did not complete the induction scheme, had inadequate follow-up (defined as no complete data until the age of 18 years) or were treated episodically during flare of symptoms were not included in the study.

The infliximab induction protocol consisted of 3 infusions of 5 mg/kg/dose at weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks in responders. Adalimumab was administered sub-cutaneously starting with 160 mg/1.73, 80 mg/1.73 and subsequently 40 mg/1.73 every other week.

Patients' demographic data, disease characteristics, previous and concomitant treatments, indications for anti-TNFα treatment and duration of treatment were retrieved from the medical records. Treatment end-points were defined as either end to follow-up (at age 18 or at the end of the study period), loss of response or treatment completion (cessation of treatment due to prolonged remission). In addition, physician's evaluation of patient's status, response to anti-TNFα treatment, dose and interval changes, adverse events, anthropometric measurements and laboratory investigations were extracted from the medical records. Laboratory evaluation included serum levels of albumin, hemoglobin (Hb), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) at initiation of anti-TNFα treatment, end of induction and at each end point (loss of response, end of follow-up or therapy completion). Anthropometric indices including height and weight were collected at the same intervals and at diagnosis as well. Disease phenotype of each patient was defined according to the Paris classification, a pediatric modification of the Montreal IBD criteria.29 Data were collected until April 2011.

2.2. Outcome measures

Due to the retrospective nature of the study, response to anti-TNFα treatment in CD patients was evaluated using the Harvey–Bradshaw index (HBI). The outcome of anti-TNFα...
treatment was defined as non-response, short-term response, prolonged response and loss of response. Short-term response was defined as a decrease in HBI score to 4 points or less during induction. Prolonged response was defined as HBI score below or equal to 4 points after at least 6 months of anti-TNFα treatment. In patients with perianal CD, response was defined as closure of all fistulas and absence of active disease on physical examination. Patients with loss of response were defined as those with a good initial clinical response to anti-TNFα, with a later relapse. Finally, non-response was defined as no clinical response to anti-TNFα induction scheme or a consistent elevation of HBI score (more than 4 points) during treatment. Adjustments in treatment schedule were defined as dose escalation or shortening of the interval between infusions.

Disease behavior was categorized based on Paris classification according to age at diagnosis (A), location (L), behavior (B), the existence of perianal disease (p) and growth retardation (G). Height, weight and BMI were converted to age- and sex-specific standard deviation scores (SDS)-Z scores, using the World Health Organization (WHO) Anthro and Anthro plus software for personal computers, version 2, 2007: software for assessing growth and development of the world’s children. Geneva: WHO, 2007 (http://www.who.int/childgrowth/software/en/).

Height velocity was evaluated using anthropometric indices collected at diagnosis as well as before and during anti-TNFα treatment. A minimal interval of 6 months was used in order to determine height velocity.

2.3. Statistical analysis

Data were collected and analyzed using SPSS (version 15.0, SPSS, Inc., Chicago, IL, USA). Continuous variables were presented as either mean ±SD or median with interquartile range (IQR) depending on the data approximation to normal distribution. In order to analyze the factors predictive of anti-TNFα failure, Fisher’s exact test was used to explore univariate associations between primary outcomes and categorical variables (i.e. diagnosis, age at diagnosis, gender, type of medication, indication, Paris classification and time from diagnosis to anti-TNFα therapy). Kaplan–Meier analysis was used to estimate the cumulative probability of losing response to anti-TNFα treatment over time. Time to event was analyzed from the date of anti-TNFα induction until treatment in pediatric Crohn’s disease

3. Results

3.1. Baseline characteristics

One hundred and two patients with CD (66 males, 36 females) completed a full induction scheme of anti-TNFα therapy. The main characteristics of the study patients are presented in Table 1.

Out of the 102 treatment courses 84 (82%) were of infliximab and 18 (18%) were of adalimumab. The median disease duration before initiation of anti-TNFα treatment was 15 months (range: 1–112, IQR: 5–35). Table 1 also summarizes disease behavior in these patients. Twenty nine patients (29%) had evidence of growth retardation (Paris classification G1). Only three patients (3%) had strictureting or penetrating disease (Paris classification B2 or B3). The most common indication for anti-TNFα treatment was steroid dependency or non responsiveness (48/102, 47%) followed by multiple disease exacerbations on maintenance treatment (35/102, 34%) and perianal disease (19/102, 19%).

3.2. Outcome of anti-TNFα treatment

The outcome status of the whole cohort is shown in Fig. 1. The median duration of anti-TNFα treatment was 15 months (range: 2–90, IQR: 4–24). Short-term response occurred in 91/102 (89%) of anti-TNFα induction courses. Prolonged response, for more than 6 months, was observed in 86/102 (84%) of patients.

The median duration of prolonged response through the end of follow-up or treatment completion was 19.7 months (range: 6–90, IQR: 14–37). Median response duration for patients who lost response during follow-up or those terminating anti-TNFα treatment due to adverse events was 8 months (range: 2–78, IQR: 3–16). Among the responders, only 56% were free of symptoms during follow up while the rest had mild persistent or recurrent symptoms (i.e. diarrhea, abdominal pain). Response rates to infliximab and adalimumab

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients’ characteristics at baseline (n=102).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), n (%)</td>
<td>66/102 (65)</td>
</tr>
<tr>
<td>Age at diagnosis (y), mean±SD (range)</td>
<td>11.3±4 (0.5–17)</td>
</tr>
<tr>
<td>Age at initiation of anti-TNFα (y), mean±SD (range)</td>
<td>13.5±3.9 (1–17.5)</td>
</tr>
<tr>
<td>Disease duration prior to anti-TNFα initiation (months), median (IQR, range)</td>
<td>15 (5–35,1–112)</td>
</tr>
<tr>
<td>Disease location at diagnosis (Paris classification), n (%)</td>
<td></td>
</tr>
<tr>
<td>L1 (distal ileum)</td>
<td>41 (40)</td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>33 (33)</td>
</tr>
<tr>
<td>L3 (ileocolonic)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>L4a/b (upper GI disease)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Presence of peri-anal disease, n (%)</td>
<td>35 (35)</td>
</tr>
<tr>
<td>Previous medications, n (%)</td>
<td></td>
</tr>
<tr>
<td>No therapy or 5-ASA</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Steroids (±5-ASA)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Steroids and thiopurines</td>
<td>78 (76)</td>
</tr>
<tr>
<td>Indication for anti-TNFα therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Steroid dependency or NR</td>
<td>48 (47)</td>
</tr>
<tr>
<td>Multiple exacerbations on maintenance treatment</td>
<td>35 (34)</td>
</tr>
<tr>
<td>Peri-anal disease</td>
<td>19 (19)</td>
</tr>
</tbody>
</table>

SD = standard deviation, IQR = interquartile range, NR = non-response, SE = side effects.
did not differ, thus, data for both medications was compiled together for simplicity.

Kaplan–Meier analysis shows that the cumulative probability of being on anti-TNFα treatment in patients on scheduled maintenance was 18%±4%, 28%±5%, 35%±6%, 41%±8% and 46%±8% after 1, 2, 3, 4 and 5 years, respectively (Fig. 2).

Sixty seven percent (61/91) of patients who continued anti-TNFα treatment beyond induction received concomitant medication at some point during the follow-up period: thiopurines alone (41/61 patients, 67%), methotrexate (11/61 patients, 18%), thiopurines with steroids (6/61 patients, 10%), steroids alone (2 cases, 3%) and 5-ASA (1 case). Ten patients (11%) required adjustments in either anti-TNFα dose or decreased administration intervals. All ten improved following treatment adjustment and returned to the formal schedule within 6 months. All patients but one, maintained remission on scheduled treatment until end of follow-up (average follow-up period post treatment adjustment was 12 months). One patient continued to experience mild symptoms during and following treatment adjustment until end of follow-up.

3.3. Adverse events

Seventeen patients (17%) experienced adverse events. Sixteen adverse reactions occurred during or after infliximab infusions (18/84 infliximab courses, 21%). Fifteen patients (15%) experienced type 1 allergic reaction during infusion, eight of which were severe. In 5 patients treatment with anti-TNFα had to be discontinued because of recurrent reactions despite prophylaxis. Other reported adverse events included arthralgia and pneumonitis (one case each) during infliximab and one case of pancreatitis during combined adalimumab and thiopurine treatment. There were no reports of malignancy during the entire follow-up and the registry could not support reliable information regarding infections’ rates. We couldn’t find any correlations between concurrent therapies during anti-TNFα treatment and rate of adverse events (specifically type 1 allergic reactions).

3.4. Clinical predictors of anti-TNFα failure

Responders had a significantly lower weight and BMI Z-scores at initiation of anti-TNFα treatment compared to non-responders, (p = 0.03 and 0.01 respectively).

None of the following features predicted anti-TNFα treatment failure: gender, age at diagnosis, disease behavior assessed according to Paris classification, age at initiation of anti-TNFα treatment, disease duration prior to anti-TNFα initiation, indications or type of anti-TNFα (infliximab vs. adalimumab), previous or concomitant medications.

3.5. Growth during anti-TNFα treatment

Mean BMI Z-score improved significantly during treatment (−0.8 to −0.4, p=0.04). Compared to non-responders, responders had significant improvement in weight as well as BMI Z-scores during induction. This improvement was maintained through the entire treatment period (p=0.002 and 0.004 respectively, Fig. 3a, b). BMI and weight changes did not differ between males and females. A trend towards increase in height velocity during treatment was observed in responders (Fig. 3c, P=0.07). However, only male responders demonstrated a significant increase in height velocity during treatment (p=0.007). A similar significance was maintained when we used a cut-off of 13 years in order to correct for patients who had completed pubertal growth.

3.6. Laboratory changes during anti-TNFα treatment

ESR decreased significantly in both responders and non-responders (Fig. 4a) during induction (p<0.001) and through the treatment endpoints (p<0.001). However, in non-responders, ESR decreased significantly during induction but increased thereafter up to loss of response (p=0.03). Responders had significantly lower ESR at the end of induction (p=0.007) and at the treatment end-points (p=0.001).

CRP decreased significantly in both responders (p<0.001) and non-responders (p=0.04) during induction (Fig. 4b). However, only responders maintained significant decrease in CRP through treatment (p<0.001). Non responders experienced a significant increase in CRP between the end of induction and the treatment end points (p=0.009). Responders had significantly lower CRP at the end of induction (p=0.01) and at treatment end-points (p<0.001) compared to non-responders.

Hb increased significantly in both responders (p<0.001) and non-responders (p=0.002) during induction (Fig. 4c) as well
as from initiation of anti-TNFα to treatment end-point (responders: \(p < 0.001\), non-responders: \(p = 0.004\)). There were no significant differences in Hb levels between responders and non-responders at the end of induction and at treatment end-points.

Albumin increased significantly in both responders (\(p < 0.001\)) and non-responders (\(p < 0.001\)) during induction (Fig. 4d). However, only responders experienced sustained increase in albumin during the whole treatment period (\(p < 0.001\)). Non-responders experienced a significant decrease in albumin between the end of induction and treatment end points (\(p < 0.001\)). Responders had significantly higher albumin level at the end of induction (\(p < 0.001\)) and at treatment end-points (\(p < 0.001\)) compared to non-responders.

4. Discussion

The current literature on long-term outcomes of anti-TNFα treatment in pediatric CD is limited.\(^4,9-13,21,22\) We report the follow-up of a large, multicenter cohort of children and adolescents with CD, treated with anti-TNFα for induction and maintenance of remission.

An intriguing unexpected finding of our study was that patients with lower weight and BMI Z-scores at initiation of anti-TNFα therapy had a significantly higher response rate over time. Our data are supported by Klassen et al.,\(^30\) who recently evaluated the effect of BMI on the response to TNFα blockade in rheumatoid arthritis. A highly significant negative association between BMI and response to anti-TNFα treatment was found in their cohort. Adipose tissue is a recognized active site that may modify the immune response through the effect of adipocytokines such as leptin, resistin, adiponectin, chemerin and visfatin, as well as classic cytokines such as TNFα, interleukin-1 (IL-1), IL-6 and monocyte chemotactic protein 1 which are assumed to be expressed by inflammatory cells that infiltrate the fat tissue.\(^31\) Adipocytokines secreted by the adipose tissue may be responsible for this phenomenon. For example, resistin, which may be increased in the plasma of IBD patients,\(^32\) can up-regulate TNFα and IL-6 secretion by the peripheral blood mononuclear cells.\(^33\) In addition, other adipokines were found to be elevated in IBD: visfatin,\(^34\) chemerin and adiponectin in UC patients and chemerin alone in CD patients. However, in Klassen’s study, there was no clear correlation between their blood levels and disease activity.\(^30\) One can argue that anti-TNFα concentration might be lower in patients with high BMI, but as the dose of infliximab is adjusted according to body weight and since the intravascular space is relatively smaller in more obese subjects, serum infliximab concentrations are expected to be higher with increased BMI. Thus, our findings support the preliminary evidence which suggests that increased BMI may play an important role in anti-TNFα resistance.

The short-term response rate of 89% observed in our study is compatible with previous reports.\(^8,10,13\) The present study shows that anti-TNFα treatment is also efficient during long-term follow-up. Approximately 35% of patients lost response to anti-TNFα treatment after 3 years. This rate is similar to studies by Hyams et al.\(^3\) and Chaparro et al.,\(^12\) who reported 33% and 28% failure rates at the same end-point, respectively. Moreover, the cumulative probability of losing response to anti-TNFα was similar to previous reports\(^9,10,12,13\) with 18%, 35% and 46% at 1, 3 and 5 years respectively (Fig. 1). Thus our results demonstrate, once again, the favorable short-term outcome of biologic treatment but at the same time indicates that nearly half of the patients lose response after 5 years.

As described in previous studies, none of the patients or disease features analyzed could predict anti-TNFα failure. In contrast with two previous studies,\(^21,22\) but in accordance with one other study,\(^10\) we did not find any association between treatment outcome and disease duration before initiation of infliximab treatment, and no difference between infliximab and adalimumab. This finding is in concordance with previous studies that reported a high efficacy of adalimumab in both adult\(^36\) and pediatric\(^15,18\) moderate to severe CD.

The pathogenesis of growth retardation in pediatric CD is multifactorial and includes inadequate energy intake, nutritional deficiencies, corticosteroid therapy, and the influence of the inflammatory process itself on growth factors.\(^37-40\)
Previously reported data concerning the effects of anti-TNFα treatment on nutrition and growth are limited, nevertheless they suggest significant improvement in growth parameters. Our data confirm the ability of anti-TNFα to improve the nutritional status and to promote linear growth in pediatric CD patients. Interestingly, height velocity increased significantly only in male responders. Diamanti et al. reported significant improvement in weight and BMI but not in linear growth and Pfefferkorn et al. reported persistent height velocity impairment despite improved disease activity. These findings are in contrast to the studies by Crombe et al. and Malik et al. who reported a positive effect of infliximab on mean height Z-score. A gender dependent effect of anti-TNFα on growth and nutritional response has also been reported by Vasseur et al. although in their study the increase in linear growth was confined to female patients. Thayu et al. also found a significant intergender difference in lean mass deficit, and showed persistent lean mass deficits in female patients during treatment. Our findings which demonstrate a significant improvement in linear growth in male compared to female responders should stimulate further research on gender specific responses of growth during treatment of CD patients.

The observed increase in weight and BMI during anti-TNFα treatment can probably be primarily attributed to the decline in the intensity of the inflammatory response and improved energy intake. Moreover, infliximab was shown to increase abdominal fat tissue in CD patients, presumably, through blockade of the TNF-induced lipolytic effect, a mechanism which may contribute to weight and BMI gain.

Laboratory markers have been extensively investigated in IBD, particularly for monitoring the effect of treatment. Of all markers, CRP is the most studied and has been shown to correlate well with disease activity. Our findings are in agreement with previous reports on CRP and ESR changes during successful treatment, with the emphasis that CRP reacts more rapidly during response. Only a few reports have investigated the influence of biologic therapy on albumin and Hb in IBD patients. Lonnkvist et al. found that both parameters increased in responsive Crohn’s patients on infliximab although albumin peaked higher and faster. In our cohort albumin showed sustained elevation in prolonged responders compared to non-responders in contrast to Hb levels which did not differ between responders and non-responders. It can be concluded that albumin is a sensitive marker for anti-TNFα response while the impact of treatment on Hb levels is milder and should be further investigated.

Treatment with anti-TNFα was generally safe in our patients. The most frequent adverse event was a type 1 allergic reaction to infliximab in 15% of patients half of whom had severe acute infusion reactions which resulted in definitive drug withdrawal in 5% of patients. These rates are comparable with previous long-term follow-up studies. No type 1 reaction was observed during adalimumab treatment which also showed a relatively low rate of adverse effects. Type 1 reactions are indeed less prevalent with the use of adalimumab compared to infliximab although the overall rate of side effects with adalimumab was somewhat lower than expected. This may be attributed to incomplete reporting of minor adverse events such as injection site pain or reactions. Similarly, our database could not provide reliable information regarding infections, partly because a portion of the follow-up was performed in community clinics where minor infections might have been easily overlooked by the treating physician.

Our data should be interpreted in the context of the following study limitations. First, this is a retrospective study,
thus, indications, use and dose adjustments were determined by the treating physician and not according to a pre-specified protocol. Second, the available data did not allow the use of the Pediatric Crohn’s Disease Activity Index (PCDAI) which is more detailed and validated than the HBI. Third, some of the responders were treated before the current pediatric treatment guidelines were available and therefore received only the induction protocol. Moreover, for most of our patients, data was available only up to 18 years of age at which time, by convention in our country, treatment is passed to adult gastroenterologists. Thus, some patients were lost to follow-up relatively early in their course of treatment. This may have resulted in a decreased number of prolonged therapies throughout the study period and thus underestimated the number of long term responders. Lastly, our findings on growth are limited by the lack of data on pubertal staging that was not available retrospectively.

In conclusion, this relatively large longitudinal cohort supports the current evidence on the long-term effectiveness and safety of anti-TNFα treatment in children with CD. The study also confirms the concerns regarding the durability of long-term anti-TNFα maintenance treatment, as approximately half of the patients lost response after 5 years. In contrast to previous studies, loss of response was not found to be associated with disease duration or location but was correlated with lower weight and BMI at the initiation of anti-TNFα treatment. This intriguing issue should be subjected to further investigation. We also confirmed that the positive effect of biologic treatment is more pronounced regarding weight and BMI with apparently limited and gender specific impact on linear growth.

Acknowledgments

Specific author contribution: all authors have made substantial contributions to the study. Dr Amit Assa has conducted the study, collected and interpreted the data. Dr Corina Hartman has participated in drafting the manuscript. Dr Batia Weiss has participated in planning the study and drafting the manuscript. Dr Efrat Brodie has participated in planning the study and drafting the manuscript. Dr Yoram Rosenbach has participated in planning the study and drafting the manuscript. Dr Noam Zivot has participated in drafting the manuscript. Prof Yoram Bujanover has participated in planning the study and drafting the manuscript. Prof Raanan Shamir has initiated the study and has participated in planning the study and drafting the manuscript.

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