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

Amit Assa [a,d,*], Corina Hartman [a,d], Batia Weiss [b,d], Efrat Broide [c,d], Yoram Rosenbach [a,d], Noam Zevit [a,d], Yoram Bujanover [b,d], Raanan Shamir [a,d]

[a] Institute of Gastroenterology, Nutrition and Liver Disease, Schneider Children's Medical Center, Petach-Tikva, Israel
[b] Pediatric Gastroenterology Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel
[c] Pediatric Gastroenterology Unit, Assaf Harofeh Medical Center, Zerifin, Israel
[d] Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

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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-

* Corresponding author at: Institute of Gastroenterology, Nutrition and Liver Disease, Schneider Children's Medical Center of Israel, 14 Kaplan St. Petach-Tikva, 49202, Israel. Tel.: +972 3 9253672.
E-mail addresses: dr.amit.assa@gmail.com (A. Assa), CorinaH@clalit.org.il (C. Hartman), Batya.Vais@sheba.health.gov.il (B. Weiss), efibroide@yahoo.com (E. Broide), yoramr@clalit.org.il (Y. Rosenbach), nzevit@gmail.com (N. Zevit), bujyoram@netvision.net.il (Y. Bujanover), shamirraanan@gmail.com (R. Shamir).

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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.

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 treatment[6,25,26] while others[23,24,27] 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 Harofeh 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