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Original Article

Anti-Tumor Necrosis Factor Therapy in Bulgarian Pediatric Patients with Inflammatory Bowel Disease – an 8-Year Experience of a Referral Centre

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Abstract

Introduction: Anti-tumor necrosis factor (anti-TNF) therapy has become a mainstay in the treatment of patients with inflammatory bowel disease over the past few decades.

Aim: The aim of this study was to present our 8-year experience with anti-TNF treatment in pediatric patients with inflammatory bowel disease.

Materials and methods: We reviewed retrospectively the medical records of all children with inflammatory bowel disease who received anti-TNF drugs between September 2013 and September 2021.

Results: The study included 48 patients in total, with a median age of 15 years (range: 11 months to 17 years). All but one of them were receiving combination therapy, which included both an immunomodulator and a biologic agent, for moderate-to-severe disease. Infliximab was administered to only half of the study participants, adalimumab was only received by 22.9%, and 27.1% were treated with more than one biologic agent. Clinical remission at 6 months was achieved by 72.9% of them and 47.9% achieved a deep remission at 12 months. A quarter of the patients required therapy escalation and 27.1% switched to another biologic agent due to adverse events, primary non-response, or secondary loss of response (18.8% switched to a second anti-TNF and 8.3% switched to an anti-integrin agent). During the study period, the following serious adverse drug reactions were observed: 3 cases of anaphylactic reactions, 1 case of allergic rash, 1 case of disseminated tuberculosis, 1 case of severe herpes simplex infection, 1 case of herpes zoster infection, and 2 cases of drug-induced psoriasis.

Conclusions: Anti-TNF agents are an effective and safe treatment option in Bulgarian pediatric patients with inflammatory bowel disease.

Keywords

anti-TNF therapy, efficacy, pediatric inflammatory bowel disease, remission, safety

INTRODUCTION

The introduction of anti-tumor necrosis factor (anti-TNF) therapy has greatly changed the treatment paradigm in the management of patients with inflammatory bowel disease (IBD).[1] Anti-TNF agents, which are indicated in cases of moderate-to-severe IBD, not only reduce the disease symptoms but also result in healing of the inflamed intestine.[2] The use of anti-TNF drugs has shifted treatment goals toward the achievement of deep and prolonged clinical and endoscopic remission, aiming to prevent complications and halt the progressive course of disease.[3] In the last decades anti-TNF therapy has become a cornerstone of adult and pediatric IBD care.[4] Unfortunately, it is not the panacea for IBD in either of these age groups. Depending on the duration of anti-TNF treatment and the outcome parameters chosen, approximately one third of treated patients do not demonstrate response to therapy (primary non-response). Furthermore, 30%–50% of the initial responders are prone to lose response to therapy during anti-TNF treatment (secondary non-response).[5] Some patients do not respond well to anti-TNF medications and experience mild to serious side effects.[6-8]

AIM

The aim of this study was to present the experience with anti-TNF therapy in pediatric patients with IBD at our referral center.

MATERIALS AND METHODS

Study design and patients

We retrospectively reviewed the medical records of all children who were diagnosed with IBD and treated between September 2013 and September 2021 at the Department of Gastroenterology and Hepatology of Prof. Ivan Mitev University Children's Hospital, Sofia. The final analysis was based on the medical records of patients who received anti-TNF therapy. The inclusion criteria were an IBD diagnosis made by experienced pediatric gastroenterologists and the administration of anti-TNF agents for more than 3 months.

All study participants were diagnosed in accordance with the Porto criteria for the diagnosis of IBD in children and adolescents.[9] Disease extent and severity had been assessed according to the Paris Classification for children and adolescents with inflammatory bowel disease and based on the clinical activity indices for children with inflammatory bowel diseases: Pediatric Crohn's Disease Activity Index (PCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI).[10-12] Endoscopic activity was assessed using the Mayo endoscopic subscore (MES) and the simple endoscopic score for Crohn's Disease (SES-CD) in patients with ulcerative colitis (UC) and Crohn's disease (CD), respectively.[13,14]

Based on the data in the medical records, we investigated the effects of anti-TNF agents among our patients with respect to efficacy and safety. We assessed the proportion of patients in clinical remission at 6 months, the proportion of patients in deep remission at 12 months, the proportion of patients in long-term remission, the proportion of patients with therapy escalation, and the proportion of patients who switched therapy due to any reason. Clinical remission was defined as PUCAI <10 points and PCDAI <10 points in patients with UC and CD, respectively. Deep remission was defined as clinical remission and normal-appearing mucosa at endoscopy. Normal-appearing mucosa or mucosal healing was defined as MES=0 points and SES-CD <3 points in patients with UC and CD, respectively.[15] A sustained deep remission lasting a minimum of two years was considered long-term remission. In addition, we analyzed all drug-related adverse events reported within the study period.

Statistical analysis

The statistical analyses we used in this study were descriptive. All data were presented in tables and graphs. The continuous variables were presented as medians and ranges, whereas the categorical variables were summarized as the number of cases (n) with percentages (%).

Ethics

All analyzed data were collected as part of the routine treatment, which had been consistent with the current standard of care. Written informed consent had been obtained from all study participants, or their legal guardians, before starting the anti-TNF therapy. In accordance with the local legislation, additional patient informed consent and ethical approval were not sought, as they were not required by the study design, which was a retrospective review of medical records.

RESULTS

The medical records of 48 children with IBD met the inclusion criteria and were included in the final analysis. This study included 32 patients with CD (18 boys and 14 girls), 13 patients with UC (5 boys and 8 girls), and 3 patients with very early onset IBD (1 boy and 2 girls). The median age of the study participants was 15 years (range: 11 months to 17 years). The median age at diagnosis was 14 years (range: 10 months to 17 years). All children had a moderate or severe disease. The demographic data and clinical characteristics of the study population are summarized in **Table 1**.

Half of our patients were treated only with infliximab, 22.9% only with adalimumab, and 27.1% with more than

Table 1. Demographic and clinical characteristics of study participants

Variable	Patients with CD n=32	Patients with UC n=13	Patients with VEOIBD n=3
Sex, n (%)			
Male	18 (56.3)	5 (38.5)	1 (33.3)
Female	14 (43.7)	8 (61.5)	2 (66.7)
Age at diagnosis, median (range)	14 years, (6 - 17 years)	14 years, (9 - 17 years)	12 months, (10 - 24 months)
Duration of symptoms before diagnosis, median (range)	5 months, (1 - 36 months)	4 months, (1 - 24 months)	2 months, (15 months)
Age at administration of anti-TNF therapy, median (range)	15 years, (6 - 17 years)	15 years, (9 - 17 years)	12 months, (11-132 months)
Disease location, n (%)			
L1	4 (12.5)		
L2	5 (15.6)	NA	NA
L3	23 (71.9)		
Upper gastrointestinal involvement, n (%)			
No	14 (43.7)		
L4a	15 (46.9)	NA	NA
L4b	3 (9.4)		
Disease behavior, n (%)			
B1	19 (59.4)		
B2	6 (18.7)	NA	NA
B3	2 (6.3)		
B2B3	5 (15.6)		
Growth failure, n (%)			
G1	27 (84.4)	NA	NA
G0	5 (15.6)		
Disease extent, n (%)			
E1		0	0
E2	NA	2 (15.4)	0
E3		2 (15.4)	1 (33.3)
E4		9 (69.2)	2 (66.7)
Disease severity, n (%)			
S0	NA	5 (38.5)	0
S1		8 (61.5)	3 (100.0)

CD: Crohn's disease; UC: ulcerative colitis; VEOIBD: very early onset inflammatory bowel disease; L1: distal 1/3 ileum ± limited cecal disease; L2: colonic disease; L3: ileocolonic disease; L4a: upper gastrointestinal involvement proximal to ligament of Treitz; L4b: upper gastrointestinal involvement distal to ligament of Treitz and proximal to distal 1/3 ileum; B1: nonstricturing and nonpenetrating disease; B2: stricturing disease; B3: penetrating disease; B2B3: penetrating and stricturing disease; G0: no evidence of growth delay; G1: growth delay; E1: ulcerative proctitis; E2: left-sided UC; E3: extensive colitis; E4: pancolitis; S0: never severe; S1: ever severe.

one biologic agent. In all of them, anti-TNF agents were administered as second- or third-line of therapy. Prior to anti-TNF administration, depending on the disease type and severity, the study participants were exposed to steroids, immunomodulators, exclusive enteral nutrition, and 5-aminosalicylates or antibiotics. Most of them were exposed to more than one therapy. Furthermore, all but one of the study participants received a combination therapy (a biologic agent plus an immunomodulator). The different types of treatment before the anti-TNF administration are presented in **Table 2**.

Almost three-fourths of the study participants (72.9%) achieved clinical remission at 6 months **(Fig. 1)**. At 12 months, deep remission was achieved by 47.9% of them

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Table 2. Therapeutic exposition of the study population

Therapy	All patients n (%)	Patients with CD n (%)	Patients with UC n (%)	Patients with VEOIBD n (%)
Steroids	47 (97.9)	31 (96.9)	13 (100)	3 (100)
Immunomodulator	47 (97.9)	32 (100)	12 (92.3)	3 (100)
5-ASA	28 (58.3)	13 (40.6)	12 (92.3)	3 (100)
Antibiotics	32 (66.7)	18 (56.3)	11 (84.6)	3 (100)
EEN	2 (4.2)	2 (6.3)	NA	NA

CD: Crohn's disease; UC: ulcerative colitis; VEOIBD: very early onset inflammatory bowel disease; 5-ASA: 5-aminosalicylic acid; EEN: exclusive enteral nutrition

(Fig. 2) and 33.3% achieved a long-term remission. Twenty-five percent of our patients treated with ant-TNF drugs required therapy escalation and 14.6% of them improved with this maneuver. More than one fourth of the study population (27.1%) switched to another biologic agent due to adverse events, primary non-response, or secondary loss of response (18.8% switched to a second anti-TNF and 8.3% switched to an anti-integrin agent).

The following serious adverse drug reactions were observed during the study period: three cases of anaphylactic reaction, one case of allergic rash, one case of disseminated tuberculosis, one case of severe herpes simplex infection, one case of herpes zoster infection, and two cases of drug induced psoriasis.

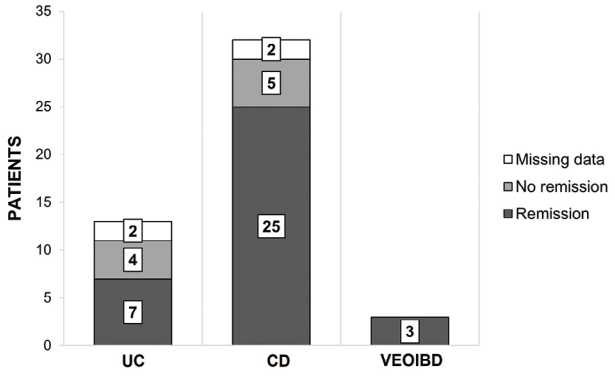

Figure 1. Rate of clinical remission at 6 months.

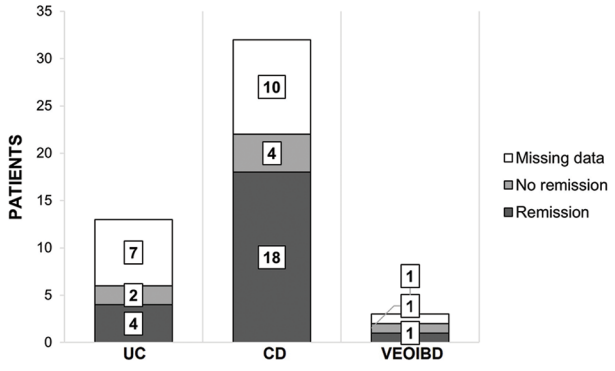

Figure 2. Rate of deep remission at 12 months.

DISCUSSION

This study demonstrated our experience with anti-TNF therapy in pediatric patients with IBD. We showed that anti-TNF agents have a good efficacy and safety profile confirming the data reported in the literature. To our knowledge, this is the first study in our country that provides results from administration of TNF-α inhibitors in children with IBD.

According to the latest guidelines for treatment of pediatric IBD, anti-TNF drugs should be administered for induction and maintenance of remission in children and adolescents with steroid refractory disease or chronically active disease despite immunomodulators, and as a first-line therapy in pediatric CD patients with active perianal fistulizing disease.[16,17] Following the national reimbursement criteria, we used the anti-TNF agents as a second- or third-line therapy in all patients in the study. In two children with VEOIBD, the treatment was off-label.

The available data on efficacy of anti-TNF therapy in pediatric IBD vary among different studies depending on the administered anti-TNF agent, the studied population, the treatment target, and the time of treatment response evaluation. Most authors assess the rate of clinical response and the rate of clinical remission after the induction phase and after one-year therapy.[18,19,21,27-29] Of course, there are also a number of studies with different time points and outcomes.[28,29] Overall, these studies demonstrate that anti-TNF agents, specifically infliximab and adalimumab, are effective in induction and maintenance of remission in moderate and severe pediatric IBD.[29] Based on the reimbursement criteria in our country and the study design, we assessed the rate of clinical remission at 6 months and the rate of deep remission at 12 months. We found a high clinical remission rate at 6 months confirming the available efficacy data.[18-21] The demonstrated rate of deep remission at 12 months was also in line with previous observations in pediatric patients with IBD treated with anti-TNF drugs.[22-26] The rates of long-term deep remission among our patients were significantly lower than the data reported in the literature. Overall, the 1- and 3-year sustained remission rates in children with CD on anti-TNF have been reported to be 50% to 80% and 40% to 70%, respectively.

However, in the UC population on anti-TNF, sustained remission for a mean period of 2 years have been reported in 40% of patients.[27] A possible explanation of this finding is that long-term data were missing in half of our patients: they had been treated for less than 2 years or had turned 18 years and were lost to follow-up.

According to the literature, up to 30% of patients with IBD do not respond to anti-TNF therapy (primary non-responders) and almost half of the patients who benefit from these drugs lose their response within the first year (secondary loss of response).[28-31] The reasons why some patients do not respond or lose response after a successful course of therapy are multifactorial and related to the metabolism of the drug or to the development of antidrug antibodies.[31] Depending on the underlying cause, there are different strategies for management of loss of response to anti-TNF therapy such as therapy escalation (dose escalation, reduction in dose interval, or both) and switch to an alternative drug.[28,32] Previous studies showed that 27% to 49% of children treated with anti-TNF drugs required adjustments in therapy to maintain remission and the median time to the adjustments was 6–9 months.[32] Our findings are in agreement with these data.

Based on the protocol of our clinic, most of the study participants were treated with a combination therapy (an anti-TNF agent and an immunomodulator). The benefit of this approach is the improved efficacy due to the synergistic effect between the 2 agents and prevention of immunogenicity.[27] The downside of a combination therapy may be an increased risk of toxicity, increased susceptibility to infections, and increased risk of malignancies.[32] However, we didn't observe a significant increase of infection rates among our patients on biologic therapy or any case of toxicity or malignancy. Generally, the serious adverse drug reactions that occurred were consistent with the safety profile of the anti-TNF agents.[33] Treatment interruption was necessary in four of the cases: the patients with anaphylactic reactions switched to an alternative biologic agent and the patient with disseminated tuberculosis received a tuberculostatic treatment for six months. Both cases of herpes infection (simplex and zoster) were treated with acyclovir and both cases of druginduced psoriasis were managed with topical steroids.

This study has strengths but also limitations. The main strength of the study is that it is the first one presenting a real life experience with anti-TNF therapy in Bulgarian children with IBD. Its main limitations are the single center retrospective design and the small sample size.

CONCLUSIONS

In conclusion, this study provided a single center retrospective look at the clinical experience of using anti-TNF agents in a pediatric IBD population. Demonstrating satisfactory efficacy data with high remission rates and good safety profile, our results confirmed the role of anti-TNF drugs as an important treatment alternative for children with IBD and supported their use in the everyday practice. However, considering the large heterogeneity between pediatric IBD patients, we would like to highlight the need for individual approach to each case. Overtreatment should be avoided and, at the same time, timely introduction of anti-TNF therapy is crucial for the favorable outcome. During treatment, all patients should be closely monitored to prevent infections or other complications and for non-responders, alternative treatment modalities should be sought. Further studies with larger sample sizes and longer follow-up are needed to evaluate the clinical predictors of response, as well the role of therapeutic drug monitoring and inflammatory biomarkers during therapy with anti-TNF agents in children with IBD.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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Author contributions

Conception and design: R.R.S.-E., P.Y., E.L., and M.B. Acquisition of data: R.R.S.-E., D.K., H.N., and P.H. Analysis and interpretation of data: R.R.S.-E. and M.B. Drafting: R.S., P.Y., E.L., D.K., and M.B. Critical revision and final approval: all the authors.

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Терапия фактора некроза опухоли у педиатрических больных с воспалительными заболеваниями кишечника в Болгарии – 8-летний опыт референс-центра

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Резюме

Введение: Терапия против фактора некроза опухоли (анти-TNF) стала основой лечения пациентов с воспалительными заболеваниями кишечника за последние несколько десятилетий.

Цель: Целью этого исследования было представить наш 8-летний опыт лечения анти-TNF у педиатрических пациентов с воспалительным заболеванием кишечника.

Материалы и методы: Мы ретроспективно рассмотрели медицинские карты всех детей с воспалительными заболеваниями кишечника, которые получали препараты анти-TNF в период с сентября 2013 г. по сентябрь 2021 г.

Результаты: Всего в исследование было включено 48 пациентов со средним возрастом 15 лет (диапазон: от 11 месяцев до 17 лет). Все, кроме одного, получали комбинированную терапию, которая включала как иммуномодулятор, так и биологический агент, при средней и тяжёлой степени заболевания. Инфликсимаб вводили только половине участников исследования, адалимумаб получали только 22.9%, а 27.1% лечили более чем одним биологическим агентом. Клинической ремиссии через 6 месяцев достигли 72.9 % из них, а глубокую ремиссию через 12 месяцев - 47.9 %. Четверти пациентов потребовалась эскалация терапии, а 27.1 % перешли на другой биологический препарат из-за нежелательных явлений, первичного отсутствия ответа или вторичной потери ответа (18.8 % перешли на второй анти-TNF и 8.3 % перешли на антиинтегриновый препарат). За период исследования наблюдались следующие серьёзные нежелательные реакции на лекарственные средства: 3 случая анафилактических реакций, 1 случай аллергической сыпи, 1 случай диссеминированного туберкулёза, 1 случай тяжёлой инфекции простого герпеса, 1 случай инфекции опоясывающего герпеса и 2 случая медикаментозного псориаза.

Заключение: Анти-TNF препараты являются эффективным и безопасным вариантом лечения болгарских педиатрических пациентов с воспалительными заболеваниями кишечника.

Ключевые слова

анти-TNF терапия, эффективность, воспалительные заболевания кишечника у детей, ремиссия, безопасность