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Adalimumab in pediatric ulcerative colitis

Adalimumab w terapii wrzodziejącego zapalenia jelita grubego u dzieci

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S u m m a r y

Introduction. Adalimumab (ADA) has been shown to be effective in adult patients with moderately to severely active ulcerative colitis. Unfortunately, data about its role in pediatric patients are sparse.

Aim. The aim of our study was to summarize the experience with adalimumab (ADA) used in therapy of pediatric patients with ulcerative colitis (UC) in our center.

Material and methods. We retrospectively analyzed data of six children with active UC who have been treated with ADA in our hospital. Data about treatment history, concomitant therapy, and biochemical parameters were collected. We evaluated short term response to ADA as well as long term outcomes. PUCAI index was used to assess clinical condition of the subjects. Endoscopic features were classified according to Baron scale.

Results. The mean age at diagnosis was 11.83 ± 2.78 years. The mean age at the time of first ADA injection was 14 ± 2.22 years. Mean duration of disease before ADA therapy was 23.8 ± 20.8 months. 5 patients were previously treated with infliximab. Indications for ADA were: hypersensitivity reaction to IFX (2 pts.), infliximab refractory UC (3 pts.), steroid dependency (1 pt.). One child didn't response to ADA and had colectomy. At week 8, 2 of 6 patients had a clinical response. Mean PUCAI score at baseline was 32.5 ± 24.23, at week 8 was 19 ± 19.49. Five patients competed the induction phase and were entered into maintenance phase of the ADA therapy. One child has been excluded from long-term analysis. He received five injections of ADA and has been transferred to the center for adults. 4 patients after 6 months of ADA therapy maintained clinical remission (PUCAI < 10), in 2 cases remission was endoscopically assessed (grade O in Baron scale). After 12 months 3 patients were in clinical remission, in 2 cases colonoscopy has been performed (Baron scale 0 or 1). PUCAI index after 6 and 12 months were retrospectively 2.5 ± 2.88; 7.5 ± 11.9.

Conclusions. Adalimumab is effective and safe treatment in pediatric ulcerative colitis intolerant to or with loss of effect to infliximab therapy. Should be considered as the rescue treatment before colectomy in this age group.

S t r e s z c z e n i e

Wstęp. Skuteczność adalimumabu (ADA) u pacjentów dorosłych ze średnio ciężką i ciężką postacią wrzodziejącego zapalenia jelita grubego została potwierdzona. Niestety brakuje danych na temat roli ADA u dzieci.

Cel pracy. Celem badania było podsumowanie doświadczeń własnych w leczeniu adalimumabem (ADA) wrzodziejącego zapalenia jelita grubego u dzieci.

Materiał i metody. Retrospektywnie przeanalizowano dane sześciu pacjentów ze średnio ciężką i ciężką postacią wrzodziejącego zapalenia jelita grubego leczonych ADA. Zebrano dane dotyczące dotychczasowej terapii, leczenia stosowanego w czasie rozpoczęcia kuracji ADA oraz przeanalizowano parametry biochemiczne. Oceniono odpowiedź krótkoterminową na leczenie adalimumabem oraz opisano długoterminowe wyniki. Do oceny odpowiedzi klinicznej wykorzystano skalę PUCAI. Odpowiedź endoskopową oceniono za pomocą skali Baron.

Wyniki. Średni wiek w momencie diagnozy wyniósł 11,83 ± 2,78 roku. Średni wiek w momencie rozpoczęcia terapii adalimumabem wyniósł 14 ± 2,22 roku. Średni czas trwania choroby przed pierwszą iniekcją ADA wyniósł 23,8 ± 20,8 roku. 5 pacjentów było wcześniej leczonych infliksymabem (IFX). Wskazaniami do terapii adalimumabem były: reakcja nadwrażliwości na IFX (2 osoby), nieskuteczność leczenia IFX (3 osoby), sterydozależność (1 osoba). Jeden pacjent nie zareagował na leczenie ADA, ostatecznie miał wykonaną kolektomię. W 8 tygodniu 2 z 6 pacjentów uzyskało odpowiedź kliniczną. Średni wynik w skali PUCAI na początku leczenia wynosił 32,5 ± 24,23 (5-75), zaś w 8 tygodniu 19 ± 19,49 (0-50). 5 pacjentów ukończyło fazę indukcji i zostało włączonych do fazy

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podtrzymującej leczenia ADA. Jeden pacjent został wykluczony z analizy długoterminowej odpowiedzi z uwagi na ukończenie 18 roku życia. 4 pacjentów włączono do dalszej analizy. Po 6 miesiącach leczenia wszyscy pacjenci byli w remisji klinicznej (PUCAI < 10), w dwóch przypadkach remisję potwierdzono endoskopowo (Baron 0). Po 12 miesiącach 3 pacjentów pozostawało w remisji klinicznej, u 2 wykonano kolonoskopię (Baron 1 i 0). PUCAI po 6 i 12 miesiącach wyniósł odpowiednio 2,5 ± 2,88; 7,5 ± 11,9.

Wnioski. Adalimumab jest skutecznym i dobrze tolerowanym lekiem u pacjentów pediatrycznych z wrzodziejącym zapaleniem jelita grubego, którzy nie tolerowali leczenia IFX lub utracili odpowiedź na IFX. Adalimumab powinien być rozważany w terapii UC u dzieci przed decyzją o wykonaniu kolektomii.

INTRODUCTION

Adalimumab (Humira, Abbott) is a humanized anti-tumor necrosis factor monoclonal antibody that blocks proteins that play an important role in abnormal inflammatory and immune responses. It has been shown to be effective in adult patients with moderate-to-severe active ulcerative colitis (UC) who were nonresponders or intolerant to standard therapy. After the publication of the results of the two randomized, placebo-controlled, double-blind trials (ULTRA 1 and ULTRA 2) (1, 2) it has been approved by U.S. Food and Drug Administration (FDA) in UC adult patients. Adalimumab is not currently licenced for use in pediatric inflammatory bowel disease and data on its role in pediatric ulcerative colitis are sparse. However, based on evidence derived from adult studies, it is used off-label in clinical practice. In this report we summarize our experience with adalimumab in six pediatric UC patients.

AIM

The aim of the study was to evaluate short term clinical response and remission as well as efficacy in maintaining clinical remission.

MATERIAL AND METHODS

We retrospectively reviewed medical charts of children affected with ulcerative colitis treated with ADA in our hospital. Six children with moderately to severely active UC were included in this study. We evaluated short term response to ADA as well as long term analysis. Patient's data about treatment history, concomitant therapy, biochemical parameters: hemoglobin (Hb), hematocrit (Htc), platelet blood count (PBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at baseline, 8 weeks, than 6 and 12 months after first ADA injection were collected. PUCAI index was used to assess clinical condition of the subjects (3). Clinical response was defined as reduction in PUCAI index ≥ 20 points and clinical remission as PUCAI index less than 10 points. Endoscopic features were classified according to Baron scale (4), mucosal healing was defined as either completely normal (score 0) or mild (score 1) in Baron scale. Disease location was classified according to Paris Classification (5).

Initial adalimumab dosages were either 40 mg (1 patient) subcutaneously or 80 mg (5 patients) subcutaneously followed by maintenance dose of 40 mg after 2 weeks than every 2-4 weeks.

Statistical analysis

The data were collected from patient's medical charts and analyzed retrospectively. The frequency of findings was presented in numbers and in percentages. All statistical tests were performed with Statistica 10.0 (StatSoft Inc., 2011). Distribution of analyzed variables was tested using Shapiro-Wilk Normality test. The Wilcoxon signed-rank test was used to verify the hypothesis. The p value < 0.05 was considered as significant.

RESULTS

Six children (2 female), with confirmed UC were treated with ADA from November 2010 to May 2013. The mean age at diagnosis was (Mean ± SD) 11.83 ± 2.78 (range 8-16) years, the mean age at the time of first ADA injection was 14 ± 2.22 (range 11-17.5) years. The mean duration of disease before ADA therapy was 23.8 ± 20.8 (range 3-60) months. Disease distribution was pancolitis (E4) in 2 cases, left-sided UC (E2) in 3 cases and extensive UC (E3) in one subject. All patients were previously treated with corticosteroids, azathiopryne and mesalazine. 5 of 6 patients failed cyclosporine therapy. One child with diagnosed UC and juvenile idiopatic arthritis (JIA) has been treated in the past with etanercept. The vast majority of patients, without one child with coexisting JIA, were previously treated with infliximab. Mean number of infliximab infusions before ADA was 2.8 ± 0.83 (range 2-4). Indications for starting adalimumab were a hypersensitivity reaction to infliximab (IFX) in 2 patients (after second infusion in one child and after third in another one), failure to achieve clinical remission with IFX in 3 subjects, steroid dependency in one case.

Short term response

From the all investigated subjects one child with steroid dependant UC, previously ineffectively treated with 3 infusions of IFX, didn't response to ADA. Due to lack of clinical and endoscopic remission temporarily required glucocorticosteroid (GKS) until colectomy. Data of five remaining patients were assessed at week 8. Generally, at week 8, 2 of 6 patients included to this study had a clinical remission, measured with PUCAI index. Mean PUCAI score at baseline was 32.5 ± 24.23 (range 5-75, n = 6) (Mean ± SD, n = number of variables), at week 8 was 19 ± 19.49 (range 0-50, n = 5). Patient with coexisting JIA after 4 ADA injections shoved clinical relapse (PUCAI 50) simultaneously drug-induced (probably

aztathiopryne related) pancreatitis has been diagnosed. After a course of intravenous GKS ADA therapy has been successfully continued. Changes in biochemical parameters at week 8 are presented in table 1. There were no statistically significant differences in the analyzed variables.

Long-term follow-up

Five patients competed the induction phase and were entered into maintenance phase of the ADA therapy. One child has been excluded from long-term analysis. He has been treated from May 2013 to August 2013, until age eighteen. Before transferring patient to the center for adults, after receiving five injections of ADA, endoscopy has been performed. Pancolitis has been diagnosed; disease activity endoscopically assessed as grade 3 in endoscopic Baron scale.

Four remaining patients have been included to the long-term analysis. Data were analyzed after 6 and 12 months of ADA therapy. After 6 months all (4) patients had clinical remission, assumed as less than 10 points in PUCAI scale. In 2 cases colonoscopy has been performed and normal mucosa has been identified (grade 0 in Baron scale). After 12 months three patients remained in clinical remission, endoscopic remission confirmed in 2 cases (Baron 0 in 1 child, Baron 1 in other one). Mean PUCAI index at 6 and 12 months were respectively 5 ± 2.88 (0-5); 7.5 ± 11.9 (0-25). One child (witch coexisting JIA) shoved another (second during ADA therapy), relapse after 12 months of treatment (PUCAI 25). Tendency to improvement in biochemical parameters has been observed, detailed data are presented in table 2.

In one patient (child with UC and coexisting JIA) ADA therapy has been finished because of second relapse during ADA treatment. Pulses of intravenous corticosteroids have been used subsequently cyclosporine with improvement. In other patient treatment of ADA has been repeated after eleven months from the termination of first series of ADA injections. Patient has been transfer to the center from adults after receiving 8 ADA injections (80 mg subcutaneously followed by maintenance dose of 40 mg). Two remaining patients finished ADA therapy without relapse to date, they are still under our observation. No adverse reactions have been observed during ADA therapy in our patients.

Table 1. Comparison of clinical and biochemical parameters at baseline and at week 8.

Variable (Mean ± SD)	N	At baseline	At week 8	p-value
PUCAI index	5	32.5 ± 24.23	19 ± 19.49	0.68
Body weight (kg)	5	45.61 ± 8.64	47 ± 8.88	0.34
Hb (g/dl)	5	10.38 ± 1.73	10.06 ± 2.28	0.68
Hct (%)	5	32.56 ± 4.29	33.04 ± 5.32	0.22
PBC (k/ul)	5	445.16 ± 98.26	401.60 ± 205.98	0.50
ESR (mm/h)	5	33.40 ± 23.21	22.20 ± 4.43	0.14
CRP (mg/dl)	5	2.13 ± 3.28	2.15 ± 2.90	0.13

SD – standard deviation, N – number of variables, Hb – hemoglobin, Hct – hematocrit, PBC – platelet blood count, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein

Table 2. Comparison of biochemical parameters after 6 and 12 months of ADA therapy.

Data	n	Mean	Mediana	Min	Max	SD
Hb (g/dl) before ADA	6	10.38	10.15	8.80	13.70	1.73
Hb (g/dl) after 6 months	4	11.12	10.95	10.20	12.40	0.99
Hb (g/dl) after 12 months	4	11.92	12.10	10.20	13.30	1.477
Hct (%) before ADA	6	32.56	31.80	28.00	40.60	4.29
Hct (%) after 6 months	4	35.40	35.80	32.00	38.00	2.576
Hct (%) after 12 months	4	37.07	37.00	34.10	40.20	2.776
PBC (k/ul) before ADA	6	445.1	418.5	356	604	98.26
PBC (k/ul) after 6 months	4	401.0	373.0	216	641	176.4
PBC (k/ul) after 12 months	4	424.7	339.5	282	738	212.3
ESR (mm/h) before ADA	5	33.40	25.00	12	72	23.21
ESR (mm/h) after 6 months	3	19.33	18.00	10	30	10.0
ESR (mm/h) after 12 months	4	27.75	25.00	12	49	18.73
CRP (mg/dl) before ADA	6	2.13	0.145	0.07	7.75	3.288
CRP (mg/dl) after 6 months	4	0.16	0.025	0.01	0.60	0.29
CRP (mg/dl) after 12 months	4	1.00	0.050	0.02	3.90	1.93

Hb – hemoglobin, Hct – hematocrit, PBC – platelet blood count, ESR – erytrocite sedimentation rate, CRP – C-reactive protein, n – number of variables, min – minimum, max – maksimum, SD – standard deviation

DISCUSSION

According to actual guidelines for managing UC in children of an international working group of specialists in pediatric IBD from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Crohn's and Colitis Organization (ECCO), adalimumab should only be used in those who lost response or were intolerant of infliximab (6). As mentioned in the introduction section FDA approved adalimumab only to treat adult patients with moderate-to-severe active ulcerative colitis who were nonresponders or intolerant to standard therapy, thus in children the drug is used off-label in clinical practice as indicated above. There are no high quality researches evaluating effectiveness of ADA in children. Adalimumab usage in pediatric UC has been presented mainly as case reports.

The efficacy of subcutaneous adalimumab for the induction and maintenance of clinical remission in adult patients with moderately to severely active ulcerative colitis despite treatment with conventional therapies has been evaluated in two pivotal, randomized, double-blind, placebo-controlled, multicenter studies (ULTRA-1 [1] and ULTRA-2 [2]). In both trials remission was defined as Mayo score ≥ 2 with no individual subscore > 1 and response was defined as a decrease in full Mayo score of ≥ 3 points and $\geq 30\%$ decrease from baseline plus a decrease in the rectal bleeding subscore (RBS) of ≥ 1 point or an absolute RBS of 0 or 1. The following results were obtained. In ULTRA 1 trial at week 8, 18.5% of patients in the ADA 160/80 group and 10.0% in the ADA 80/40 group were in remission, compared with 9.2% in the placebo group. Overall, in ULTRA 2 trial in the 8th week of treatment clinical remission was obtained in 16.5% of patients (9.3% for placebo) and at week 52 of 17.3% (8.5% for placebo). It is noteworthy that among patients with prior exposure to TNF-α antagonists rate of remission at week 8 was lower than in anti-TNF-α naïve patients respectively 9.2 vs 21.3%, corresponding values week 52 were 10.2 vs 22%.

In the literature there are many studies concerning on ADA therapy in UC adults patients. McDermott et al. published the results of a prospective single--center study evaluating the efficacy of adalimumab maintenance therapy (7). The study included 23 people, most of which (87%) were previously treated with infliximab. Mean duration of therapy was 23 months. Treatment failure was not associated with age, gender, extent of disease, smoking, or the amount of inflammatory markers (CRP). The percentage of patients whose therapy was ineffective at 6, 12 and 24 months of treatment was respectively 50, 65 and 72%. Another study evaluating clinical remission and response, as well as mucosal healing at week 52 in adult patients with moderately to severely active ulcerative colitis who participated in a double-blind placebo-controlled adalimumab induction trial (ULTRA 1) was conducted by Reinisch et al. (8). At week 52 rates of clinical remission, clinical response, and mucosal healing were 29.5, 53.6, and 46.7%, respectively. Clinical response at weeks 4 and 12 was achieved in 53% (16/30) and 60% (18/30) of patients, respectively, and clinical remission was obtained in 10% and 27% of patients, respectively in study conducted by Taxonera et al. (9). After a mean 48 weeks of follow-up, 1/2 of patients continued on adalimumab. Authors highlighted that all patients who achieved clinical response at week 12 were colectomy free at long term. The current evidence indicates that adalimumab is effective for the treatment of adult patients with different types of ulcerative colitis, including biologically naïve and difficult-to-treat patients (10-13). Gies et al. pointed out in their prospective study that the efficacy results from published randomized clinical trials are not always equivalent to those seen in "real-life" clinical practice (14). The induction response rate in their "real-live" clinical practice study (within the first 14 weeks) was higher for IFX (96.4%) and ADA (80.0%) than those reported in the initial randomized placebo-controlled trials for IFX ACT I (69.4%) and II (64.5%) trials (15) and ADA (54.6%) (16).

Unfortunately, pediatric data are restricted primarily to retrospective studies of ADA off-label use in ulcerative colitis. The present study describes our results of adalimumab therapy in children with ulcerative colitis, in vast majority previously treated with infliximab. We found that at week 8, 2 of 6 patients responded to adalimumab, while they also had a clinical remission, assumed as less than ten points in PUCAI scale. Five patients competed the induction phase and were entered into maintenance phase of the ADA therapy. Mean PUCAI score at baseline was 32.5 ± 24.23 (range 5-75, $n = 6$) (Mean $\pm$ SD, n = number of variables), at week 8 was 19 ± 19.49 (range 0-50, $n = 5$).

In present trial we evaluated long term outcomes in our patients. In our experience 4 of 6 of ADA treated UC children had clinical remission after 6 month of ADA therapy, and half of investigated children after 12 months respectively. Mean PUCAI index at 0, 6 and 12 months were respectively 32.5 ± 24.23 (5-75); 5 ± 2.88 (0-5); 7.5 ± 11.9 (0-25). Additionally biochemical parameters as: hemoglobin, hematocrit, platelet blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at baseline, 6 and 12 months after first ADA injection were collected from patients medical charts. Tendency to improvement was observed after 6 and 12 months of therapy. We found no statistically significant differences between analyzed variables what is to be expected due to the small size of the group.

There are single studies focusing on adalimumab usage in pediatric ulcerative colitis. Noe et al. conducted in 2008 a retrospective chart review of pediatric IBD patients treated with adalimumab (17). They included ten patients to their study, only 3 of them with UC, all with prior exposure to IFX. Initial adalimumab dosages were either 40 mg subcutaneously or 80 mg subcutaneously.

All patients received 40 mg subcutaneously every 2 weeks for maintenance. The response was defined as either a decrease in the disease activity index severity or remission after 3-6 months of treatment. Eight out of 10 patients responded to adalimumab, 6 with CD and 2 with UC. More precisely assessing patients with UC the mean pre- and post-treatment Lichtiger Colitis Activity Index score (LCAI) were 9 and 5.1, respectively; the medians were 9 and 4.5, respectively. According to LCAI scale grade between 0-9 means no disease. No adverse reactions have been reported.

Another study summarized the United Kingdom and Republic of Ireland paediatric IBD adalimumab experience (18). Seventy-two patients, only one ulcerative colitis patient, from 19 paediatric-centres received adalimumab, most of them (94%) had previously received infliximab (UC patient also). Remission rates were 24, 58 and 41% at 1, 6 and 12 months, respectively. Unfortunately data about ulcerative colitis patient are scarce. There were 15 (21%) adverse events reported including four (6%) serious adverse events with two sepsis related deaths in patients who were also on immunosuppression and home parenteral nutrition (3% mortality rate).

There are also available, unfortunately only as conference abstract, data of two studies. In first study Romagnoli et al. evaluated short term response to ADA in four children with mean age of 11.8 years (range: 9.8-12.7) with active UC (19). PUCAI index at 0, 3 and 6 months were respectively: (mean ± SD) 36.2 ± 30.9, 1.2 ± 2.5 and 5 ± 5.8. Additionally authors analyzed calprotectin, and values at 0, 3 and 6 months were respectively: 413.5 ± 262.2, 36.3 ± 30.2 and 35.1 ± 26.1 (normal values lower than 50 mcg/g). All patients were considered responders to ADA at 3 and 6 months. I the second trial Volonaki et al. have assessed the efficacy of adalimumab in ten pediatric patients with median age 14 years (6.8y-16.6y) at the time of first adalimumab injection. As in the previous study data are only available as conference abstract. All of investigated children had failed infliximab after 6.5 months median duration of therapy. Authors obtained results similar to those presented in our study. 30% (3/10) of patients showed sustained clinical response to adalimumab with histological evidence of mucosal healing (follow-up 16, 22 and 24 months respectively). The remaining 7 patients required treatment escalation, finally 4 of them ended up with colectomy (4/10, 40%).

In our cohort no adverse reaction were observed during therapy. Adalimumab treatment is generally well tolerated. In clinical trials the overall safety profile in patients with UC was comparable with placebo, rates of adverse reactions were similar to the ones that occurred for the other approved indications for adalimumab (20, 21).

According to our knowledge this study is the only report summarizing the results of adalimumab treatment of pediatric ulcerative colitis. The limitation of our study is the retrospective character of data analysis and the relatively small size of the patient group. A multicenter prospective trial of adalimumab in pediatric CD is required.

CONCLUSIONS

Infliximab so far is the only biological drug licenced for the treatment of pediatric patients with ulcerative colitis. FDA approved three monoclonal anti-TNF-alpha antibodies to treat adults with moderate to severe ulcerative colitis with an inadequate response to conventional therapy, or who are intolerant, or have medical contraindications for such therapy. Apart from infliximab and adalimumab, recently golimumab has been approved. Based on data for adults and case studies in children adalimumab is used off-label. Currently, this new therapeutic option is the integral part of the pediatric ulcerative colitis treatment algorithm and with time probably will be used more extensively.

The results of our research confirm that adalimumab is effective and save treatment in pediatric ulcerative colitis intolerant to or with loss of effect to infliximab therapy. It should be considered as the rescue treatment before colectomy in this age group. Therefore, the goal is to select the candidates who will best benefit from the drug.

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