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Evaluation of the efficacy and safety of adalimumab therapy in pediatric patients with Crohn's disease

Ocena skuteczności i bezpieczeństwa terapii adalimumabem u dzieci z chorobą Leśniowskiego-Crohna

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Słowa kluczowe
adalimumab, dzieci, indukcja remisji

S u m m a r y

Introduction. Crohn's disease belongs to the group of inflammatory bowel disease (IBD). Prompt diagnosis and early optimal treatment warrants successful outcome, which is disease remission. Introduction of biological drugs for the treatment of IBD increased the efficiency of remission.

Aim. The aim of the study was to evaluate the effectiveness of induction and maintenance remission of the disease and safety of adalimumab therapy in pediatric patients with Crohn's disease.

Material and methods. The study included 9 patients with Crohn's disease with mean age 7.35 years at diagnosis. All patients were treated in the past with IFX or ADA. To assess the severity of the disease and the effectiveness of treatment authors used PCDAI scale (Pediatric Crohn's Disease Activity Index) and value of laboratory tests – ESR, CRP, hemoglobine, hematocrite – during enrolment to therapy, after third dose and after 6 and 12 months of treatment. The authors assessed safety of adalimumab therapy by evaluation of adverse events occurring during the drug administration and between doses.

Results. 8 patients (89%) achieved induction of remission, 1 patient (11%) didn't respond to the treatment, while this is the patient previously treated both IFX and ADA. Regard to adverse events (AE), the authors did not register any AE during administration of the drug, and those which occurred between doses of the drug were not different from those in a healthy population.

Conclusions. Adalimumab therapy allows to induction and maintenance remission. The safety profile of adalimumab in pediatric population is comparable with that seen in the adult population.

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

Wstęp. Choroba Crohna należy do grupy nieswoistych zapaleń jelit (IBD). Wczesna diagnoza i optymalne leczenie gwarantują pomyśle wyniki terapii, czyli uzyskanie remisji choroby. Wprowadzenie leków biologicznych do leczenia IBD zwiększyło efektywność uzyskiwania remisji choroby.

Cel pracy. Celem pracy była ocena skuteczności indukcji i utrzymania remisji choroby oraz bezpieczeństwa terapii adalimumabem u dzieci z chorobą Leśniowskiego-Crohna.

Materiał i metody. Badaniem objęto 9 pacjentów z chorobą Leśniowskiego-Crohna w średnim wieku 7,35 roku w chwili diagnozy. Wszyscy pacjenci leczeni byli w przeszłości IFX lub ADA. Do oceny aktywności choroby i skuteczności leczenia stosowano skalę PCDAI (Pediatric Crohn's Disease Activity Index) oraz wartości badań laboratoryjnych: OB, CRP, hemoglobiny, hematokrytu w trakcie kwalifikacji do leczenia, po trzeciej dawce, a także po 6 i 12 miesiącach leczenia. Autorzy oceniali bezpieczeństwo terapii adalimumabem poprzez ocenę działań niepożądanych występujących podczas podawania leku i pomiędzy dawkami.

Wyniki. 8 chorych (89%) osiągnęło indukcję remisji, 1 (11%) pacjent nie odpowiedział na leczenie, przy czym jest to pacjent uprzednio leczony zarówno IFX, jak i ADA. W odniesieniu do działań niepożądanych (AE), autorzy nie zarejestrowali żadnych podczas podawania leku, a te, które miały miejsce między dawkami leku, nie różniły się od występujących w zdrowej populacji.

Wnioski. Terapia adalimumabem pozwala na indukcję i utrzymanie remisji choroby. Profil bezpieczeństwa stosowania adalimumabu w populacji pediatrycznej jest porównywalny z obserwowanym w populacji dorosłych.

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INTRODUCTION

Recently there has been a worldwide increase in the incidence of the Crohn's disease in the adult and pediatric population (1, 2). The aim of the treatment of Crohn's disease is to induce and then maintenance remission. In Poland treatment regimen is based on "step-up" strategy. It involves the use of drugs from the lowest level of the "treatment pyramid in IBD" (fig. 1) through gradual introduction drugs with increasing potency. Choosing the appropriate treatment depends on the severity of the disease, its extent or presence of the disease complications. Current treatment regimens according to the ECCO/ESPEGHAN guidelines, particularly in the newly diagnosed patients and those who are still in the maturation period, recommend the use of total enteral nutrition (EEN) for 6-8 weeks. In case of intolerance or lack of clinical improvement within 2 weeks of use EEN, corticosteroids in full dose for 2-4 weeks with subsequent, weekly, gradual dose reduction are recommended. In case of severe disease and poor prognosis, simultaneously immunosuppressive therapy with azathioprine or methotrexate, in order to maintain longer remission, is recommended. Biological treatment, in Crohn's disease, stays at the top of the pyramid treatment (3). In Poland, for pediatric patients, Infliximab and Adalimumab are available. The indications for the therapy with anti-TNF are active, severe inflammation of the intestines and/or perianal lesions with the ineffectiveness of the drugs with less potency (1, 3-8). "Top-down" therapy – attempt to induce induction of remission, starting from the top of the pyramid treatment, in Poland is rarely used.

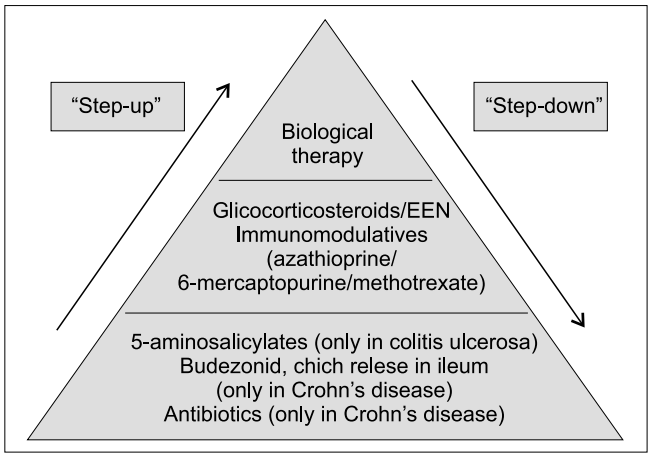

Fig. 1. Treatment pyramid in IBD.

The first approved biological drug, introduced for treatment inflammatory bowel disease, was Infliximab (IFX). It is a chimeric human-murine monoclonal immunoglobulin G (Ig) subclass G1. The drug is given intravenously at dose 5 mg/kg of body weight. It consists in 75% of human and 25% of murine components. The presence of murine components, potentailly can cause immunogenicity. Administration of each next doses of drug may result in production of antibodies against drug causing lower effectiveness of treatment and symptoms of intolerance of the drug. Numerous data from the literature describe adverse reactions associated with the administration of IFX. The most common are allergic reactions, with varying degrees of severity – from mild like redness of the skin or tachycardia, through serious – up to anaphylactic shock inclusive. Temporarily interruption or slowing infusion, with antihistamines usually causes resolution of symptoms. In some cases, however, it is necessary to discontinuation drug infusion. Because of these, searching for the new substance, constructed entirely of human aminoacid sequences was taken. Such drug is adalimumab (ADA). It is a recombinant, fully human monoclonal antibody with the immunomodulating activities. It is administered subcutaneously. It is used to induce and maintain disease remission (1, 2, 4, 9-11). Both drugs showed comparable efficacy in the induction of remission. The decision which drug will be use depends on the availability, patient preference and costs of the treatments. In Poland there is treatment program with infliximab for pediatric patients with Crohn's disease paid by the National Health Fund, that is why adalimumab is rarely used, most common in case of intolerance or loss of response to infliximab. However, current ECCO/ESPEGHAN guidelines are putting both drugs equally. Moreover, subcutaneous administration of adalimumab creates the possibility of therapy at home, which is especially important for children, compared to IFX which is administered intravenously and patient must be hospitalized (3). As mentioned above, in Poland therapeutic program for treatment Crohn's disease with adalimumab is still not available (despite the good performance of first-line therapy), that is why treatment with this preparation is possible only within hospital resources and limited to the hospital environment. In addition, an existing therapeutic program allows treatment with infliximab only severe Crohn's disease, with PCDAI above 52 points. Recently, definition of the severity of Crohn's disease in children has been changed. Currently disease with PCDAI above 40 points is considered to be severe and classifying the patient with PCDAI above 52 points indicates that achieving the expected effect of the treatment will be more difficult. Experts call for lowering the criteria for inclusion to the therapeutic program, it is known that due to the long-term course of the disease and its devastating impact, both on the body and psyche of children and young people, each delayed in treatment makes worse prognosis and makes it more difficult to achieve disease remission. However, it didn't reflected for inclusion criteria to the therapeutic program.

Adalimumab is currently the only anti-TNF drug, which has a pediatric registration in all three therapeutic areas: rheumatology (juvenile idiopathic arthritis from 2 y.), dermatology (psoriasis in children and adolescents aged 4 y.) and gastroenterology (Crohn's disease from 6 y.). No other TNF or biological drug with a different mechanism of action don't have confirmed

the efficacy and safety profile in the pediatric population as much as adalimumab.

AIM

The aim of the study was to evaluate the effectiveness of induction and maintenance remission of the disease and safety of adalimumab therapy in pediatric patients with Crohn's disease.

MATERIAL AND METHODS

Therapy with biological drugs is initiated from the 3 induction doses. Cut-off line for adalimumab dose is patient weight of 40 kg. For patients weighing less than 40 kg drug is administered in the regimen 80-40-20 mg/dose/every 2 weeks, patients weighing more than 40 kg respectively 160-80-40 mg/dose/every 2 weeks. It is recommended to administrate each subsequent doses at two-week intervals. When we can observe loss of response to a drug, in practice, decreasing the interval of administration on a weekly injection is possible. To assess the severity of disease and the effectiveness of treatment authors used a PCDAI scale (Pediatric Crohn's Disease Activity Index) and value of laboratory tests – ESR, CRP, hemoglobine, hematocrite, during qualifications for the treatment, at 3 dose in order to assess the induction of remission, after 6 months of treatment and in 3 patients even after 12 months of treatment.

The authors conducted a prospective evaluation of patients treated with ADA in the Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute, between 2012-2014. The analysis included 9 patients (6 girls and 3 boys) with a mean age of 7.35 years (median 7.9 years, range 1-13.7 years) at the time of diagnosis Crohn's disease. The diagnosis was based on the Porto criteria. At the time of enrolment for the therapy with adalimumab patients mean age was 11.8 years (median 11.8 years, range 7-15.5 years). From diagnosis to start current therapy of ADA passed an average of 4.5 years (median 4.3 years). All patients were previously treated with infliximab (IFX) and 3 of them also with adalimumab (ADA). The interval between the previous and the current biological therapy was on average 6.9 months (median 3 months). In 3 patients who were treated in the past with ADA since the end of the previous ADA treatment to start the current passed 15.5 months (median 11.5 months). Disease classification was based on the Paris scale. 4 patients were treated with Azathioprine, 3 with Methotrexate, 7 with mesalazine. Patient characteristics is presented in table 1.

Table 1. Patients characteristics.

Gender	F/M	6 (67%)/3 (33%)
Age – the average (median, range)	At diagnosis	7.35 (7.9; 1-13.7)
	During qualification for the current therapy	11.8 (11.8; 7-15.5)
Classification of the disease – Paris scale	A1a	4 (44%)
	A1b	5 (56%)
	L1	2 (22%)
	L2	4 (45%)
	L3	3 (33%)
	B1	5 (56%)
	B2	2 (22%)
	B3	2 (22%)
Earlier treatment	IFX	9 (100%)
	ADA	3 (33%)
The distance from the previous biological therapy – the average (median)	IFX	6.9 months (3 months)
	ADA	15.5 months (11.5 months)
Concomitant treatment	Azatioprine	4 (44%)
	Metotrexat	3 (33%)
	Mesalazine	7 (78%)

Depending on body weight, patient with weight > 40 kg received a first dose 160 mg of adalimumab (Humira), the second 80 mg, while patients weighing < 40 kg received a starting dose of 80 mg of the ADA. Subsequent doses amounts 40 mg and were administered at intervals of 2-3 weeks. The drug was administered subcutaneously in a hospital. During the administration occurrence or absence of adverse events (AE) were reported and patients informed about all of AE that occur between doses of the drug.

RESULTS

During qualifications for the treatment average value of PCDAI was 13 pts (median 7.5, range 5-55). PCDAI scoring range was very wide. Patients with low PCDAI scores were qualified for the treatment with adalimumab in order to maintain remission of the disease, which was achieved during the previous treatment (surgical/biological) that could not be continued – 2 patients didn't presented a therapeutic effect after treatment IFX, 3 patients experienced parenteral symptoms (joint pain, erythema nodosum, skin changes), 2 patients developed an allergic reaction after administration of IFX. Moreover, five of the patients were treated surgically in the past. The mean (median and ranges) value of laboratory test during qualifications were as follows: ESR – 40.2 mm (34, 17-77); CRP 1.41 mg/dL (0.92, 0.06-2.95); HGB 12.0 g/dL (11.8, 10.9-13.3); HTC 36.3% (35.6, 33.8-39.6). Rating the remission induction was carried out after 3 doses. The average value of PCDAI was 7.2 points (median 5, range 0-17.5), medium (as medians and ranges) value of laboratory tests were as follows: ESR – 21.5 mm (21, 6-40); CRP 0.89 mg/dL (0.48, 0.09-2.66); HGB 12.0 g/dL (12.0, 10.8-14.2); HTC 36.7% (35.8, 33.1-42.5). In the assessment after 6 months of treatment the following results were observed: the average value of PCDAI was

3.3 points (median 3.75, range 0-5), medium (as medians and ranges) of laboratory tests were as follows: ESR – 28.6 mm (28, 5-49); CRP 1.16 mg/dL (0.8, 0.07-2.62); HGB 12.0 g/dL (12.0, 8.8-15); HTC 36.9% (36.3, 29.6-45). After a year of treatment only 3 patients were evaluated, the results were as follows: average value PCDAI was 2.5 points (median 2.5, range 0-5), medium (as medians and ranges) value of laboratory tests were as follows: ESR – 39.3 mm (46, 4-68); CRP 0.38 mg/dL (0.14, 0.06-0.96); HGB 12.9 g/dl (12.2, 11-15.4); HTC 38.6% (35, 35-46.6). Data are presented on the figure 2. An analysis of the nutritional status of patients at the time of acceptance for the treatment with ADA, after 3 doses and after 6 and 12 months of treatment were assessed. We evaluated the value of albumin and BMI. During qualification for treatment the average value of albumin was 41.8 (median 43.2, range 38.0-44.8), mean BMI was 17.6 (median 17.3, range 13.0-21.1). After 3 doses the average value of albumin was 41.1 (median 43.8, range 35.4-45.7), mean BMI was 17.6 (median 18.2, range 12.7-21.2). After 6 months of treatment the average value of albumin was 42.9 (median 43.35, range 37.2-47.2). Mean BMI was 20 (median 20.2, range 16.6-23.1) and after 12 months, the mean albumin was 42.2 (median 42.4, range 39.8-44.5), mean BMI was 20.6 (median 20.6, range 20-21.2). These values are shown in figure 2. Patients are currently treated from an average of 11.7 months (median 7 months, range 3-25 months). In the described groups, only in 1 patient ADA therapy was stopped after 2 dose (no response to treatment and exacerbation of disease [PCDAI during qualifications was scored at 5 points, after 3 dose at 17.5 points]), the remaining 8 patients continue treatment.

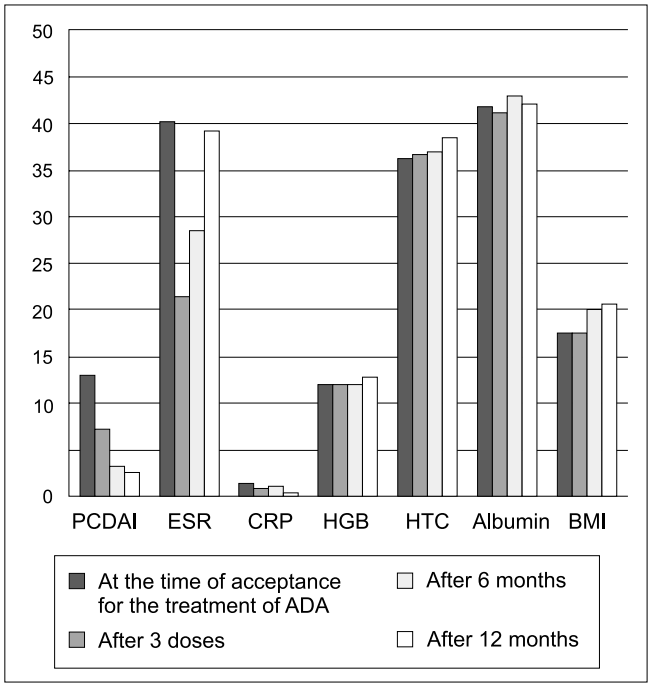

Fig. 2. Values of PCDAI and laboratory tests at the time of acceptance for the treatment of ADA, after 3 doses and after 6 and 12 months of treatment.

During drug administration there were no adverse effects in any patients. Between doses in 2 patients there were no adverse events, in 2 patients occurred upper respiratory tract infections (1 – a viral infection and laryngitis required antibiotic therapy; 1 – respiratory infection after the IV dose, treated with Augmentin, conjunctivitis after VIII dose, chickenpox treated with acyclovir after the IX dose, rotavirus and adenovirus infection after XI dose, exacerbation of disease after dose XI [fever, joint pain, swelling of the knees, elbows, ankles, redness of the skin over the joints, blood in the mucous from anus, around the stoma bullous lesions with purulent discharge, similar changes in other regions of the body]), 2 patients had acute gastroenteritis, 1 patient appeared pain in joints requiring treatment with methylprednisolone administered intra joints and in 1 patient after VI dose developed acute pyelonephritis, which caused a temporary exacerbation of underlying disease. In 2 patients maintained anemia (1 patient on a vegetarian diet).

DISCUSSION

Crohn's disease is a chronic and destructive disease that may affect the entire gastrointestinal tract – from the mouth to the anus. What is characterized, the inflammation is found segmentally. The primary goal of treatment is to induced remission and maintain it as long as possible, primarily through medication. Sometimes patients require surgical procedures to control an inflammation in the intestine. Introduction new drugs to the therapy, especially biologics like IFX and ADA had a significant impact on improving the results of treatment of Crohn's disease. In comparison to infliximab, adalimumab has a similar mechanism of action and effectiveness, but it is a purely human antibody. This is advantage over the IFX, which includes a mouse component and more often can cause allergic reactions (7, 8, 10, 12). The literature is dominated by the trials in the adult population, because adalimumab was registered for pediatric patients several years ago – for many years has been used besides the registration.

Song et al. conducted a meta-analysis of studies evaluating the efficacy and safety of adalimumab therapy in adult patients. The review were included six randomized controlled trials comparing the work with the ADA and placebo. In comparison to placebo, ADA showed higher efficiency in inducing and maintaining long-term remission of the disease in both patients originally included to the biological treatment and patients who stopped tolerate or not responded to IFX. The authors, however, observed that the effectiveness of ADA in patients with prior exposure to IFX was lower, compared to the group who previously did not had biological therapy. The authors thought that less potency of ADA can be the result of longer course and severity of the disease. Also, the time from the loss of response to IFX to include another anti-TNF drug could lead to disease progression. In addition, the above meta-analysis showed that the ADA is more effective compared to placebo in active Crohn's disease with fistulas. Au-

thors analyzed also that, in comparison with placebo, ADA does not increase the risk of AE (4).

In the study IMAGINE, the authors evaluated 192 patients aged 6-17 years with Crohn's disease, according to the scale PCDAI scored > 30 points, in whom conventional treatment did not worked. Induction therapy with adalimumab was conducted – dose 0 and after 2 weeks (patients with body weight > 40 kg received 160 mg and 80 mg, and with body weight < 40 kg respectively 80 mg and 40 mg). At week 4, 188 patients were assigned into two groups according to the clinical response achievement (defined as a decrease of PCDAI about ≥ 15 points from baseline; 82.4% and prior exposure to infliximab 43.6%). Patients were also randomized into two groups according to maintenance treatment with adalimumab in high doses (40 mg or 20 mg per kg of body weight ≥ 40 kg and < 40; n = 93) or low dose (20 mg or 10 mg per kg body weight ≥ 40 and < 40 kg; n = 95) given every two weeks, for 48 weeks. Clinical remission (PCDAI ≤ 10) was assessed in 26 weeks. 152/188 patients (80.9%) completed all 26 weeks of the study. At 26 weeks, 63 patients (33.5%) achieved clinical remission, with no statistically significant difference between the groups receiving high and low dose of the drug (38.7 vs 28.4%; p = 0.075). The authors obtained a similar remission rates in patients treated with adalimumab in monotherapy and in a group that also in treatment schedule received immunomodulatory drugs. This analysis demonstrates the ability to use the ADA in monotherapy, compared to IFX, what is advantage of ADA therapy in terms of the need for long-term therapy. The safety of ADA therapy was also assessed – the authors did not registered serious side events (SAEs) of therapy, also during 5 years follow-up (13).

In the meta-analysis the work which evaluate the safety of the ADA is included. The study was conducted among 1069 adults patients compared with the control group 607 patients receiving placebo. The authors assessed absence of the changes in the place of drug administration, and the symptoms between doses, such as infections, abdominal pain, nausea, sore throat, headaches. There were no significant difference compared to placebo – what shows that ADA does not increase the risk of common side effects. In the study SAEs, like pneumonia, sepsis, tuberculosis, drug-induced lupus, cancer – were observed in 6 patients. In our study, there was no SAEs, although this may be due to the small size of the group (4).

Regarding to pediatric patients Cozijnsen et al., conducted study to assess the efficacy of ADA and to compare the efficacy of treatment with ADA in patients who have lost response to IFX and those who never not answered to IFX. 53 patients enrolled into the study were previously treated with IFX. 12 patients received ADA in monotherapy, rest of the group combined treatment with tiopurines (n = 21), methotrexate (n = 11), steroids (n = 7) or EEN (n = 2). Median follow-up was 12 months (range 5-23). Induction of remission was obtained in 34 patients (64%) after a median 3 months of treatment, and maintained for a further two years in 50% of them. 11 patients (21%) responded to treatment, but did not receive the induction of the remission. 18 patients (34%) randomized to non-responders are patients with primary non-response (n = 4), loss of response to treatment (n = 11) or with the occurrence of side effects which was the reason to discontinuation therapy (n = 3). Adverse events were reported in 21 patients (40%), mostly infections. Only 1 patient experienced a serious adverse event (sepsis, sinusitis and subsequently meningitis). It is worth noting that the majority of patients who did not respond to treatment with ADA are patients who have not responded to IFX therapy, and smaller proportion of these patients were those who had lost response to IFX (10).

It should be also mentioned about the efficacy of ADA in patients with lesions around the anus. Dewint et al. conducted a double-blind randomized trial comparing combination therapy with adalimumab and ciprofloxacin with adalimumab in monotherapy in the treatment of Crohn's disease with fistulas (ADAFI). The authors showed that combined therapy is more effective than monotherapy in achieving closure of fistulas. However, after ending antibiotic therapy, the beneficial effect of initial combination therapy is not retained (14).

In our work, we obtained similar results in the analysis of efficacy and safety of the ADA therapy. 8 patients (89%) received induction of remission, 1 patient (11%) did not respond to the treatment, it is the patient treated in the past with IFX (exacerbation of the disease after 7th doses of IFX) and ADA (exacerbation of the disease after 6th doses). Regarding to side effects, we did not registered any adverse events during administration of the drug, and those which occurred between doses of the drug were not different from events occurring in a healthy population (viral infection). One of the greatest advantages of ADA, as mentioned above, is fact that it is only human antibody that does not cause allergic reactions, it makes these drug safer to use in comparison with IFX. Because of the subcutaneous route of administration, home administration is possible, hospitalization is not required, which is a huge advantage in the pediatric population.

CONCLUSIONS

Adalimumab therapy is an effective and safe treatment for Crohn's disease in the pediatric population. In our study, authors did not observed SAEs during administration, and the AE recorded between administration of doses appear to be similar to those found in healthy populations.

LIMITATIONS OF THE STUDY

An undoubted limitation of our study is the fact that it describes a small group of patients. Still more studies are needed, preferably multicenter, which will be conducted on a large population of pediatric patients.

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