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Cohort profile: pediatric patients with Crohn's disease qualified to biologic therapy

Charakterystyka pacjentów pediatrycznych z chorobą Crohna kwalifikowanych do leczenia biologicznego

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Słowa kluczowe
leczenie biologiczne, choroba Crohna, dzieci, charakterystyka pacjentów

Summary

Introduction. Treatment with modern therapies is an economic problem in every country. Therefore, there are therapeutic programs of National Health Fund (NHF) in Poland which enable to apply such expensive treatment. Currently, Polish NHF programs include biologic therapy with infliximab (IFX) for pediatric patients aged 6-18 years with severe Crohn's disease (CD).

Aim. The aim of this study was to describe the clinical profile of pediatric patients hospitalized in the Department of Gastroenterology, Hepatology and Feeding Disorders, Children's Memorial Health Institute in Warsaw, who have been qualified to biologic therapy with either infliximab (IFX) or adalimumab (ADA).

Material and methods. We have performed a retrospective analysis of 107 children age 13.0 ± 9.3 years diagnosed with CD and treated with IFX and/or ADA within the period of 8 year; time between 2005 and 2013. The data on patient's demographics, including age, sex, and age at disease onset as well as on the course and behavior of CD have been collected.

Results. One hundred and seven CD patients (M: 54, F: 53) aged 13.0 ± 9.3 years were analyzed. Eighty one children (75.7%) received IFX, 26 (24.3%) ADA, and 8 (7.5%) were treated with both agents. Mean disease duration was 5.5 ± 0.83 years. The most frequently found location of lesions was L3 (56.1%). Extraintestinal manifestations were reported in 18 patients (16.8%), and arthralgia/arthritis was the most frequently found condition among them (77.8%). The most frequently found complication were nutritional and growth disorders, observed in 10 patients (9.3%). Mean PCDAI score at qualification was (median±) 52.5]±27.5. Mean SES-SD (median [interquartile range]) score at qualification was 1 (1.0-22.0).

Conclusions. Pediatric patients qualified to biologic therapy have rather severe than moderate course of disease with high PCDAI score.

Streszczenie

Wstęp. Współczesne stosowanie nowoczesnych terapii jest problemem ekonomicznym w każdym kraju. Dlatego też dostępność leków biologicznych w Polsce jest możliwa dzięki programom terapeutycznym prowadzonym przez Narodowy Fundusz Zdrowia (NFZ). Aktualnie w programach terapeutycznych NFZ mieści się terapia infliximabem dla pacjentów pediatrycznych (6-18 rok życia) z ciężką postacią choroby Crohna (CD).

Cel pracy. Celem pracy było scharakteryzowanie pacjentów Kliniki Gastroenterologii, Hepatologii i Zaburzeń Odżywiania IP-CZD kwalifikowanych do leczenia infliximabem (IFX) lub/i adalimumabem (ADA).

Materiał i metody. Przeprowadzono retrospektywną analizę 107 dzieci w wieku 13,0 ± 9,3 lat ze zdiagnozowaną CD i leczonych IFX i/lub ADA na przestrzeni 8 lat, w latach 2005-2013. Analizowane informacje obejmowały dane demograficzne, takie jak wiek, płeć, wiek w czasie diagnozy oraz aktywność kliniczną i postać choroby u pacjentów leczonych preparatami biologicznymi.

Wyniki. Przeanalizowano 107 pacjentów z CD (Ch: 54, Dz: 53) w wieku 13,0 ± 9,3. Osiemdziesięciu jeden przyjmujących IFX (75,7%), 26 (24,3%) ADA i 8 (7,5%) oba leki.

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Najczęstszą lokalizacją była L3 (56,1%). Objawy pozajelitowe odnotowano u 18 pacjentów (16,8%), przy czym najczęstszym z nich było zapalenie/bóle stawów (77,8%). Najczęściej obserwowanymi komplikacjami były zaburzenia wzrastania i niedożywienie u 10 chorych z CD (9,3%). Średni wynik w skali PCDAI przy kwalifikacji wynosił (mediana±] 52,5 ± 27,5. Średni wynik w skali SES-SD przy kwalifikacji wynosił 18 (1,0-22,0).

Wnioski. Pacjenci pediatryczni kwalifikowani do leczenia biologicznego prezentowali raczej ciężki niż umiarkowanie ciężki przebieg choroby z wysoką punktacją w skali PCDAI.

INTRODUCTION

Treatment with modern therapies is an economic problem in every country. According to statistics, an average cost of biologic therapy with anti-TNF-α agents for patients with rheumatoid arthritis is estimated at approximately 45 000 to 60 000 PLN (1). Therefore, there are therapeutic programs of National Health Fund (NHF) in Poland which enable to apply such expensive treatment. However, the NHF registration procedure is very complicated and takes long. Currently, Polish NHF programs include biologic therapy with infliximab (IFX) for pediatric patients aged 6-18 years with severe Crohn's disease (CD). Unfortunately, the NHF qualification – requirements for pediatric patients under 18 years are very strict. To fulfill them, small patient has to score at least 51 points according to Pediatric Crohn's Disease Activity Index (PCDAI). In practice, this means that a child have to be in a very poor condition to have a refunded treatment. Thus, efficacy of therapy is worse and it is difficult to achieve satisfactory outcomes in a short time. Whereas, due to chronic, long-term course of disease and its destructive impact on both patient's constitution and mentality, only early treatment can bring expected results (2, 3). That is why, both experts and practitioners consider the NHF program economically groundless and unjust regarding the patients.

AIM

The aim of this study was to describe the clinical profile of pediatric patients hospitalized at the Department of Gastroenterology, Hepatology and Feeding Disorders, Children's Memorial Health Institute in Warsaw, who have been qualified to biologic therapy with either IFX and/or ADA within the period of 8 years; between 2005 and 2013.

MATERIAL AND METHODS

We have performed a retrospective analysis of patients diagnosed with CD and treated with biologic therapy with either IFX and/or ADA at the Department of Gastroenterology, Hepatology and Feeding Disorders, Children's Memorial Health Institute. The analysis included period of 8 years – between 2005 and 2013. The diagnosis of CD was based on Porto criteria (4). The localization of lesions was described using Paris classification (5) as following: L1 – disease limited to lower small intestine with or without caecum involvement, L2 – any exclusively colonic location between caecum and rectum, L3 – disease of the terminal ileum and any location in colon, and L4a – proximal to ligament of Treitz, and L4b – ligament of Treitz to above distal ileum. The endoscopic features of CD were described using simple endoscopic scoring system for CD (SES-CD) which is based on the score of 0-3 of the following four endoscopic variables: ulcer size, ulcerated and affected surfaces, and stenosis determined in five ileocolonic segments (6).

The data have been collected on the base of both electronic and paper case reports. The database included following informations: age, gender, date of diagnosis, time delay between CD related symptoms and establishing of diagnosis, phenotype and disease location (according to Paris classification), disease clinical course (according to PCDAI), endoscopic features of CD (according to SES-CD), extraintestinal manifestation, and disease complications.

RESULTS

During the period of 8 years, 107 patients (M:F – 54:53, respectively) with CD at the mean age of 13 ± 9.3 years have been treated with biologic agent. Eighty one children (75.7%) received IFX, 26 (24.3%) ADA, and 8 patients (7.5%) were treated with both agents. The most frequently found location of lesions was L3 reported in 60 patients (56.1%), L1 was found in 13 children 9 (12.1%), L2 in 32 (31.8%), and 16 patients (14.8%) had additionally upper disease (L4b). Disease behavior with fistula was found in 10 patients (9.3%), 4 children (3.7%) required surgical intervention because of complicated CD behavior. Extraintestinal manifestations (EIM) were reported in 18 patients (16.8%), and arthralgia/arthritis was the most frequently found condition, observed in 14 children with EIM (77.8%), osteoporosis was noted in 2 child (11.1%), and erythema nodosum in 2 patients (11.1%). The most frequently observed complications in CD patients were nutritional and growth disorders found in 10 children (9.3%), and, anemia reported in 6 patients (5.6%). Mean PCDAI score at qualification was 52.5 ± 27.5 and mean SES-SD score at qualification was 18 (1.0-27.0). Table 1 includes detailed characteristic of children qualified to biologic therapy.

DISCUSSION

Recommendations on the use of biologic therapy for adult patients with CD are precisely established by European Crohn's and Colitis Organization (ECCO) consensus on CD diagnosis and management (7). However, there is no clear and unanimous evidence-based statement on the use of biologic agents for pediatrics.

Table 1. Detailed characteristics of CD patients treated with biologic therapy (n = 107).

Parameter	Characteristic
Gender: – males – females	 54 (50.5%) 53 (49.5%)
Age (years)	13.0 ± 9.3
Mean duration time of disease (years)	8.4 ± 7.3
PCDAI	52.5 ± 27.5
Involved region: – caecum (L1) – left-side (L2) – ileocolon (L3) – upper disease (L4)	 12.1% 31.8% 56.1% 14.8%
SES-CD (ranges)	18 (0;22)
Extraintestinal manifestations (18) – arthralgia/arthitis – osteoporosis – erythema nodosum	 14/18 2/18 2/18
Disease complications – nutritional and grouth disorders – anaemia	 10 (9.3%) 6 (5.6%)

The criteria used in clinical trials depend on individual research protocols, while their use within refunded therapeutic programs is established by country health policy. In both cases patient have to be in poor clinical condition, mostly defined by PCDAI score, and failed other, conventional treatments to get biologic agent. Still, demographic and clinical characteristic of pediatric patients with CD qualified to biologic therapy have not been published so far. Our analysis of 107 children has demonstrated that predominant disease localization was L3, which is also the most frequent localization of CD in general (8, 9). We have not reported the predominance of any sex in analyzed patients, however male predominance is observed in many studies in Europe, North America and Asia, with the male to female ratio by 1.3-1.6 (10, 11). Eighty one patients have received IFX, while 26 ADA. There were also 8 children who have been treated with both agents. In those patients, ADA was administered mainly as a second line biologic therapy, when there was either no response to INF or intolerance to this chimeric antibody observed. The reason for predominance of patients treated with IFX may be that IFX was introduced to pediatrics as the first biologic agent, and therefore has been better studied. Moreover, only IFX is registered in pediatric CD in Poland. ADA is used only in clinical trials. The majority of children qualified to biologic treatment had rather severe than moderate course of disease. Mean PCDAI score in those patients was 52.5, 10 (9.3%) children had CD behavior complicated with fistula, and 4 (5.6%) of them required surgery. This outcomes only confirm the fact that biologic agents are predominately used in most severe cases, as a "rescue" therapy when response to conventional treatment including steroids and immunomodulators is not achieved. Thus, efficacy of therapy is worse and it is difficult to achieve satisfactory outcomes in a short time. Despite, NHF qualification requirements for patients under 18 years are very strict, and a child have to be in a very poor condition to get refunded treatment. It is such a pity, since several trials have shown that early treatment of CD with more aggressive therapy, such as immunomodulators and anti-TNF agents, leads to a superior clinical outcome, including healing of the mucosa (mucosal healing – MH), compared with standard therapy alone (12-14). MH has been indicated to be associated with a reduced risk of complications, and a reduced need for surgeries and hospitalizations (15, 16). In our analysis, the most frequently found disease complications were nutritional and growth disorders (8.4%) and anemia (5.6%), which are typical problems in chronic conditions affecting alimentary tract. Malnutrition results from both impaired absorption and increased energy loss due to chronic inflammatory state. This is particularly important in children, who need special nutritional support. Therefore, according to ECCO guidelines, nutritional treatment is recommended to be the first line therapy for pediatric CD (7). Anemia, a CD complication which reported prevalence varied between 6.2 and 73.7% (17), is caused by intestinal blood loss as well as chronic inflammation. According to current guidelines, intravenous iron supplementation is recommended in management of this complication due to its safety, effectiveness and lack of oral iron supplementation hazards such as intestinal inflammation enhancement and colon carcinogenesis (18). Extraintestinal manifestations were reported in 18 patients (16.8%), and the most frequently reported condition was arthritis/arthralgia, found in 14 (77.7%) of these children. Since IFX has been proved efficient in management of extraintestinal symptoms of IBD (19, 20), it is another clinical situation to consider biologic therapy when poor response to conventional treatment is observed.

CONCLUSIONS

Pediatric patients qualified to biologic therapy have rather severe than moderate course of disease. They are predominantly in poor clinical condition with high PCDAI score and lack of response to other, conventional treatments at qualification to such biologic agent. Moreover, according to NHF therapeutic program, qualification conditions for pediatric patients with CD under 18 years are too strict and should be verified.

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