

Monika Szychta[1], Anna Wiernicka[1], Maciej Dądalski[1], Piotr Landowski[2], Beata Klincewicz[3], Katarzyna Karolewska-Bochenek[4], Grażyna Czaja-Bulsa[5], Elzbieta Jarocka-Cyrta[6], Bartosz Korczowski[7], Malgorzata Sladek[8], Jaroslaw Kierkus[1]

ASSESSMENT OF INDUCTION THERAPY WITH INFLIXIMAB IN CHILDREN WITH MODERATE TO SEVERE ULCERATIVE COLITIS: A MULTI-CENTER STUDY

OCENA TERAPII BIOLOGICZNEJ INFLIKSYMABEM U DZIECI ZE ŚREDNIO-CIĘŻKĄ I CIĘŻKĄ POSTACIĄ WRZODZIEJĄCEGO ZAPALENIA JELITA GRUBEGO: BADANIE WIELOOŚRODKOWE

[1]Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland
[2]Chair and Department of Pediatrics, Pediatric Gastroenterology, Hepatology and Nutrition, Medical University of Gdansk, Poland
[3]1st Chair of Pediatrics, Department of Pediatric Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan, Poland
[4]Department of Pediatric Gastroenterology and Nutrition, Medical University of Warsaw, Poland
[5]Pediatric Nursery Unit of Pomeranian Medical University, Division of Pediatrics, Gastroenterology and Rheumatology of Zdroje Hospital in Szczecin, Poland
[6]Department of Pediatrics, Gastroenterology and Allergology. Medical University of Bialystok, Poland
[7]Department of Pediatrics. State Hospital no 2. Medical College. University of Rzeszow, Poland
[8]Department of Pediatrics, Gastroenterology and Nutrition, Jagiellonian University Medical College, Cracow, Poland

Abstract

The aim of the study: *Assessment of clinical and endoscopic efficacy of induction therapy with infliximab in children with ulcerative colitis.*

Material and methods: *This is a retrospective analysis of medical records of pediatric patients with moderate to severe UC who had received at least one infusion of infliximab in Polish pediatric academic clinical centers from 2003 to 2013. The primary endpoint was clinical remission rate at week 10, (PUCAI score <10 points) while the secondary endpoints were: clinical response rate (>19-points decrease in PUCAI), mucosal response rate (defined as an improvement of the Baron score), and mucosal healing rate (Baron score 0 or 1).*

Results: *44 patients, at mean age of 14±3.9 years, were included into the study. 38 (86%) patients completed induction therapy regimen with infliximab and were finally included into the analysis. Clinical response and remission rates at week 10 there were 36% and 25% respectively. There was significant drop of PUCAI (58.31±15.5 vs. 24.23±23.83) and Baron score (2.63±0.49 vs. 1.44±0.99) at this time point. Mucosal response and mucosal healing rate were 57% and 48% respectively. Infliximab failure defined as non-clinical and non-mucosal response at week 10, occurred in 16 patients. Infliximab-associated adverse events occurred in 3 patients, with all severe hypersensitivity reactions to infliximab.*

Conclusions: *Infliximab induction therapy was safe and effective in Polish moderate to severe UC pediatric patients with 50% rate of mucosal improvement. However, clinical response rate was lower than previously reported.*

Key words: infliximab, ulcerative colitis, children

Streszczenie

Cel: *Ocena kliniczna i endoskopowa terapii biologicznej infliksymabem u dzieci ze średnio-ciężką i ciężką postacią wrzodziejącego zapalenia jelita grubego.*

Materiał i metody: *Retrospektywnie dokonano analizy dokumentacji medycznej pacjentów pediatrycznych ze średnio-ciężką i ciężką postacią wrzodziejącego zapalenia jelita grubego, którzy przebyli leczenie indukujące infliksymabem w akademickich ośrodkach klinicznych od 2003 do 2013 roku. Odpowiedź kliniczną oceniono przy użyciu pediatrycznej skali aktywności choroby (Pediatric Ulcerative Colitis Activity Index – PUCAI). Z kolei do endoskopowej oceny błony śluzowej jelita grubego wykorzystano czterostopniową skalę Baron (wynik 0-3). W 10. tygodniu obserwacji analizowano odsetek pacjentów w remisji klinicznej, którą definiowano jako wynik PUCAI <10 punktów. Ponadto jednoczasowo oceniono: odsetek pacjentów, którzy odpowiedzieli na zastosowane leczenie (obniżenie wyniku PUCAI >19 punktów), odsetek pacjentów z odpowiedzią błony śluzowej jelita grubego na leczenie (definiowaną jako poprawa wyniku w skali Baron w ocenie endoskopowej) oraz odsetek pacjentów z zagojoną błoną śluzową jelita (w remisji endoskopowej – wynik 0 lub 1 w skali Baron).*

Wyniki: *44 pacjentów, w średnim wieku 14±3,9 lat, włączono do badania. 38 (86%) pacjentów ukończyło pełne leczenie indukujące infliksymabem. W 10. tygodniu obserwacji odsetek pacjentów, którzy odpowiedzieli na leczenie wynosił 36%. 25% pacjentów było w remisji klinicznej. Nie obserwowano znaczącego spadku wyniku PUCAI (58,31±15,5 vs 24,23±23,83) oraz wyniku w skali Baron (2,63±0,49 vs 1,44±0,99). Poprawę stanu błony śluzowej jelita grubego stwierdzono u 57% pacjentów. Z kolei 48% dzieci było w remisji endoskopowej (wynik 0 lub 1 w skali Baron). U 16 pacjentów leczenie infliksymabem okazało się nieskuteczne (brak odpowiedzi klinicznej i endoskopowej w 10. tygodniu obserwacji). U 3 dzieci wystąpiły ciężkie reakcje nadwrażliwości po podaniu leku.*

Wnioski: *Terapia biologiczna infliksymabem u dzieci ze średnio-ciężką i ciężką postacią wrzodziejącego zapalenie jelita grubego okazała się skuteczna i bezpieczna. U około 50% pacjentów stwierdzono wygojenie błony śluzowej jelita grubego. 16 (36%) pacjentów nie odpowiedziało na zastosowane leczenie. Odsetek remisji klinicznej (25%) był niższy w porównaniu do wcześniejszych badań.*

Słowa kluczowe: infliksymab, wrzodziejące zapalenie jelita grubego, dzieci

DEV PERIOD MED. 2016;XX,3:205-211

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory condition of the colon characterized by highly variable clinical manifestation in pediatric patients with a 30% to 40% colectomy rate at 10 years. Clinical course of the disease in children tends to be more severe, and extensive disease location is reported in 60% to 80% of all cases [1]. Most patients are successfully managed with conventional therapies including aminosalicylic preparations, steroids, immunomodulators, and calcineurine inhibitors. However, some patients suffer from disabling condition due to ineffectiveness or side effects of the mentioned drugs [2]. Colectomy is the treatment of choice in severe UC refractory to medical therapy but is associated with surgical complications, decreased fertility and psychosocial burdens [3]. In the last decade, infliximab (IFX) has become an alternative option for moderate to severe UC in adult patients with active UC whose disease has not responded to conventional treatment resulted in inducing clinical remission, promoting mucosal healing, and reducing the need for colectomy [4].

Treatment with IFX in pediatric population with UC is limited by small experience. Children with corticosteroid dependency and steroid refractory UC treated with IFX showed a significant increased rate of corticosteroid-free remission and decreased colectomy rate, therefore IFX is recommended as the first line treatment in children [5].

The objective of this study was to examine clinical and endoscopic efficacy of induction therapy with IFX in children with moderate to severe UC.

DEFINITIONS

Induction therapy with IFX was administered 5 mg/kg at 0, 2 and 6 week of the follow-up. Patients found as moderate to severe stage of UC had at baseline (week 0) PUCAI >30 points.

The endoscopic extension of the disease was assessed according to Paris classification, meanwhile the endoscopic severity of the disease was based on Baron scale. According to the Baron system, patients were given a score between 0 and 3 with 0 representing normal mucosa. A score of 1 represented abnormal but not hemorrhagic mucosa. A score of 2 was given for bleeding with light intervention with an instrument of the mucosa but no spontaneous bleeding, while 3 was given to spontaneous bleeding before the instrument was introduced. Endoscopic remission was defined as a Baron Score of ≤1.

Infliximab failure was defined as non-clinical and non-mucosal response at week 10.

MATERIAL AND METHODS

This is a retrospective, cross-sectional study, which included all pediatric patients with moderate to severe

UC, treated with IFX at Polish academic clinical centers for the period of 10 years (2003-2013). Data were collected from the patients' medical records. The inclusion criteria were: confirmed diagnosis of UC (based on medical history, physical examination, laboratory tests, endoscopic examination with biopsy taken from the each segment with histology exam, and radiology), moderate to severe UC, treatment with IFX. All the procedures were reviewed and approved by the Independent Review Board. The patients and their caregivers gave their written informed consent before the start of any procedure.

Clinical disease activity based on the PUCAI score, endoscopy Baron score and laboratory parameters (erythrocyte sedimentation rate – ESR, hemoglobin concentration and platelet count) were determined at baseline and at week 10. The PUCAI score and Baron score were calculated post hoc in some cases based on data from medical records. The primary endpoint of the study was clinical remission defined as a PUCAI <10 points. The secondary endpoints included clinical response defined as a >19-point decrease in PUCAI, mucosal response defined as an improvement of the Baron score, and mucosal healing defined as the Baron score equal to 0 or 1. Patients who have been exposed to IFX therapy and failed to respond are referred to as primary non-responders. Patients who had no clinical improvement after three infusions of IFX were considered as secondary non-responders.

STATISTICAL ANALYSIS

Data were analyzed using Statistica for Windows package (StatSoft, USA). Statistical characteristics of parametric variables are presented as means ± standard deviations (SD), and the characteristics of qualitative and discrete variables as numbers and percentages. Non-parametric variables recorded at weeks 0 and 10 were compared with the Wilcoxon signed-rank test. The differences were considered as statistically significant at $p<0.05$.

RESULTS

Finally, we included 44 patients (23 F and 21 M) into the study. Patients' demographics and clinical characteristic are presented in table I. The mean age at the first IFX infusion was 14±3.9 years. The endoscopic extension of the disease at the baseline, assessed according to Paris classification was: E2 in 11 (25%) patients, E3 in 10 (23%) and E4 in 23 (52%); none of the children presented with E1 UC at the baseline. The severity of the disease at the baseline corresponded to S0 in 7 (16%) patients and to S1 in 37 (84%). One patient (2%) presented with the Baron score 1, whereas Baron score 2 and 3 were recorded in 17 (39%) and 26 (59%) children respectively. Mean PUCAI and Baron score at the baseline amounted 58.8 15.1 points and 2.57 ± 0.55 respectively.

Six patients did not complete the induction regiment with all three doses of IFX. In three cases (6.82%) infusion was stopped due to the early severe drug-related adverse events (within the first hour of IFX infusion in one case, after second infusion in two other patients), in another three cases induction therapy with IFX was discontinued because of primary non-response. Outcomes of patients after IFX induction therapy are presented in the flow diagram (fig. 1).

A total of 11 (25%) patients presented with clinical remission at the 10th week, another 16 (36%) showed clinical response. Mucosal response and mucosal healing were achieved in 25 (57%) and 21 (48%) patients respectively. Mean PUCAI score for 38 patients who completed induction therapy decreased significantly between week 0 and week 10, from 58.31±15.5 to 24.23±23.83 ($p=0.000001$).

The endoscopic severity of UC assessed by Baron score decreased significantly after the induction therapy with IFX from 2.63±0.49 to 1.44±0.99 ($p=0.00001$). Moreover, we observed significant decrease in patients who presented with Baron scores 2 or 3 ($p=0.00001$), and concomitant increase in subjects with Baron scores 0 or 1 ($p=0.00001$). There were missing data regarding endoscopic examination in 4 cases at the 10th week (3 patients with clinical remission and one secondary non-responder). Mucosal response and mucosal healing were achieved in 25 (57%) and 21 (48%) patients, respectively. Lack of mucosal healing [non-responders (n=8) with no improvement in endoscopic evaluation assessed by Baron score] after IFX induction therapy corresponded with clinical active disease. Lack of the response was observed in 5 (11.36%) patients while in 3 (6.81%) patients PUCAI score decreased by 30 points after the third IFX dose (PUCAI=20-35 points). On contrary, among patients with mucosal healing (n=21; Baron 0 or 1) at the 10th week only 2 patients (9.5%) were clinical non-responders with PUCAI score 40 and 45 (fig. 2).

At the 10th week, induction therapy with IFX, resulted in significantly higher hemoglobin concentrations ($p=0.001$), significantly lower erythrocyte sedimentation rate ($p=0.02$) and significantly lower platelet count ($p=0.006$) compared to baseline (tab. II).

Colectomy was performed in 13.6 % (6/44) of IFX treated children, 2 patients were primary non-responders patients, 3 lost the response and in 1 child because of hypersensitivity reaction to IFX (fig. 1).

No delayed adverse drug reactions were observed throughout the course of the study.

DISCUSSION

IFX induction therapy was safe and effective in the analyzed population of children with 50% rate of mucosal improvement. To our knowledge this the first multicenter study considering clinical response and efficacy of IFX in children with UC. However, this was a subject of previous single-center studies [6-9]. Previous studies of pediatric patients with UC showed that the remission rate after IFX treatment reaches up to 38-40% [5]. The remission rate of our patients (25%) was relatively worse compared to those studies.

The optimal determinants of clinical response to the IFX therapy are still not identified. Children with UC lasting shorter than 20 months and individuals who required blood transfusions before IFX introduction

Table I. Characteristics of patients with ulcerative colitis (UC).

Tabela I. Charakterystyka pacjentów z wrzodziejącym zapaleniem jelita grubego.

Characteristics ***Charakterystyka***	**UC**
Patients, n *Liczba pacjentów*	44
Gender (male/female), n (%) *Płeć (chłopcy/dziewczynki), liczba (%)*	21 (48)/23 (52)
Age at first IFX infusion, years (mean ±SD) *Wiek w momencie podania pierwszej dawki infliksymabu-IFX, w latach (średnia ± odchylenie standardowe-SD)*	14±3.9
Duration of the disease, months (mean ±SD) *Czas trwania choroby, w miesiącach (średnia ±SD)*	33.17±27.7 (n=43, 1-132)
Extension of the disease, n (%) *Zasięg zmian zapalnych jelita grubego wg paryskiej klasyfikacji, liczba (%)* E1 E2 E3 E4 Severity of the disease, n (%) *Ciężkość rzutu choroby wg montrealskiej klasyfikacji* UC, *liczba (%)* S0 S1	 - 11 (25) 10 (23) 23 (52) 7 (16) 37 (84)
PUCAI (mean ±SD) *Aktywność choroby wg PUCAI (średnia ±SD)* PUCAI <10, n (%) PUCAI 10-34, n (%) PUCAI 35-64, n (%) PUCAI >65, n (%)	59±15.13 - 3 (7) 20 (45) 21 (48)
Baron score (mean ±SD) *Wynik wg endoskopowej skali Baron* Baron 1, n (%) Baron 2, n (%) Baron 3, n (%) Baron 4, n (%)	2.57 ±0.55 1 (2) 17 (39) 26 (59) -
Previous treatment before IFX therapy, n (%) *Stosowane leczenie przed terapią IFX, liczba (%)* Corticosteroids (Glikokortykosteroidy) Aminosalicylates (Aminosalicylany) Azathioprine (Azatiopryna) Cyclosporine (Cyklosporyna)	 44 (100) 44 (100) 42 (95) 30 (68)
Concomitant medications, n (%) *Towarzyszące leczenie, liczba (%)* Corticosteroids (Glikokortykosteroidy) Amnosalicylates (Aminosalicylany) Azathioprine (Azatiopryna) Cyclosporine (Cyklosporyna)	 37 (84) 43 (98) 30 (68) 7 (15)

SD = standard deviation (*odchylenie standardowe*); PUCAI = Pediatric Ulcerative Colitis Activity Index, *pediatryczna skala aktywności choroby*; E1 = ulcerative proctitis (*zmiany ograniczone do odbytnicy, nie przekraczające zagięcia prostniczo-esiczego*); E2 = distal to splenic flexure (*zmiany położone dystalnie do zagięcia śledzionowego*); E3 = hepatic flexure distally (*zmiany położone dystalnie do zagięcia wątrobowego*); E4 = proximal to hepatic flexure (*zmiany położone proksymalnie do zagięcia wątrobowego*); S0 = never severe (*łagodny*); S1 = ever severe (*ciężki*); IFX = infliksymab.

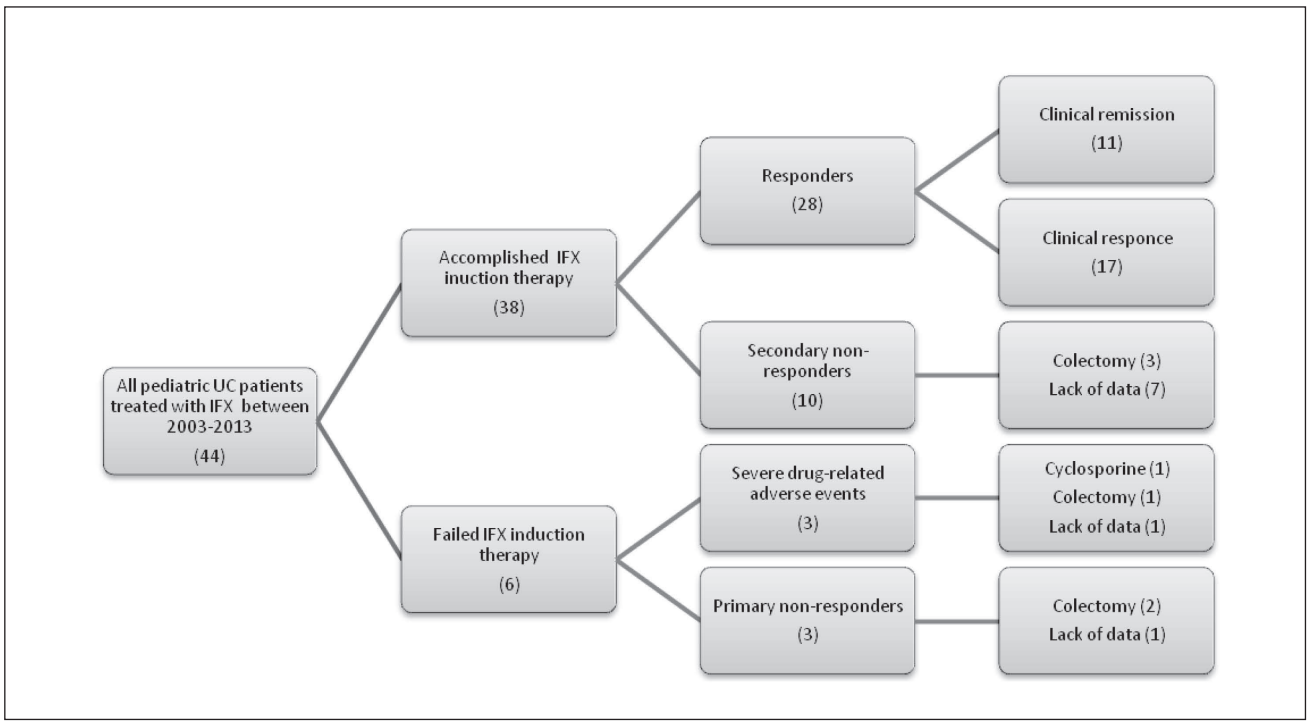

Fig. 1. Flow diagram of patient's follow-up after infliximab induction therapy.

Ryc 1. Schemat obserwacji pacjentów po leczeniu infliksymabem.

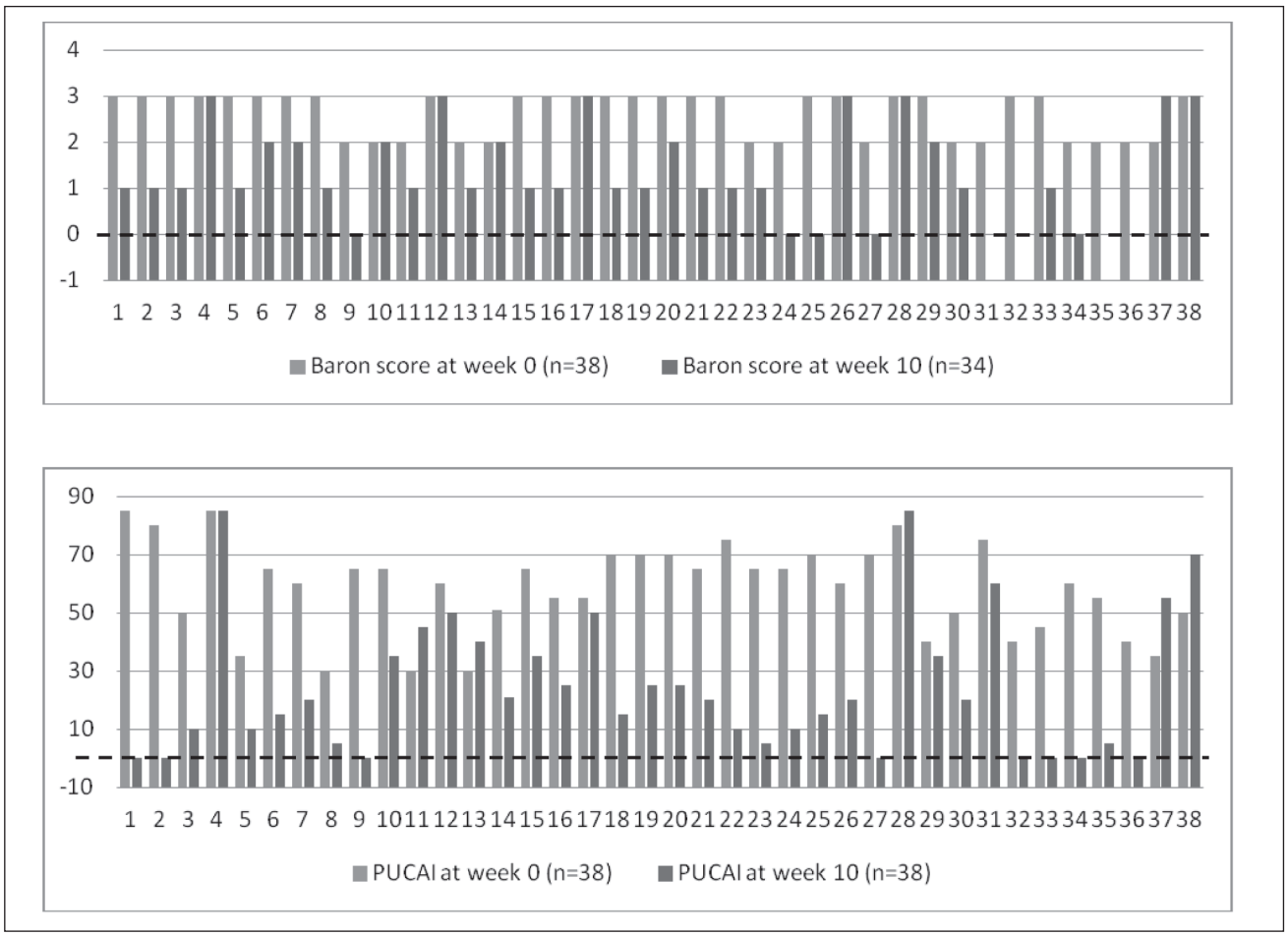

Fig. 2. Comparison of Baron score and Pediatric Ulcerative Colitis Activity Index (PUCAI) at week 0 and at week 10.

Ryc. 2. Porównanie wyników w skali Baron i pediatrycznej skali aktywności choroby (PUCAI) w 0. i 10. tygodniu obserwacji.

Table II. The selected parameters of clinical response at 0 and 10 week of the follow-up.
Tabela II. Wybrane parametry odpowiedzi klinicznej w 0. i 10. tygodniu obserwacji.

Variable	Week 0	Week 10	p-value
PUCAI (mean ± SD) *Wynik wg PUCAI (średnia ± odchylenie standardowe)*	58.31±15.5	24.23±23.83	0.00001
Baron score (mean ±SD) *Wynik wg skali Baron (średnia ± odchylenie standardowe)*	2.63±0.49	1.44±0.99	0.00001
Hb (g/L) *Stężenie hemoglobin (g/l) (średnia ± odchylenie standardowe)*	99±17.8	111±17.0	0.001
ESR (mm/h) *Odczyn Biernackiego – OB (mm/h)*	37±26.57	24±23.46	0.02
PLT (10^9/L) *Liczba płytek (10^9/L)*	455±166.87	362±99.36	0.006

SD = standard deviation (*odchylenie standardowe*); PUCAI = Pediatric Ulcerative Colitis Activity Index (*pediatryczna skala aktywności choroby*); Hb = hemoglobin (*stężenie hemoglobin*); ERS = erythrocyte sedimentation rate (*Odczyn Biernackiego – OB*); PLT = platelets (*liczba płytek*).

may show limited response to this therapeutic agent [10]. Those two parameters are associated with higher rate of colectomies within a year. In our study mean duration of the disease before IFX induction therapy in both analyzed groups was similar and amounted 30.7±22.8 (n=12, range 5-77, lack of data in one case) months in non-responders and 34±21.5 (n=28, range 1-132) in responders group. No correlation was found between shorter duration of disease and limited response to IFX therapy. Among 17 children with disease duration below 20 months there was only 3 (23%) non-responders patients. However, to enlarge chance for positive response to initial IFX treatment higher doses showed should be considered in patients with low body mass index, low albumin concentration and high ESR prior to the introduction of the IFX therapy [11].

UC defined as quiescent, mild, moderate and severe disease can be diagnosed in patients with ESR <23, 23-29, 30-37 and >37 mm/h, and CRP concentrations amounting to <2.5, 2.5-5, 5.01-9 and >9 mg/L, respectively [12]. This observation is in line with our results. However, we showed that endoscopic appearance of UC correlates significantly with either CRP or ESR (0.55 and 0.41 respectively, ($p<0.001$) All the data mentioned above suggest that our patients had higher baseline activity of the disease than those analyzed previously, which may explain lower rate of clinical response.

PUCAI score is a good prognostic parameter for evaluation of remission among children with moderate to severe UC treated with IFX. Remission assessed in endoscopy according to Mayo endoscopic score at week 8 can be seen in 33% of patients with the PUCAI-defined remission and 31% of individuals with the evidence for mucosal healing. [13]. There are several studies concerning the impact of IFX therapy on mucosal healing in polish pediatric IBD patients on endoscopic and histologic level [14]. Our study confirms previous results as mucosal healing was achieved in 48% of patients and 9.5% were clinical non-responders with PUCAI index 40 and 45. Among mucosal non-responders 62.5% patients were also clinical non-responders.

The consensus statement of the European Crohn's and Colitis Organization (ECCO) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) for managing acute severe UC in children does not list endoscopic assessment as a measurement of the response to steroid treatment and second-line therapy [5]. However, the ECCO committee to determine the best outcome measures in pediatric IBD based on a literature review and modified Delphi process established an international expert panel [15]. The experts recognized the importance of mucosal healing and defined steroid-free mucosal healing as a primary outcome measure for all new category drugs with at least one post intervention endoscopy per trial (at weeks 8-12 and/or week 54). The presence of mucosal healing is associated with lower rates of hospitalizations and surgeries [16]. The notion that achieving mucosal healing may potentially change the natural history of the disease and decrease the need for surgery has placed mucosal healing in the center of interest as being the desired treatment target in pediatric CD [17]. However, the role of mucosal healing in preventing progression of the disease has not been clearly demonstrated to date.

The limitation of our study stems from its retrospective character. Moreover, PUCAI index and Baron score were calculated post hoc in some cases based on data from medical records. However, we have included all pediatric patients with UC, who have been treated with IFX since 2003.

CONCLUSIONS

This multicenter analysis confirmed that the induction therapy with IFX is efficient and safe in children with moderate to severe UC and improves mucosal status in about 50% of the cases. The remission rate of our patients (25%) was relatively worse compared to previous studies.

REFERENCES

1. Sawczenko A SB. Presenting features of inflammatory bowel disease in Great Britain and Ireland. Arch Dis Child. 2003;88:995-1000.
2. Kugathasan S DM, Keljo D, Moyer MS, Rufo PA, Wyllie R, Zachos M, Hyams J. Severe colitis in children. J Pediatr Gastroenterol Nutr. 2005;41:375-385.
3. Øresland T BW, Sampietro GM, Spinelli A, Windsor A, Ferrante M, Marteau P, Zmora O, Kotze PG, Espin-Basany E, Tiret E, Sica G, Panis Y, Faerden AE, Biancone L, Angriman I, Serclova Z, de Buck van Overstraeten A, Gionchetti P, Stassen L, Warusavitarne J, Adamina M, Dignass A, Eliakim R, Magro F, D'Hoore A; European Crohn's and Colitis Organisation (ECCO). European evidence based consensus on surgery for ulcerative colitis. J Crohns Colitis. 2015;9:4-25.
4. Lawson MM TA, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006;19:CD005112.
5. Turner D LA, Escher JC, Griffiths AM, Russell RK, Dignass A, Dias JA, Bronsky J, Braegger CP, Cucchiara S, de Ridder L, Fagerberg UL, Hussey S, Hugot JP, Kolacek S, Kolho KL, Lionetti P, Paerregaard A, Potapov A, Rintala R, Serban DE, Staiano A, Sweeny B, Veerman G, Veres G, Wilson DC, Ruemmele FM; European Crohn's and Colitis Organization; European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr. 2012;55:340-361.
6. Mamula P MJ, Brown KA, Hurd LB, Piccoli DA, Baldassano RN. Infliximab as a novel therapy for pediatric ulcerative colitis. J Pediatr Gastroenterol Nutr. 2002;34:307-311.
7. Russell GH KA. Infliximab is effective in acute but not chronic childhood ulcerative colitis. J Pediatr Gastroenterol Nutr. 2004;39:166-170.
8. Tiemi J KS, Sdepanian VL. Effectiveness of infliximab in Brazilian children and adolescents with Crohn disease and ulcerative colitis according to clinical manifestations, activity indices of inflammatory bowel disease, and corticosteroid use. J Pediatr Gastroenterol Nutr. 2010;50:628-633.
9. Hyams J DL, Blank M, Johanns J, Guzzo C, Winter HS, Kugathasan S, Cohen S, Markowitz J, Escher JC, Veereman-Wauters G, Crandall W, Baldassano R, Griffiths A; T72 Study Group. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10:391-399.e1.
10. Mir SA N-SD, Smith EO, Gilger MA, Kellermayer R. Duration of disease may predict response to infliximab in pediatric ulcerative colitis. J Clin Gastroenterol. 2014;48:248-252.
11. Falaiye TO MK, Lu Z, Saville BR, Horst SN, Moulton DE, Schwartz DA, Wilson KT, Rosen MJ. Outcomes following infliximab therapy for pediatric patients hospitalized with refractory colitis-predominant IBD. J Pediatr Gastroenterol Nutr. 2014;58:213-219.
12. Turner D MD, Hyams J, LeLeiko N, Otley A, Markowitz J, Kasirer Y, Muise A, Seow CH, Silverberg MS, Crandall W, Griffiths AM. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or both? A systematic evaluation in pediatric ulcerative colitis. J Crohns Colitis. 2011;5:423-429.
13. Turner D GA, Veerman G, Johanns J, Damaraju L, Blank M, Hyams J. Endoscopic and clinical variables that predict sustained remission in children with ulcerative colitis treated with infliximab. Clin Gastroenterol Hepatol. 2013;11:1460-1465.
14. Wiernicka A SS, Cielecka-Kuszyk J, Dadalski M, Kierkus J. Histological healing after infliximab induction therapy in children with ulcerative colitis. World J Gastroenterol. 2015;21:10654-10661.
15. Ruemmele FM HJ, Otley A, Griffiths A, Kolho KL, Dias JA, Levine A, Escher JC, Taminiau J, Veres G, Colombel JF, Vermeire S, Wilson DC, Turner D. Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee. Gut. 2015;64:438-446.
16. Mazzuoli S GF, Antonelli E, Salemme M, Bassotti G, Villanacci V. Definition and evaluation of mucosal healing in clinical practice. Dig Liver Dis. 2013;45:969-977.
17. Ruemmele FM VG, Kolho KL, Griffiths A, Levine A, Escher JC, Amil Dias J, Barabino A, Braegger CP, Bronsky J, Buderus S, Martín-de-Carpi J, De Ridder L, Fagerberg UL, Hugot JP, Kierkus J, Kolacek S, Koletzko S, Lionetti P, Miele E, Navas López VM, Paerregaard A, Russell RK, Serban DE, Shaoul R, Van Rheenen P, Veereman G, Weiss B, Wilson D, Dignass A, Eliakim A, Winter H, Turner D; European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014;8:1179-1207.

Author's contributions/Wkład Autorów
According to the order of the Authorship/Według kolejności

Conflicts of interest/Konflikt interesu
The Authors declare no conflict of interest.
Autorzy pracy nie zgłaszają konfliktu interesów.

Received/Nadesłano: 08.06.2016 r.
Accepted/Zaakceptowano: 06.07.2016 r.

Published online/Dostępne online

Address for correspondence:
Monika Szychta
Klinika Gastroenterologii, Hepatologii, Zaburzeń Odżywiania i Pediatrii; Instytut „Pomnik – Centrum Zdrowia Dziecka"
Al. Dzieci Polskich 20, 04-730 Warszawa
tel. (22) 815-73-84
e-mail: moniczekg@op.pl

Aldona Wierzbicka-Rucińska[1] Wojciech Jańczyk[2], Agnieszka Ługowska[3], Dariusz Lebensztejn[4], Piotr Socha[2]

DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF CHILDREN WITH LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D). REVIEW OF THE LITERATURE AND OWN EXPERIENCE

DIAGNOSTYKA I POSTĘPOWANIE TERAPEUTYCZNE U DZIECI Z NIEDOBOREM LIZOSOMALNEJ KWAŚNEJ LIPAZY (LAL-D). PRZEGLĄD LITERATURY I DOŚWIADCZENIA WŁASNE

[1]Department of Biochemistry, Radioimmunology and Experimental Medicine
[2]Gastroenterology, Hepatology and Eating Disorders,
Children's Health Memorial Institute, Warsaw, Poland
[3]Department of Genetics, Institute of Psychiatry and Neurology, Warsaw, Poland
[4]Department of Pediatrics, Gastroenterology and Allergology,
Medical University of Bialystok, Poland

Abstract

Lysosomal acid lipase deficiency may present at any age (in infants, children and adults). Its presenting features commonly include elevated serum transaminase activity levels, hypercholesterolemia, fatty liver, progressive liver fibrosis, and cirrhosis. Nonspecific clinical manifestations can lead to a delay in the diagnosis of both children and adults. The early development of fibrosis and cirrhosis suggests that the lysosomal accumulation of cholesterol esters and triglycerides in the liver is a potent inducer of fibrosis. Elevated levels of low-density lipoprotein-cholesterol or low levels of high-density lipoprotein-cholesterol with elevated transaminase activity should raise the suspicion of lysosomal acid lipase deficiency in the diagnostic workup. Still, some patients may not present with abnormal triglyceride and cholesterol concentrations. Early onset LAL-D has a different clinical presentation, with acute symptoms, including liver failure, and can be confused with many other metabolic conditions or with lymphohistiocytosis. The dried blood spot test enables rapid diagnosis and should be widely applied when the cause of liver disease remains unknown.

Key words: lysosomal acid lipase deficiency (LAL-D), cholesteryl ester storage disease, LIPA deficiency, Wolman disease

Streszczenie

Niedobór lizosomalnej kwaśnej lipazy (ang. Lysosomal acid lipase deficiency, LAL-D), może pojawić się w każdym wieku (u niemowląt, dzieci i dorosłych). Objawem choroby często jest wzrost aktywności aminotransferaz, hipercholesterolemia, stłuszczenie wątroby, postępujące zwłóknienie wątroby, a także marskość. Niespecyficzne objawy kliniczne mogą doprowadzić do opóźnień w diagnostyce u dzieci i dorosłych. Enzym LAL uczestniczy w reakcji odłączania kwasów tłuszczowych od triglicerydów i estrów cholesterolu w obrębie lizosomu. Podwyższone stężenie LDL-C (lipoprotein o niskiej gęstości) lub niskie stężenie HDL-C (lipoprotein o wysokiej gęstości) powinny wzbudzić podejrzenia niedoboru lizosomalnej kwaśnej lipazy. Wczesny rozwój LAL-D jest niespecyficzny, może przebiegać z objawami takimi jak ostra