Evaluation of the infliximab therapy of severe form of pediatric Crohn's disease in Poland: Retrospective, multicenter studies

Barbara M. Iwańczak[1, A–F], Józef Ryżko[2, C,E, F], Piotr Jankowski[2, B, C, F], Małgorzata Sładek[3, B, C, E, F], Agata Wasilewska[3, B, C, F], Mariusz Szczepanik[4, B, C, F], Edyta Sienkiewicz[5, B, C, F], Anna Szaflarska-Popławska[6, B, C, F], Sabina Więcek[7, B, C, F], Grażyna Czaja-Bulsa[8, B, C, F], Bartosz Korczowski[9, B, C, F], Jolanta Maślana[10, B, C, F], Franciszek Iwańczak[1, E], Magdalena Kacperska[8, B, C, F]

[1] Department and Clinic of Paediatrics, Gastroenterology and Nutrition, Wroclaw Medical University, Poland
[2] Children's Memorial Health Institute, Warsaw, Poland
[3] Department of Pediatrics, Gastroenterology and Nutrition, Jagiellonian University School of Medicine, Kraków, Poland
[4] Department of Pediatric Gastroenterology and Metabolic Disorders, Poznan University of Medical Science, Poland
[5] Department of Pediatric Gastroenterology and Nutrition, Medical University of Warsaw, Poland
[6] Department of Pediatrics, Allergology and Gastroenterology, Collegium Medicum, Nicolaus Copernicus University of Toruń, Bydgoszcz, Poland
[7] Department of Pediatrics, Medical University of Silesia, Gastroenterology Unit, Upper Silesian Child Health Care Center, Katowice, Poland
[8] Pediatric Nursery Unit of Pomeranian Medical University, Division of Pediatrics, Gastroenterology and Reumatology of Zdroje Hospital, Szczecin, Poland
[9] Department of Pediatrics, State Hospital, Medical College, Rzeszów, Poland
[10] Province Children's Hospital, Kielce, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of article

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Address for correspondence
Barbara Iwańczak
E-mail: barbara@iwanczak.com

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Abstract

Background. Registration of infliximab in Poland has increased chances to induce clinical remission and mucosal healing in the severe form of pediatric Crohn's disease.

Objectives. The aim of this retrospective study was to assess the results and safety of infliximab therapy in the severe form of pediatric Crohn's disease.

Material and methods. The study included 153 children with severe form of non-fistulizing Crohn's disease treated with infliximab. The clinical activity of Crohn's disease was assessed according to PCDAI scale, endoscopic scoring was graded according to SES-CD, body mass was measured with body mass index (BMI). Infliximab was administered at the dose 5 mg/kg body mass in the 0.2 and 6th week, and then, after clinical response, every 8 for the period of 12 months.

Results. One hundred thirty-six children (88.89%) achieved clinical response after induction therapy and 75.21% of children after the maintenance therapy. 39.68% of children achieved remission as graded with endoscopic scoring SES-CD. There was a statistically significant increase in body weight following the treatment. Side effects such as anaphylaxis, rash, and the activation of EBV infection appeared in 9 children at the time of infliximab injection. In other children the drug was well tolerated.

Conclusions. Induction and maintenance therapy with infliximab resulted in clinical remission of Crohn's disease in 75.21% of children, and in the intestinal mucosa healing in 39.68% of children.

Key words: Crohn's disease, infliximab, children

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Crohn's disease (CD) and ulcerative colitis (UC) are classified as inflammatory bowel diseases of unknown etiology and with no causative treatment. Increased incidence of pediatric Crohn's disease together with the constant incidence of ulcerative colitis has been observed during the last decade.[1] Crohn's disease may be diagnosed in people of all age groups, but most frequently in children over the age of 10 years, with its peak incidence occurring between 15–40 years of age. In 25–30% of patients first symptoms appear under the age of 20 years.[1,18,20] In Crohn's disease, inflammatory changes affect full thickness of the bowel wall and occur segmentally with locations that can affect all parts of the gastrointestinal tract from mouth to rectum. The disease course is more severe in children than in adults. Crohn's disease is characterized by greater extension of intestinal lesions, higher incidence of exacerbations, fistulas and perianal changes, inhibited physical and sexual development, loss of body weight and malnutrition.[7,21,23] The primary goal of Crohn's disease treatment is to obtain clinical remission and mucosal healing, physical development and improvement of the quality of life and the normalization of biochemical parameters including the fecal calprotectin determination.[20] Patients are treated with 5-ASA preparations, thiopurine, glucocorticoids, nutritional preparations, antibiotics, biological agents and surgical treatment. Recent guidelines regarding the induction therapy of mild-to-moderate Crohn's disease recommend nutritional therapy, steroids, antibiotics and biopharmaceuticals; whereas in the maintenance therapy thiopurine, methotrexate, and biological therapy are recommended.[20] Early immunosuppressive and biological therapies should be introduced in children that have a high risk of suffering a severe course of the disease which includes: very early age of onset, the presence of deep ulcerations in endoscopic examination, inflammatory changes in the upper gastrointestinal tract, rectum and entire colon, growth delay, severe osteoporosis and the presence of fistulas.[20]

The aim of this study was to present a retrospective evaluation of effects and safety of infliximab therapy in the severe form of pediatric Crohn's disease.

Material and methods

To assess the effects of treatment with inflixamib the authors have invited university pediatric gastroenterology centers and pediatric departments in regional hospitals in Poland, which treated pediatric Crohn's disease in the years 2004–2013. Each center received a personal questionnaire for the biological treatment which included the patient's age, sex, body mass index (BMI), location and manifestation of disease activity, pharmacological, nutritional, and surgical treatment, inductive and maintenance effects of biological therapy with infliximab. The diagnosis of Crohn's disease was based on Porto criteria.[11] However, the location and manifestation of the disease were assessed based on the Paris Classification.[15] The inclusion criteria for the pediatric infliximab treatment was a severe, active form of Crohn's disease measured by the Pediatric Crohn's Disease Activity Index (PCDAI) above 50 pts., the absence of clinical response to previous treatment with corticosteroids, immunosuppressants and nutritional treatment.[8,12] Infliximab was used in the induction treatment at a dose of 5 mg/kg in the 0.2 and 6th week after the first intravenous infusion. Maintenance infliximab therapy was administered to patients with clinical response, i.e. reduced disease activity by < 12.5 points (or more) and PCDAI level below 30 pts. for at least 2 weeks after the third dose of infliximab at doses: 5 mg/kg every 8 weeks (6 doses), together with the induction therapy for the period of 12 months. Clinical remission in Crohn's disease is defined as its activity after the maintenance treatment amounting to ≤ 10 points in the PCDAI scale. The endoscopic activity of the disease was scored before and after the maintenance treatment with infliximab according to SES-CD (Simplified Endoscopic Activity Score for Crohn's Disease). Mucosal healing was defined as 0 pts. according to SES-CD.[3]

In the years 2004–2013, 424 children in Poland were treated with infliximab.[12] Two hundred twenty one (221) completed questionnaires from 10 health-care institutions were submitted in order to assess the results of the treatment of pediatric Crohn's disease. Two hundred eight (208) children were qualified. Out of this number, 153 children were diagnosed with non-fistulizing Crohn's disease, whereas 55 were diagnosed with fistulizing Crohn's disease. Thirteen patients provided in their questionnaires incomplete clinical data and, therefore, they were not included in the final evaluation of treatment (Table 1). In this study the authors have assessed only the effects of treatment with infliximab in 153 children with non-fistulizing Crohn's disease. The effects of treatment of 55 children with fistulizing Crohn's disease are going to be developed separately.

The results were statistically analyzed. Basic descriptive statistics were calculated as an arithmetic mean (x), standard deviation (SD), median. The authors have compared results of clinical (PCDAI) and endoscopic (SES-CD) activity, BMI (body mass index) before treatment and 1 year after treatment with the Student's t-test for dependent samples. The authors have also calculated the correlation

Table 1. Number of children with Crohn's disease in Poland treated with infliximab in the years 2004–2013

Total number of treated children	424
The number of received questionaires treated with infliximab	221 (52.12%)
To the assessment of infliximab therapy were qualified	
a) Crohn's disease without fistulas	153 (69.23%)
b) Crohn's disease with fistulas	55 (24.89%)
c) incomplete data	13 (5.88%)

between PCDAI, SES-CD, BMI with Pearson's correlation coefficient. Results were considered to be statistically significant at $p < 0.05$.

The study was approved by the Bioethical Committee of Wroclaw Medical University.

Results

Characteristics of pediatric patients have been presented in Table 2. Crohn's disease was most frequently diagnosed in children between 10–17 years of age (77.83%). Very young children under the age of 5 years accounted for 4.52% of patients, children between 6–10 years of age accounted for 17.65% patients. The disease duration ranged from 1–84 months, with a mean of 25 months. In 7 cases (3.16%) Crohn's disease or ulcerative colitis were diagnosed in a patient's sibling or a parent. Parenteral manifestation of Crohn's disease was observed in 31 patients (14.03%), and that was most commonly anemia, arthralgia, erythema nodosum, osteopenia; whereas 23 children (10.4%) were diagnosed with other co-morbidities.

Location of inflammation in Crohn's disease has been presented in Table 3. Its most frequent location was terminal ileum and colon (42.97%), colon 14.03%, in 1/3 distal ileum (13.12%). Inflammation was often accompanied by changes in the upper gastrointestinal tract. Manifestation of Crohn's disease has been presented in Table 4. In 128 children (57.92%) Crohn's disease was inflammatory, non-stricturing and non-penetrating, in 38 children (17.19%) structuring, in 37 children (16.74%) penetrating, and in 18 children (8.14%) stricturing and penetrating. Fifty-five (24.88%) children were diagnosed with fistulizing Crohn's disease. Forty (18.1%) children suffered from growth retardation (Table 4).

The effects of induction treatment in 153 children have been presented in Table 5. Clinical response occurred in 136 children (88.89%) after 3 doses of infliximab; clinical improvement has not been observed in 14 children (9.15%); in 3 children (1.96%) treatment has been discontinued due to the anaphylactic shock that occurred during the administration of the second (2 children) and third dose of infliximab (1 child).

The effects of the maintenance treatment were evaluated in 117 children; 36 children did not qualify for further maintenance treatment: 14 children due to lack of clinical response following the induction therapy, 3 children due to the anaphylactic shock. Nineteen patients over the age of 18 years were transferred for further biological therapy in gastroenterology departments for adults.

The effects of maintenance treatment have been presented in Table 6. Clinical remission has been achieved in 88 (75.21%) children, endoscopic remission (0 pts. in SES-CD scale) has been achieved in 25 out of 63 children (39.68%). Eighteen children experienced exacerbated clinical symptoms during the maintenance therapy and 8 children (6.84%) required surgical treatment. Relapse of

Table 2. Characteristics of the children with Crohn's disease treated with infliximab

Assessed parameter	Number of children	
	n	%
Sex: male	118	53.39
female	103	46.60
Age at diagnosis (years) < 5	10	4.52
6–10	39	17.65
11–17	172	77.83
IBD in family	7	3.16
Concomitant disorders	23	10.40
Extraintestinal symptoms	31	14.03

n – number.

Table 3. Localization of Crohn's disease in 221 children treated with infliximab

Location		Number of children	
		n	%
L1	distal 1/3 ileum	29	13.12
L2	colonic	31	14.03
L3	ileocolonic	95	42.97
L4	upper disease	2	0.91
L1 + L4		14	6.34
L2 + L4		15	6.79
L3 + L4		35	15.84
Total		221	100.00

Table 4. Clinical manifestation of Crohn's disease in 221 children treated with infliximab

Behavior of Crohn's disease			Number of children	
			n	%
B1	non-stricturing, non-penetrating		128	57.92
B2	stricturing		38	17.19
B3	penetrating		37	16.74
B4	stricturine and penetrating		18	8.14
P	fistulas	perianal	50	22.62
		other	5	2.26
G0	no evidence of growith delay		181	81.90
G1	growth delay		40	18.10

Table 5. Results of induction therapy in 153 children with Crohn's disease without fistulas

Clinical assessment	n	%
Clinical response	136	88.89
Lack of response	14	9.15
Anaphylactic stock	3	1.96
Total	153	100.00

Table 6. Results of induction and maintenance therapy with infliximab of 117 children with Crohn's disease after 54 weeks of the treatment

Results of therapy	Number of children	
	n	%
Clinical remission	88	75.21
Endoscopic remission	25/63	39.68
Exacerbation of the disease during treatment	18	15.39
Anaphylactic shock (after 4th and 6th dose)	3	2.56
Surgical treatment	8	6.84
Reccurence of the disease before one year after the end of treatment	18/70	25.71
New treatment: • infliximab • adalimumab	 6/18 3/18	 35.29 16.66

Table 7. Comparison of clinical activity (PCDAI), endoscopic activity (SES-CD) and BMI before (I) and after one year (II) infliximab treatment

Assessed parameter	No. of children	Results								p
		I (before treatment)				II (one year after treatment)				
		x	medina	range	SD	x	medina	range	SD	
PCDAI	78	57.66	55	52–85	6.65	9.39	5	0–62.5	14.36	< 0.001
SES-CD	61	14.51	12	1–39	9.9	5.32	3	0–32	7.24	< 0.001
BMI (kg/m^2)	78	17.37	17.05	13.0–30.5	2.91	19.23	20.05	15.80–33.12	2.37	0.008

x – mean; SD – standard deviation.

Table 8. Adverse events in children with Crohn's disease treated with infliximab

Adverse symptoms	Only induction therapy (36 children)		Induction and maintenance therapy (117 children)		Total (153 children)	
	n	%	n	%	n	%
Anaphylactic shock	3	8.33	3	2.56	6	3.92
Generalized rush			1	0.85	1	0.65
EBV infection activation			1	0.85	1	0.65
Increase of blood pressure and tachycardia			1	0.85	1	0.65
Total	3	8.33	6	5.13	9	5.88

disease occurred after 1 year of treatment in 18 out of 70 (25.71%) children, 9 of whom were again subjected to the biological treatment (Table 6).

In Table 7, the authors have compared the results of PCDAI, SES-CD and BMI before and after one-year therapy with infliximab. The authors have reported significantly reduced clinical (PCDAI) and endoscopic (SES-CD) activity of Crohn's disease and statistically significant increased body weight (BMI). However, a comparison of the relationship between measured parameters has shown, with the Pearson correlation coefficient, a statistically significant correlation between PCDAI and SES-CD before ($r = 0.24$, $p = 0.037$) and after the treatment ($r = 0.4$, $p = 0.001$). Side effects such as anaphylaxis, rash, activation of EBV infection, increased blood pressure and tachycardia occurred in 9 children during intravenous infliximab infusion (Table 8). Infliximab was well tolerated in other children. During the treatment patients also received preparations of 5-ASA, azathioprine or methotrexate.

Discussion

Crohn's disease is a chronic inflammation of intestines characterized by a progressive course with periods of remission and exacerbation. The natural course of disease is characterized by inflammation of the intestinal mucosa that gradually covers layers of intestinal walls and leads to fibrosis, stenosis and to the development of fistulas. The course of the disease is more severe in children compared to adults, since lesions are more extensive, and there occur disturbances in growth and puberty; parenteral symptoms complications and surgical interventions appear more often.[6,21] It is assumed that early onset of the disease increases the possibility of its severe progressive course. Diagnosis of severe Crohn's disease in children under the age of 5 years may be associated with genetic disorders[5,15] Disorders of IL-10 mutation or its receptor, as well as other genetic disorders[6,15,18,20] have been reported in the youngest children. The authors have reported that

Crohn's disease was most frequently diagnosed in children over 10 years of age (77.83%). Children under 5 years of age accounted for 4.52%, and aged 6–10 years for 17.65% (39) of all respondents. More boys were sick compared to girls (53.39% vs. 46.60%). These results are consistent with what other authors have reported.[1,20]

5-ASA preparations, glucocorticoids, immunomodulators, nutritional therapy, antibiotics, anti-TNF-α preparations and surgical treatment are used in Crohn's disease treatment. These are non-specific anti-inflammatory drugs. They inhibit the formation and the release of inflammatory mediators, reduce the number of cells and inhibit the activity of a body's defense cells. Corticosteroids are characterized by rapid onset of action and the induction of clinical remission. In mild-to-moderate activity of pediatric Crohn's disease with the ileocaecal location to induce remission, topical budesonide, rather than systemic glucocorticosteroids treatment, can be administered. However, corticosteroids should not be used in therapy that maintains disease induction, because they do not lead to mucosal healing. Azathioprine, 6-mercaptopurine and methotrexate are important drugs maintaining disease remission. Preparations of 5-ASA should be used only in patients with a very mild form of Crohn's disease.[20] Methotrexate is recommended in maintenance treatment of children with a severe course of disease with unfavorable prognostic factors following unsuccessful thiopurine therapy.[20]

Recently, the main goals of treatment have changed. Currently, the primary objective of treatment is not only clinical remission, improved nutrition, growth and quality of life, but above all, induction of mucosal healing, i.e. deep mucosal remission (DR-deep remission).[20] These results can be achieved with the total enteral nutrition (exclusive enteral nutrition – EEN) for the period of 6–8 weeks, with thiopurines or biological therapy.[20] Different types of the treatment mentioned above have been administered to children. Due to the relapse of disease or the lack of improvement after the treatment and the severe active course of the disease, children with the PCDAI scale activity exceeding 50 pts. were included in the biological therapy with infliximab. Infliximab is the first biological drug approved by the US Food and Drug Administration (FDA), and then it got approval in Europe and Poland for the treatment of Crohn's disease and ulcerative colitis. Infliximab is an IgG1 monoclonal antibody directed against tumor necrosis factor (TNF-α-Tumor Necrosis Factor). It is a human-mouse chimeric antibody with high affinity to both soluble and trans-epithelial form of TNF-α. Infliximab has been approved in Poland for the treatment of severe active form of pediatric Crohn's disease (PCDAI > 50 pts.) in patients aged 6–17 years, not subjected to typical treatment, or after the presence of contraindications or intolerance symptoms or resistance to used medications.[12] As this study has shown, infliximab was also, following the consent of the regional Bioethics Committees, used in the youngest children with severe course of disease despite registration recommendations.

Many studies have demonstrated the efficacy of biological therapy, thiopurines, nutritional therapy both in the induction and in maintaining remission, and in the mucosal healing.[2,4,5,7,9,10,13,16,17,22] D'Haens et al.[17] have reported that treatment with infliximab and azathioprine is more effective in inducing mucosal remission compared to glucocorticoid.[17] Another study has proven that treatment with infliximab in combination with azathioprine is much more effective compared to treatment with azathioprine only, and patients with the mucosal healing required fewer hospitalizations and surgical treatment.[2,16,20] Treatment with infliximab in the induction and in maintaining remission has been effective. Height gain and the possibility to reduce corticosteroids doses could be observed in patients. In the 54th week of treatment infliximab was more effective at a dose of 5 mg/kg every 8 weeks than every 12 weeks. Hyams et al. confirmed the efficacy of infliximab treatment in the course of a 3-year follow-up.[10] Withdrawal of glucocorticoids was possible in most children. Ruemmele et al. in their studies confirmed clinical efficacy, tolerability and the safety of infliximab.[19] They achieved clinical remission in 83% of children using intravenous infusions every 8 weeks. Kierkuś et al. have demonstrated the efficacy of infliximab in clinical remission and mucosal healing in children. Assessing results of induction therapy with infliximab in 66 children in the 10th week of the treatment, the authors have achieved clinical remission in 33%, clinical response in 39%, and mucosal healing in 22.7%. Only 28% children did not respond to treatment with infliximab. In another study, the authors have analyzed results of treatment with infliximab maintaining the clinical remission with or without azathioprine. They have not obtained statistically significant differences in maintenance treatment between the two groups of sick children.[14]

These results are comparable to the results from other studies. Following one year of infliximab therapy, the authors received clinical remission in 75.21% of children, and endoscopic remission in 39.68% of children. Moreover, the nutritional status of children has improved and statistically significant weight gain has been reported following one year of therapy with infliximab. Infliximab was generally well tolerated. Side effects such as anaphylaxis, urticaria, and activation of EBV infection appeared in 5.88% of children. In the remaining children, the drug was well tolerated.

Despite prior ineffective immunosuppressive therapy, the authors proved the efficacy of induction therapy and the infliximab therapy maintaining remission of the disease in the treatment of severe pediatric Crohn's disease. Apart from clinical remission of disease, the authors have reported mucosal healing, improvement in nutritional status, and, thus, better quality of life of pediatric patients. Infliximab was safe and well tolerated in the majority of them.

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