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Induction and Maintenance Infliximab Therapy for the Treatment of Crohn's Disease with Perianal Fistulas in Children: Retrospective, Multicenter Study

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Abstract

Background. Infliximab is a biological drug used for the treatment of Crohn's disease in children.
Objectives. The aim of this retrospective study was the estimation of effectiveness and safety of infliximab in the treatment of Crohn's disease with perianal fistulas in children.
Material and Methods. Analysis comprised 50 children with Crohn's disease with perianal fistulas aged 9 to 18 years (16 girls and 34 boys) who failed to respond to conventional therapy. The children were divided into two groups: the first group contained 23 children with simple fistulas and the second – 27 children with complex fistulas. All children were treated with infliximab, administered in the dose of 5 mg per kilogram of the body mass. In the induction phase infliximab was administered at weeks 0, 2 and 6 and after clinical response in maintenance phase the drug was administered every 8 weeks; together for 12 months.
Results. In 76% of children after induction therapy with infliximab and in 71.87% after maintenance therapy the complete closure of fistula occurred. During the first year after the treatment a recurrence of a fistula was observed in 30.43% of the children. In two children anaphylactic shock was observed during injection of infliximab. The remaining children tolerated the drug well.
Conclusions. The treatment with infliximab was effective in the majority of fistulazing Crohn's disease and caused the closure of perianal fistula which improved quality of life (**Adv Clin Exp Med 2016, 25, 3, 523–530**).

Key words: Crohn's disease, perianal fistulas, infliximab.

Crohn's disease is a chronic inflammatory disease which can affect each part of the gastrointestinal system. Observed changes are segmental, comprise the whole intestinal wall and may lead to such complications as fibrosis, strictures and fistulas. Children older than 10 years are affected most frequently. In 25% of all cases the disease begins in patients who are younger than 20 years [1–3]. The disease in children is characterized by abdominal pain, chronic diarrhea, bloody stools, fever, arrest of the growth and sexual development as well as perianal changes with abscesses, fistulas and extraintestinal symptoms [4–5]. According to Keljo et al. [6] frequency of perianal changes such as skin tags, fissures, fistulas, abscesses and rectal strictures ranges from 13.6% to 62%. Palder et al. [7], in analysis of Crohn's disease in 325 children, observed that perianal changes had developed in 62% of them. The most frequent were: fissures (in 185 cases, 51%), skin tags in 114 children (35%), fistulas in 41 children and rectal abscesses in 47 children. According to Eglinton et al. [8] the risk of perianal changes development in the course of Crohn's disease in children is 26.5%. Genotype analysis revealed a link of the risk with neutrophil cytosolic factor 4 (NCF4) gene compared with both non- and perianal Crohn's disease patients. Other authors demonstrated the link of the development of fistulas in Crohn's disease with such genes as IRGM (immunity related guanosine triphosphatase protein type M) and OCTN (carnitine, organic cathion transporter) localized on chromosome 5q31 (IBD5) [9–11]. Inflammatory process within intestinal wall in patients with Crohn's disease may lead to delamination of it and creation of fistula. Fistulas can be present between large intestine lumen and the skin in the perianal area; less frequently skin of abdomen, between intestinal lumen and urinary bladder or vagina and between the large and small intestinal loops. Disturbed drainage of inflammatory content of the fistula leads to congestion and to creation of an abscess.

Clinical course of Crohn's disease with perianal changes depends on the type of changes, the presence of a rectal or anal stricture, which occur as a consequence of long-term inflammation. Anal fistulas are completely curable, condylomata are usually of mild character and partially diminish during treatment. Non-inflammatory condylomata are not painful and do not require treatment; moreover, they should not be removed surgically since they heal poorly and reoccur. In the patients with uncertain diagnosis, speciments from condylomata can be sampled and examined for granulomas, which are present in 30% of the patients with Crohn's disease. Treatment of fistulas is most difficult which in turn may lead to constipation, stool incontinence, recurrent infections and sepsis as well as to a decrease in life quality and surgery [6, 12].

Fistulas can be divided into simple and complex [13]. Simple fistuals are localized predominantly closer to the margin of the anus, have short canal and there is no abscess present. Complex fistuals may be numerous, branched, they are accompanied or not by the abscess and their external orifice is localized further from the anal orifice. Treatment of fistulas involves antibiotics, thiopurines, metotrexate and biological drugs as well as surgical treatment. Up to 50% of fistulas that are superficial and limited to the anal canal is self-healing. Contrary, complex fistulas, both with or without abscess, vaginal, recto-vesical and interloop fistulas are difficult to treat and very frequently require surgical treatment. Various scales of activity and classifications have been used in Crohn's disease with fistulas; they evaluated not only the activity of fistulas but also other perianal changes [14–18]. Present et al. [19] described simple and reliable scale of activity of fistulas in Crohn's disease. In that scale they took into consideration the closure of the fistula and improvement or remission. Lack of exudation during a gentle push of the vicinity of fistula has been regarded as the closure. Improvement has been defined as the closure of more than 50% of fistulas which were present at the initial point or decrease of mucous secretion. Remission has been defined as the closure of all fistulas which persisted at least during two visits of the patient. National Health Fund therapeutic program of treatment of Crohn's disease with fistulas in children aged 6 to 18 years includes treatment with infliximab in all patients who have not responded to antibiotics, immunosuppressive drugs and surgical treatment regardless to disease activity [21].

Objective

The objective of this retrospective study was to estimate the efficiency and safety of the treatment with infliximab of Crohn's disease with perianal fistulas in children who have not responded to conventional therapy.

Material and Methods

From the multicenter study on the treatment with infliximab of children with Crohn's disease conducted in the years 2004–2013 in Poland, a group of children with fistualas was selected [21, 22]. Two hundred twenty one individual patients questionnaires were collected from 10 centers in which the treatment with infliximab

Table 1. Localization of 55 fistulas in Crohn's disease in 221 children

Fistula localization	No. of children	
	n	%
Perianal fistulas	33	60.00
Perianal fistulas and abscess	17	30.90
Ileocutaneous fistula	2	3.64
Interloop fistula	1	1.82
Rectovaginal fistula	1	1.82
Recto-vesical fistula	1	1.82
Total	55	100.00

was conducted. In 55 (24.88%) children from this group fistulas were present; in 22.62% – perianal fistulas and in 2.25% – fistulas with other localization. The results of the treatment with infliximab of 153 children with Crohn's disease without fistulas were described in another paper [22]. In this study we analyzed the treatment with infliximab of 50 children with Crohn's disease with simple and complex fistulas. In 33 out of 55 children (60%) perianal fistulas were present, in 17 (30.9%) perianal fistulas with an abscess and in same cases intestine interloop, to the vagina or to the urinary bladder (Table 1).

Diagnosis of Crohn's disease was based on Porto Criteria [23]. Beside these criteria in 16 patients the diagnosis was confirmed by MR enterography, in four by enteroclysis and in two – by fistulography. In four children the rectal structure was observed. In all 50 children with Crohn's disease inflammatory changes were localized in the ileum and colon. According to National Health Fund recommendation, the criterion of qualification to the treatment with infliximam program was the presence of fistula independently of Pediatric Crohn's Disease Activity Index), age of patients from 6 to 18 years and failure to respond to previous treatment with antibiotics, immunosuppressive drugs as well as failure of surgical treatment [21]. All the children in our study aged from 9 to 18 years were divided into two groups. 23 children with simple fistuals were assigned to the group I, and 17 children with complex fistulas to the group II. Complex fistulas, branched or with accompanying abscess were relatively common.

In the induction phase of the treatment infliximab was given in the dose 5 mg/kg of body mass at weeks 0, 2 and 6. All children in whom clinical response was observed, meaning that the clinical activity of disease decreased or fistula closed, were given maintenance therapy: 5 mg/kg of infliximab, every 8 weeks for the period of 12 months. In all patients clinical activity of the disease was assessed before and after the treatment using PCDAI. In 38 children C-reactive protein (CRP) concentration was measured, in 33 children endoscopic activity was assessed according to Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) and in 44 children Body Mass Index – BMI was calculated [24, 25].

All results were subjected to statistical analysis. In descriptive part the means and standard deviations were calculated. The results of the treatment in the groups with simple and complex fistulas were compared using χ^2 test and the significance of difference between groups before and after the treatment of dependent data of clinical activity (PCDAI, CRP, SES-CD, BMI) was assessed by *t*-student test. Correlation between PCDAI, CRP and SES-CD were assessed using Pearson's correlation test. All differences were regarded as statistically significant when p-value was smaller than 0.05. STATISTICA 10PL package was used in all statistical calculations. Approval from the Wroclaw Medical University Bioethical Commission was obtained to conduct the study.

Results

Table 2 presents the characteristics of treated children. Crohn's disease with fistulas was diagnosed more frequently in boys than in girls: 34 (68%) vs. 16 (32%) ($p < 0.05$). Only two children were younger than 10 years, the remaining 48 children were 10 to 18 years old. The duration of the disease ranged from 1 to 60 months (16.09 ± 15.71 months). In 12 patients concomitant diseases or extraintestinal diseases were observed. A brother of one of our patients was also diagnosed with Crohn's disease. In 11 children (22.0%) growth retardation was observed and in 4 (8.0%) sexual development was also retarded. Any statistical differences between children with simple and complex fistulas were observed.

Results of induction therapy are presented in Table 3. In 38 children (76.0%) the closure of fistula was observed and in 4 partial improvement (decrease of exudation). Lack of improvement was observed in 6 children (12.0%) and in 2 children (4%) an anaphylactic shock occurred during infusion of infliximab. In one child varicella infection appeared during the treatment. In 2 children reoccurrence of fistula was observed after third dose of infliximab. There were no statistical differences in the treatment results between children with simple and complex fistulas.

Results of induction and maintenance treatment in 32 children are presented in Table 4.

Table 2. Characteristics of the 50 children with perianal fistulas in Crohn's disease treated with infliximab

Parameter	No. of children treated with infliximab						
	total		simple fistulas 23 children		complex fitulas 27 children		p-value
	n	%	n	%	n	%	
Sex: males females	34 16	68.0 32.0	17 6	73.91 26.08	17 10	62.96 37.03	ns.
Age (years): < 10 10–18	2 48	4.0 96.0	1 22	4.34 95.62	1 26	3.70 96.29	ns.
Inflammatory bowel diseases in family	1	2.0	1	4.34	0		–
Concommitant diseases	5	10.0	2	8.69	3	11.11	ns.
Extraintestinal manifestations	7	14.0	3	13.04	4	14.82	ns.
Growth retardation	11	22.0	6	26.08	5	18.51	ns.
Sexual development retardation	4	8.0	2	8.69	2	7.40	ns.
Duration of disease (1–60 months)	x ± SD	16.09 15.71		16.34 15.64		15.85 15.78	ns.

ns. – statistically not significant.

Table 3. Results of induction infliximab therapy in 50 children with perianal fistula in Crohn's disease

Clinical assessment	No. of children treated with infliximab						p-value
	total (50 children)		simple fistulas (23 children – 46%)		complex fistulas (27 children – 54%)		
	n	%	n	%	n	%	
Closure of fistula	38	76.0	18	78.26	20	74.07	ns.
Partial improvement	4	8.0	1	4.34	3	11.11	ns.
Lack of imrpovement	6	12.0	3	13.04	3	11.11	ns.
Anaphylactic shock	2	4.0	1	4.34	1	3.70	ns.
Relapse of disease after 3rd dose of infliximab	2	4.0	1	4.34	1	3.70	ns.

ns. – statistically not significant.

In 23 children (71.78%) the closure of fistula was observed; in 4 children (12.5%) partial closure occurred. In 5 (15.62%) children reoccurrence of fistula during maintenance treatment was observed and 17 children had to be surgically treated due to fistula or abscess. During one year after completion of the treatment, reoccurrence of fistula was observed in 7 out of 23 children (30.43%). Comparison of children with simple and complex fistulas demonstrated a statistical difference only in the number of surgeries which was greater in the case of complex fistulas.

Analysis of clinical activity of Crohn's disease in children with simple or complex fistulas demonstrated a statistically significant decrease of clinical activity and concentration of CRP after induction and maintenance therapy as compared to the start of therapy. Endoscopic activity of the disease also decreased after 12-months treatment and BMI increased (Table 5).

Comparison of PCDAI, CRP, endoscopic activity and BMI between children with simple fistula and children with complex fistula did not show a statistically significant difference (Table 6).

An analysis of correlations between assessed parameters demonstrated a connection between the age of patients and BMI. BMI increased together with age both in children with simple and with complex fistulas. A positive correlation was also observed between disease clinical activity (PCDAI), endoscopic activity (SES-CD) and CRP during the first examination before introduction of infliximab therapy. Along with the increase of PCDAI endoscopic activity and CRP in children with simple and complex fistulas were also increasing.

Table 4. Results of induction and maintenance infliximab therapy in 32 children with perianal fistula Crohn's disease

Clinical assessment	No. of children treated with infliximab						p-value
	total (32 children)		simple fistuals (14 children)		complex fistulas (18 children)		
	n	%	n	%	n	%	
Closure of fistula	23	71.87	10	71.42	13	72.22	ns.
Partial closure	4	12.5	1	7.14	3	16.66	ns.
Reccurence of fistula and/or abscess during maintenance treatment	5	15.62	3	21.42	2	11.11	ns.
Surgical treatment (fistulas, abscesses)	17	53.12	1	7.14	16	88.88	< 0.05
Reccurence of fistula within one year after treatment	7/23	30.43	3/10	30.00	4/13	30.76	ns.

Table 5. Comparison of clinical activity (PCDAI), endoscopic activity (SES_CD), CRP and BMI in children with Crohn's disease with simple and complex fistulas treated with infliximab (I – before treatment, II – after induction treatment, III – after maintenance treatment

Parameter	Simple fistulas						Complex fistulas					
	duration of treatment			p-value			duration of treatment			p-value		
	I x ± SD	II x ± SD	III x ± SD	I/II	I/III	II/III	I x ± SD	II x ± SD	III x ± SD	I/II	I/III	II/III
PCDAI	47.00 ± 17.04	11.73 ± 9.60	6.15 ± 8.01	0.001	0.001	ns.	44.59 ± 18.26	10.92 ± 9.56	7.50 ± 9.70	0.001	0.001	ns.
CRP	35.82 ± 50.28	5.27 ± 13.41	0.99 ± 1.70	0.01	0.001	ns.	19.31 ± 20.20	3.50 ± 5.63	3.04 ± 5.12	0.004	0.004	ns.
SES-CD	10.72 ± 5.95	–	1.63 ± 2.97	–	0.001	–	9.23 ± 4.93	–	2.76 ± 4.24	–	0.001	–
BMI	18.10 ± 2.74	–	19.81 ± 3.49	–	0.003	–	18.76 ± 3.49	–	20.51 ± 3.46	–	0.001	–

Table 6. Comparison of clinical activity (PCDAI), endoscopic activity (SES_CD), CRP and BMI in children with Crohn's disease with simple and complex fistulas treated with infliximab (I – before treatment, II –10 weeks of treatment, III –54 weeks of treatment

Parameter		Simple fistulas	Complex fistulas	p-value
		x ± s	x ± s	
PCDAI:	I before treatment	47.00 ± 17.04	44.59 ± 18.26	ns.
	II 10 weeks	11.73 ± 9.60	10.92 ± 9.56	ns.
	III 54 weeks	6.15 ± 8.01	7.50 ± 9.70	ns.
CRP:	I before treatment	34.38 ± 49.37	19.31 ± 20.20	ns.
	II 10 weeks	5.01 ± 13.10	3.50 ± 5.63	ns.
	III 54 weeks	0.99 ± 1.70	3.04 ± 5.12	ns.
SES CD:	I before treatment	11.84 ± 6.08	9.23 ± 4.93	ns.
	III 54 weeks	1.63 ± 2.97	2.76 ± 4.24	ns.
BMI:	I before treatment	18.26 ± 2.74	18.76 ± 3.49	ns.
	III 54 weeks	19.90 ± 2.92	20.51 ± 3.46	ns.

Discussion

Crohn's disease is a chronic inflammatory disease of the intestines without an elucidated etiology. It is characterized by periods of remission and relapse. Its chronic inflammatory activity leads to the creation of fistulas and abscesses which in children can be sometimes observed at the time of disease diagnosis. Clinical course of the disease which begins in childhood is particularly severe; the disease is localized most frequently in the terminal part of the ileum and colon and frequently leads to fistulas localized mainly in the perianal area. Therefore, the main objective of disease management should be long-term remission and prevention of complications such as intestinal constriction and fistulas, limitation of hospital admissions and surgical procedures as well the improvement of life quality. Commonly used drugs such as azathioprine, 6-mercaptopurine and methotrexate may slightly diminish the risk of complications and delay them only in some cases. Biological treatment with TNF-alfa inhibitors improve the condition of intestinal mucosa, and diminish the number of hospital admissions and surgeries [20, 26]. The results of the treatment of fistulas are also improved [6, 13, 17, 19, 27–31]. However, there is a lack of credible studies on the prevention of fistulas in Crohn's disease in children.

Our analysis demonstrated that Crohn's disease with fistulas was present in 96% of children older than 10 years. Only in two children the disease was present at the age of 9–10 years. Boys were affected more frequently than girls (68.0% vs. 32.0%, $p < 0.01$) and the duration of Crohn's disease ranged from 1 to 60 months (average 16.09 ± 15.71 months). There were no significant differences between the age and duration of the disease between children with simple and complex fistulas.

Healing of abscess and closure of fistula are the principal goals of the management of Crohn's disease with fistulas. The presence of abscess, both superficial and deep, usually requires a surgical incision, drainage as well as antibiotics, immunosuppressants or monoclonal antibodies anti-TNF-alfa. Good results were obtained by the means of antibiotics: metronidazol and ciprofloxacine [32]. Korelitz et al. [33] and Kirschner et al. [34] demonstrated positive results of the treatment with 6-mercaptopurine and azathioprine in adults. Great expectations are connected to biological treatment. Numerous authors analyzing the results of infliximab therapy in adults with Crohn's disease observed that in more than a half of the patients fistulas were completely closed after induction therapy; slightly worse results were seen after maintenance therapy [19, 27, 29, 30, 35, 36]. Crandall et al. [37] obtained good results with infliximab in treating Crohn's disease with fistulas in children at 54th week of the treatment. In 16 (73%) children they obtained a clinical response; from these children in 15 a complete closure of fistula was observed and in one child – partial closure. We obtained similar results. After a year of the treatment in 71.87% a complete closure of fistula was observed and in 12.5% – partial closure. In 30.43% of the children reoccurrence of fistula was observed. Other authors also describe good results of the treatment with infliximab of fistulas in children [38, 39]. De Ridder et al. [39] obtained a long clinical response in 56% of the patients. Retrospective review of literature demonstrated that in 70% of the patients treated with infliximab fistula was closed within three months. In another study the authors assessed both strategies: "top down" vs. "step up" [40]. In children with fistulas treated with infliximab with "top down" strategy, at 8th week a complete closure of the fistula was observed in 58% of the children and only in 17% with "step up" strategy. After a year of treatment with infliximab fistulas were closed in 50% of patients in "step up" strategy compared to 100% in "top down" [40]. However, these interesting results are based on a small number of patients. It is worth noting that ECCO experts do not recommend anti-TNF-alfa drugs as the first line drugs in monotherapy. Concomitant use of thipurines, antibiotics and surgical treatment is required [1, 26].

In the assessment of the treatment, not only the lack of exudation from the fistula, which can be a sign of external orifice closure, but also a meticulous assessment of the canal of fistula is important. Frequently, despite the lack of exudation from the fistula, its canal remains intact and the activity of the fistula returns after the completion of treatment, which was frequently observed in children treated by us. MRI and transrectal ultrasound study may be helpful in the assessment of treatment [13, 42].

In the summary it should be emphasized that in 24.8% of children with Crohn's disease fistulas, mainly perianal, were present. Fistulas were observed most frequently in boys older than 10 years. Among perianal fistulas 46% were simple fistulas and 54% – complex fistulas, often with the presence of an abscess. Induction and maintenance therapy with infliximab confirmed its efficiency in the treatment of fistulas. After 54 weeks of treatment a total closure of fistula was observed in 71.8% of the children and in 12.5% – a partial closure. In 30.34% of the children reoccurrence of fistula was observed within a year after treatment. The treatment with infliximab should be recommended as a treatment of active perianal fistulas after inefficient treatment with antibiotics, thopurines or surgical treatment. The treatment with infliximab was safe, decreased the number of hospitalizations and improved the quality of life of the patients.

References

[1] **Adamski Z, Linke K, Samborski W:** Leczenie biologiczne w dermatologii, gastroenterologii i reumatologii. Ed.: Samborski W. Termedia, Poznań 2010.

[2] **Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM:** Epidemiology of pediatric inflammatory bowel disease: A systemic review of international. Inflamm Bowel Dis 2011, 17, 423–439.

[3] **Małecka-Panas E, Słomka M:** Przewlekłe nieswoiste choroby zapalne jelit. MedPharm Polska, Wrocław, 2012.

[4] **Griffiths AM:** Specificites of inflammatory bowel disease in childhood. Best Pract Res Clin Gastroenterol 2004, 18, 509–523.

[5] **Ryżko J, Bartnik W, Socha P, Czubkowski P:** Odrębności kliniczne nieswoistych zapaleń jelit u dzieci. Pediatr Pol 2003, 78, 355–361.

[6] **Keljo DJ, Markowitz J, Langton C, Lerer T, Bousvaros A, Carvalho R, Crandall W, Evans J, Griffiths A, Kay M, Kugathasan S, LeLeiko N, Mack D, Mamula P, Moyer MS, Oliva-Hemker M, Otley A, Pfefferkorn M, Rosh J, Hyams JS:** Course and treatment of perianal disease in children newly diagnosed with Crohn's disease. Inflamm Bowel Dis 2009, 15, 383–387.

[7] **Palder SB, Shandling B, Bilik R, Griffiths AM, Sherman P:** Perianal complications of pediatric Crohn's disease. J Pediatr Surg 1991, 26, 513–515.

[8] **Eglinton TW, Roberts R, Pearson J, Barclay M, Merriman TR, Frizelle FA, Gearry RB:** Clinical and genetic risk factors for perianal Crohn's disease in a population-based cohort. Am J Gastroenterol 2012, 107, 589–596.

[9] **Vermeire S, Pierik M, Hlavaty T, Claessens G, van Schuerbeeck N, Joossens S, Ferrante M, Henckaerts L, Bueno de Mesquita M, Vlietinck R, Rutgeerts P:** Association of organic cation transporter risk haplotype with perianal penetrating Crohn's disease but not with susceptibility to IBD. Gastroenterology 2005, 129, 1845–1853.

[10] **Latiano A, Palmieri O, Cucchiara S, Castro M, D'Incà R, Guariso G, Dallapiccola B, Valvano MR, Latiano T, Andriulli A, Annese V:** Polymorphism of the IRGM gene might predispose to fistulizing behavior in Crohn's disease. Am J Gastroenterol 2009, 104, 110–116.

[11] **Armuzzi A, Ahmad T, Ling KL, de Silva A, Cullen S, van Heel D, Orchard TR, Welsh KI, Marshall SE, Jewell DP:** Genotype-phenotype analysis of the Crohn's disease susceptibility haplotype on chromosome 5q31. Gut 2003, 52, 1133–1139.

[12] **Talia V:** Perianal Crohn's disease in children and adolescents. Am J Gastroenterol 1996, 91, 922–926.

[13] **De Zoeton E, Brad A, Pasternak BA, Mattei P, Kramer RE, Kader HA:** Diagnosis and treatment of perianal Crohn disease: NASPGHAN Clinical Report and Consensus statement. J Pediatr Gastroenterol Nutr 2013, 57, 401–412.

[14] **Hughes LE:** Clinical classification of perianal Crohn's disease. Dis Colon Rectum 1992, 35, 928–932.

[15] **Parks AG, Gordon PH, Hardcastle JD:** A classification of fistula-in-ano. Br J Surg 1976, 63, 1–12.

[16] **Pikarsky AJ, Gervaz P, Wexner SD:** Perianal Crohn disease: A new scoring system to evaluate and predict outcome of surgical intervention. Arch Surg 2002, 137, 774–777.

[17] **Van Assche G, Vanbeckevoort D, Bielen D Coremans G, Aerden I, Noman M, D'Hoore A, Penninckx F, Marchal G, Cornillie F, Rutgeerts P:** Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. Am J Gastroenterol 2003, 98, 332–339.

[18] **Vermeire S, Van Assche G, Rutgeerts P:** Perianal Crohn's disease: Classification and clinical evaluation. Dig Liver Dis 2007, 39, 959–962.

[19] **Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ:** Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999, 340, 1398–1405.

[20] **Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P:** Mucosal healing predicts long-term outcome of maitenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009, 15, 1295–1301.

[21] **Iwańczak B, Ryżko J, Kierkuś J, Jankowski P, Sładek M, Wasilewska A, Landowski P, Szczepanik M, Krzesiek E, Sienkiewicz E, Szaflarska-Popławska A, Więcek S, Kwiecień J, Kacperska M, Korczowski B, Maślana J:** Leczenie biologiczne nieswoistych zapaleń jelit u dzieci w latach 2004–2013 w Polsce. Pol Merk Lek 2014, 36, 312–315.

[22] **Iwańczak B, Ryżko J, Jankowski P, Sładek M, Wasilewska A, Szczepanik M, Sienkiewicz E, Szaflarska-Popławska A, Więcek H, Czaja-Bulsa G, Kacperska M, Korczowski B, Maślana J, Iwańczak F:** Ocena leczenia infliksymabem ciężkiej postaci choroby Leśniowskiego – Crohna u dzieci w Polsce. Badania ankietowe, retrospektywne, wieloośrodkowe (in press).

[23] IBD Working Group of the European Society for Paediatric Gastroenterology Hepatology and Nutrition. Inflammatory bowel disease in children and adolescents: Recomendations for diagnosis – the Porto criteria. J Pediatr Gastroenterol Nutr 2005, 41, 1–7.

[24] **Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, Griffiths AM, Katz AJ, Grand RJ, Boyle JT:** Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr 1991, 12, 439–447.

[25] **Daperno M, D'Haens G, Van Assche G. Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JY, Colombel JF, Rutgeerts P:** Development and validitation of a new simpified endoscopic activity score for Crohn's disease: The SES-CD. Gastrointest Endosc 2004, 60, 505–512.

[26] **Ruemmele FM, Veres G, 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; ECCO/ESPGHAN:** Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohn's Colitis 2014, 8, 1179–1207.
[27] **Bouguen G, Siproudhis L, Gizard E. Wallenhorst T, Billioud V, Bretagne JF, Bigard MA, Peyrin-Biroulet L:** Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. Clin Gastroenterol Hepatol 2013, 11, 975–981.
[28] **Vermeire S, Pierik M, Hlavaty T, Claessens G, van Schuerbeeck N, Joossens S, Ferrante M, Henckaerts L, Bueno de Mesquita M, Vlietinck R, Rutgeerts P:** Association of organic cation transporter risk haplotype with perianal penetrating Crohn's disease but not with susceptibility to IBD. Gastroenterology 2005, 129, 1845–1853.
[29] **Schwartz DA, Herdman CR:** Review article: The medical treatment of Crohn's perianal fistulas. Aliment Pharmacol Ther 2004, 19, 953–967.
[30] **Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE:** Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology 2005, 128, 862–869.
[31] **Ardizzone S, Maconi G, Colombo E, Manzionna G, Bollani S, Bianchi Porro G:** Perianal fistulae following infliximab treatment: Clinical and endosonographic outcome. Inflamm Bowel Dis 2004, 10, 91–96.
[32] **Thia KT, Mahadevan U, Feagan BG, Wong C, Cockeram A, Bitton A, Bernstein CN, Sandborn WJ:** Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: A randomized, double-blind, placebo-controlled pilot study. Inflamm Bowel Dis 2009, 15, 17–24.
[33] **Korelitz BI, Present DH:** Favorable effect of 6-mercaptopurine on fistulae of Crohn's disease. Dig Dis Sci 1985, 30, 58–64.
[34] **Kirschner BB:** Safety of azathioprine and 6-mercaptopurine in pediatric patients with inflammatory bowel disease. Gastroenterology 1998, 115, 813–821.
[35] **Sands BE, Blank MA, Diamond RH, Barrett JP, Van Deventer SJ:** Maintenance infliximab does not result in increased abscess development in fistulizing Crohn's disease: Results from the ACCENT II study. Aliment Pharmacol Ther 2006, 23, 1127–1236.
[36] **Cezard JP, Nouaili N, Talbotec C, Hugot JP, Gobert JG, Schmitz J, Mougenot JF, Alberti C, Goulet O:** A prospective study of the efficacy and tolerance of a chimeric antibody to tumor necrosis factors (remicade) in severe pediatric crohn disease. J Pediatr Gastroenterol Nutr 2003, 36, 632–636.
[37] **Crandall W, Hyams J, Kugathasan S, Griffiths A, Zrubek J, Olson A, Liu G, Heuschkel R, Markowitz J, Cohen S, Winter H, Veereman-Wauters G, Ferry G, Baldassano RN:** Infliximab therapy in children with concurrent perianal Crohn disease: Observations from REACH. J Pediatr Gastroenterol Nutr 2009, 49, 183–190.
[38] **Ruemmele FM, Lachaux A, Cézard JP, Morali A, Maurage C, Giniès JL, Viola S, Goulet O, Lamireau T, Scaillon M, Breton A, Sarles J:** Groupe Francophone d'Hépatologie, Gastroentérologie et Nutrition Pédiatrique. Efficacy of infliximab in pediatric Crohn's disease: A randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. Inflamm Bowel Dis 2009, 15, 388–394.
[39] **de Ridder L, Escher JC, Bouquet J, Schweizer JJ, Rings EH, Tolboom JJ, Houwen RH, Norbruis OF, Derkx BH, Taminiau JA:** Infliximab therapy in 30 patients with refractory pediatric crohn disease with and without fistulas in the Netherlands. J Pediatr Gastroenterol Nutr 2004, 39, 46–52.
[40] **Kim MJ, Lee JS, Lee JH, Kim JY, Choe YH:** Infliximab therapy in children with Crohn's disease: A one-year evaluation of efficacy comparing 'top-down' and 'step-up' strategies. Acta Paediatr 2011, 100, 451–455.
[41] **Schwartz DA, Loftus EV Jr, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, Sandborn WJ:** The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology 2002, 122, 875–880.
[42] **Savoye-Collet C, Savoye G, Koning E, Dacher JN, Lerebours E:** Fistulizing perianal Crohn's disease: Contrast-enhanced magnetic resonance imaging assessment at 1 year on maintenance anti-TNF-alpha therapy. Inflamm Bowel Dis 2011, 17, 1751–1758.

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