Kaczor Patryk, Lipa Katarzyna, Jabłońska Magdalena Julia, Leis Kamil, Kałużny Krystian, Gałązka Przemysław. Biological therapies in Crohn's disease. Journal of Education, Health and Sport. 2018;8(9):643-650 eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.1412373
http://ojs.ukw.edu.pl/index.php/johs/article/view/5949

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part b item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eissn 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 02.08.2018. Revised: 18.08.2018. Accepted: 10.09.2018.

Biological therapies in Crohn's disease

Patryk Kaczor[1], Katarzyna Lipa[1], Magdalena Julia Jabłońska[1*], Kamil Leis[1], Krystian Kałużny[2], Przemysław Gałązka[3]

[1]Faculty of Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-067 Bydgoszcz, Poland
[2]Chair and Clinic of Rehabilitation, Faculty of Health Sciences, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-067 Bydgoszcz, Poland
[3]Department of General and Oncological Surgery for Children and Adolescents, Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-094 Bydgoszcz, Poland
*corresponding author: Magdalena Julia Jabłońska, madziajablonska96@wp.pl, tel.: 52 585-40-15, ul. M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz

Abstract

Crohn's disease is one of the chronic inflammatory diseases of the digestive tract. Pathophysiology of this disease involves the genetic and environmental factors, but the most important causative factor is anti-inflammatory reaction of the organism, which eventually leads to inflammatory changes, fibrosis and necrosis. Glucocorticosteroids are commonly used in therapy and may cause many negative side effects. Nowadays, new biological medicines are being tested, which are supposed to be an alternative method of treating Crohn's disease. Infliximab, adalimumab, certolizumab pegol, natalizumab, etanerecept, vedolizumab and ustekinumab are the examples of those drugs, on which the research was already carried out.

They lead to healing of the mucous membrane of the digestive tract, and thus to remission of the disease.

Keywords: Crohn's disease, chronic inflammatory disease, biological therapy

Introduction

Crohn's disease is a part of the group of chronic inflammatory diseases, which mainly include local changes in the gastrointestinal part of the digestive tract. The patients feel the symptoms through their whole life, while they are being diagnosed mostly at the end of the second or early third decade of their life - 80% of the patients are diagnosed before the age of 40 **[1]**. In North America there are approximately 26-198,5 people who have developed Crohn's disease for 100,000 adults, while there are approximately 0,1-13,9 cases of Crohn's disease for 100,000 children, with increasing rate in recent years **[2]**.

The first descriptions of Crohn's disease appeared already in the 17th and 18th centuries, however - the breakthrough was made just in 20th century **[3]**. In 1903, the Polish surgeon Antoni Leśniowski described cases of chronic intestinal inflammations **[4]** with its pathological changes. In 1932, the American gastroenterologist Burrill Bernard Crohn with the surgeon Leon Ginzburg and surgeon-pathologist Gordon Oppenheimer, based on doctor Berg's case reports, created the most accurate description of the disease, since then named - from the first in alphabetical order name placed in the publication - Crohn's disease **[3]**.

Crohn's disease - characteristics, pathophysiology

Patients diagnosed with Crohn's disease do not always demonstrate identical symptoms. A lot of them may experience chronic signs for months or years before diagnosis. The most frequent, but not always present, symptoms are fever, abdominal pain, intestinal obstructions, weight loss and diarrhoea with the possible presence of mucus and blood **[1, 5]**. The most typical symptom of Crohn's disease is pain in the right lower abdominal quadrant, which increases after eating. A diagnosis in most cases is made already at the time of presence of full-thickness, discontinuous inflammation of small and large intestine, in most cases excluding the rectum. The ulcers resembling a look of cobblestone are deep, arranged linearly with a clearly elevated margin. The microscopic image reveals infiltrates composed of lymphocytes and neutrophils **[6]**.

Crohn's disease has a complex, multifactorial etiology that has not yet been fully discovered so far. The development of the disease is the result of an abnormal response of the immune system of people, who are genetically prone to bacterial antigens **[2]**. Based on studies, which included given population, it has been found that genetic factors play an important role in the pathogenesis of inflammatory bowel diseases **[7]**. It is assumed that environmental factors also affect the development of the disease, mainly in people with a genetic predisposition **[6]**. It was shown that Crohn's disease occurred in both subjects in 30.3% of monozygotic twins, whereas in the case of dizygotic twins - only in 3.6% **[7]**. Studies involving the German population showed the occurrence of Crohn's disease in both subjects in 35% of monozygotic twins and in 3% of dizygotic twins **[5]**. A rare autosomal recessive mutation in the gene encoding the IL-10 cytokine and the receptor for interlekin-10 was associated with severe cases of Crohn's disease in newborns **[7]**. Meta-analyses and genome-wide studies have identified 71 potential gene areas on 17 chromosomes responsible for the development of Crohn's disease so far **[5]**. The probability of occurrence of Crohn's disease is also increased by the NOD2/CARD15 gene mutation **[2]**.

The main environmental factors, which affect the development of Crohn's disease are inadequate diet, drugs, exposure to infections, past infections and personal hygiene. Nicotine has a special negative influence on the development of the disease. In the European population, 64% of cigarette smoking cases were found in families, which members already developed Crohn's disease. Organisms of people not exposed to tobacco smoke and non-smokers were less prone to getting sick than those, who smoked in an active or even passive way **[6]**. A significantly increased risk of developing Crohn's disease was found in people, who started using tobacco at young age. However, there was no association between Crohn's disease and viruses, including *measles*, and bacteria - *Yersinia spp.* and *Listeria spp.* **[5]**.

The most important role in the pathophysiology of Crohn's disease play an anti-inflammatory response, which consists of granules built of macrophages, multinucleated giant cells and epithelial cells. The complex response of the immune system eventually results in the development of fibrosis and necrosis. In endoscopic images and in preparations obtained from samples removed during surgery, numerous grainy inflammatory changes have been found **[1]**.

Available biological medicines

Currently, the goal in treatment of Crohn's disease is to restore bowels their original function, stop the progression of the disease and induce remission. Glucocorticoids are the basis in treatment, however - usage of them is associated with a wide spectrum of side effects,

which include delayed development and growth disorders. The body may also develop steroid-resistance or steroid-dependence. Another therapeutic method is nutritional treatment, which has similar effects as the usage of glucocorticoids, but not every patient tolerates special diet well. In order to restore original structure of gastrointestinal mucous membrane and thus to change prognosis for the better, biological medicines were introduced in the treatment of Crohn's disease **[2]**. The aim of the therapy are the factors responsible for the body's inflammatory reaction - interleukins, including IL-10, IL-12 and IL-23, as well as interferon-gamma, TNF-alpha and CD3- and CD4-lymphocytes. There are attempts of influencing the presentation of antigens by various cells, including macrophages and dendritic cells, and the spread of leukocytes in the body, including their possibility of adhesion **[5]**. The level of tumor necrosis factor (TNF) in the blood, stool and mucus of the patient with Crohn's disease is elevated, which indicates the important role of this cytokine in the pathogenesis of the disease **[8]**.

Biological medicines currently used in the treatment of Crohn's disease are primarily adalimumab and infliximab, which belong to the group of monoclonal anti-TNF-alpha antibodies. Two other antibodies also used in the therapy are natalizumab and certolizumab pegol, whose effectiveness has been already confirmed by studies carried out on adult patients **[2]**. Treatment of Crohn's disease with the usage of anti-TNF-alpha medicines is now becoming crucial, especially for adults **[9]**. Etanerecept, which binds to TNF, leading to inhibition of its action, was also used in already accomplished studies **[10]**. The medicine that affects leukocytes is vedolizumab. Other tested drugs are briakinumab and ustekinumab, which are interleukin blockers **[5]**.

The influence of biological medicines on Crohn's disease

Infliximab is a mouse-human chimeric IgG1-class monoclonal antibody. It primarily leads to the induction of remission, but also is used to maintain remission in patients, including children, suffering from severe forms of Crohn's disease. The usage of infliximab in children may also lead to the complete healing of the mucous membrane and thus to remission of Crohn's disease. A step-up strategy is used in the dosage of the preparation, which involves adjusting the appropriate intensification of treatment to the stage of the disease. Using the medicine in accordance with the top-down model allows to achieve the better effects of the therapy, the earlier is the stage of Crohn's disease. The chimericity of the preparation may lead to the development of antibodies by the treated organism, which may eventually result in the loss of response to the administered drug **[2]**. Infliximab works by combining with the TNF-

alpha precursor, thereby blocking its activity, probably by preventing TNF-alpha from binding to its receptors. The cells producing TNF-alpha can thus be destroyed **[11]**. Of the 48 patients who underwent IFX-therapy (infliximab), 82% achieved the remission at the end of it. 12, 24 and 36 months after starting IFX-treatment, respectively 82.7%, 92.9% and 91.6% of patients responded to infliximab therapy **[9]**. Complications of Crohn's disease include difficult to eradicate fistulas. There were carried out studies on 63 adult patients, who had had fistulas for at least 3 months as a complication. After treatment with infliximab, 68% of those treated with 5 mg/kg dose (group 1.) and 56% of those treated with 10 mg/kg dose (group 2.) showed a response to therapy in partial fistula closure. After completing therapy, 55% of patients from group 1. and 38% of patients from group 2. showed complete closure of fistulas **[11]**. There have been also carried out studies on 5 patients with a low dose of infliximab - 3 mg/kg. After 18 months of treatment, the patients underwent endoscopy, which revealed remission without side effects. After 30 months of therapy, endoscopy also showed remission, still without any negative aftereffects. In 2 of the 5 patients, who underwent therapy with lower dose, anti-IFX antibodies were developed despite the reduced amount of given preparation **[12]**.

Adalimumab is a part of the group of fully human anti-TNF-alpha IgG1-class antibodies, it is also a monoclonal antibody. It is used in the case of intolerance or loss of the body's response to therapy with the usage of infliximab **[2]**. There were carried out studies about ADA-therapy (adalimumab) on a group of 30 patients, which showed, that at the end of it the symptoms of remission were present in 59% of patients. 12, 24 and 36 months after starting ADA-treatment, respectively 60.9%, 79% and 87.5% of patients responded to adalimumab therapy **[9]**. This medicine has a high specificity to human TNF. Studies carried out on a group of 299 patients, 74 of whom were treated with placebo, proved that the usage of adalimumab is effective and eventually leads to remission. The studies also confirmed, that the adalimumab is well tolerated by the body **[8]**.

Certolizumab pegol is a Fab fragment of a human anti-TNF-alpha antibody and is a part of the group of monoclonal antibodies. Patients, who had not been treated with biological therapy until the time they underwent treatment with the usage of Certolizumab pegol showed a stronger response of the body to the medicine. The half-life of this antibody can be extended by fusion with polyethylene glycol **[2]**. Certolizumab pegol, unlike adalimumab and infliximab, does not contain an Fc fragment of the antibody, and thus does not induce neither apoptosis nor cytotoxicity. The studies were carried out on a group of patients, some of whom underwent treatment with certolizumab pegol with 400 mg dose, and the rest with placebo. The

medicine caused a slight increase in the body's response to the therapy, but - like placebo - did not lead to remission **[13]**.

Natalizumab is an anti-alpha-4-integrin, which is found on leukocytes, antibody. It is a part of the group of human monoclonal antibodies. This medicine is not widely used in the treatment of Crohn's disease due to the possibility of side effects, such as progressive multifocal leukoencephalopathy **[2]**. The point of the usage of natalizumab is to inhibit the migration and adhesion of leukocytes to the tissues, where the inflammatory process is present. The first stage of the study - ENACT-1 - was carried out on a group of 905 patients for 12 weeks. 181 of them were treated with placebo and 724 with natalizumab with 300 mg dose, which was administered at the beginning of the study, and then at the 4^{th} and 8^{th} week of the study. At 12^{th} week, follow-up examinations were carried out. Patients from both groups, who showed effects of the medicine or placebo administered, were assigned to the second stage of the study - ENACT-2 - for the next 48 weeks. Of the patients who received natalizumab, 175 continued the treatment and 179 were relocated to the placebo group. Of the patients who received placebo, 35 continued to receive it and 39 started the therapy with natalizumab. In the second stage of the study, patients received either natalizumab or placebo, respectively, every 4 weeks - starting from 12^{th} to 56^{th} week of the entire study. Patients who received natalizumab during the study showed a slightly better response of the body in the form of remission. The side effects of the therapy with natalizumab, including progressive multifocal leukoencephalopathy, outweigh the positive aspects of this medicine **[14]**.

Etanerecept is a genetically modified medicine, the purpose of which is to inactivate TNF. Etanerecept was made by combining the Fc fragment of human IgG1-class antibody with the human TNF p75 receptor. This medicine is effective and commonly used in the treatment of rheumatoid arthritis. Studies were carried out on a group of 43 patients with Crohn's disease. 20 patients received etanerecept for 12 weeks with 25 mg dose, which is used in the treatment of rheumatoid arthritis, while the rest of patients received a placebo. After 4 weeks of therapy, the results of Etanerecept-treated patients were similar to the group, who received placebo. Finally, the study proved that the usage of this medicine in the treatment of Crohn's disease is neither effective nor dangerous **[10]**.

Vedolizumab is a human IgG1-class monoclonal antibody against alpha-4-beta-7-integrin. The medicine only affects lymphocytes in intestinal cells, bypassing the rest of lymphocytes in the body, including these found in the brain. Thereby it reduces the risk, compared to the usage of natalizumab, of exposing the patient to progressive multifocal leukoencephalopathy. A 52-week randomized studies were carried out on a group of 1115

patients in 39 countries, 967 of whom received vedolizumab with 300 mg dose and the remaining 148 patients were treated with placebo. After 6 weeks of therapy, 14.5% of the group receiving the medicine and 6.8% of the placebo group had symptoms of remission of Crohn's disease. At the end of the studies, it was proven that the patients receiving vedolizumab were more likely to induce the remission than those receiving placebo. However, there was no significant effect on CDAI-100, which is the activity index of Crohn's disease **[15]**.

Ustekinumab is a medicine, which has proven action against psoriasis in adults **[5]**. The medicine is a human monoclonal antibody, which has an inhibitory effect on the activity of IL-12 and IL-12. These interleukins are involved in the pathophysiology of Crohn's disease. The clinical studies were carried out on a group of 4 patients from paediatric departments. The introductory dose was 90 mg of ustekinumab given subcutaneously at the time of initiation of treatment and then at 4th week of therapy. Then the same dose was given every 8 weeks for maintenance. Half of the patients showed the body's response to ustekinumab and continued treatment with the medicine, while the remaining 2 patients were excluded at the 6th and 7th month of the study, respectively, due to lack of results. In order to confirm the effectiveness of ustekinumab and its further usage in paediatric departments for the treatment of patients with Crohn's disease, and the safety of its usage, it is necessary to carry out additional studies in the future **[16]**.

Summary

The first descriptions of Crohn's disease were already created in 17th century, but these days it is still a problem and there have not yet been discovered a solution, which would completely eliminate it. The disease affects patients of all ages, 80% of whom are diagnosed before the age of 40. The main goal in the treatment of Crohn's disease is to restore original function of the bowels by healing their mucous membrane. Nowadays, infliximab and adalimumab are the most often used biological medicines, on which the most research has been carried out so far and have the most proven effectiveness of all biological therapies so far tested. Biological drugs provide an alternative to standard therapy with usage of glucocorticosteroids. The patients affected with Crohn's disease, who were undergoing of biological therapy showed much better prognosis, and many of them also induced deep remission.

References:

1. Freeman HJ: Natural history and long-term clinical course of Crohn's disease. *World Journal of Gastroenterology* **20(1)**, 31-36 (2014)

2. Wegner A, Szychta M, Kierkuś J: Rola terapii biologicznej w podtrzymaniu remisji u dzieci z chorobą Leśniowskiego i Crohna, *Pediatria Polska* **88(2)**, 131-137 (2013)

3. Wasilewska A, Marciniak R, Drews M: Leśniowski-Crohn Disease - Historical Overview, *Polish Journal of Surgery* **81(7)**, 329-336 (2009)

4. Lichtarowicz AM, Mayberry JF: Antoni Lésniowski and his contribution to regional enteritis (Crohn's disease), *Journal of the Royal Society of Medicine* **81(8)**, 468-470 (1988)

5. Baumgart DC, Sandborn WJ: Crohn's disease, *The Lancet* **380**, 1590 - 1605 (2012)

6. Derkacz A, Olczyk P, Komosinska-Vassev K: Diagnostic Markers for Nonspecific Inflammatory Bowel Diseases, *Disease Markers* (2018)

7. Cho JH, Brant SR: Recent Insights Into the Genetics of Inflammatory Bowel Disease, *Gastroenterology* **140(6),** 1704-1712 (2011)

8. Hanauer SB et al.: Human anti–tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I Trial, *Gastroenterology* **130(2)**, 323-333 (2006)

9. Nuti F et al.: Biological therapy in a paediatric Crohn's disease population at a referral center, *Journal of paediatric gastroenterology and nutrition* **58(5)**, 582-587 (2014)

10. Sandborn WJ et al.: Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial, *Gastroenterology* **121(5)**, 1088-1094 (2001)

11. Present DH et al.: Infliximab for the treatment of fistulas in patients with Crohn's disease, *New England Journal of Medicine* **340(18)**, 1398-1405 (1999)

12. Sorrentino D et al: Low dose infliximab for prevention of postoperative recurrence of Crohn's disease: long term follow-up and impact of infliximab trough levels and antibodies to infliximab, *Public Library of Science* **10(12)** (2015)

13. Sandborn WJ et al.: Certolizumab pegol for the treatment of Crohn's disease, *New England Journal of Medicine* **357(3)**, 228-238 (2007)

14. Sandborn WJ et al.: Natalizumab induction and maintenance therapy for Crohn's disease, *New England Journal of Medicine* **353(18)**, 1912-1925 (2005)

15. Sandborn WJ et al.: Vedolizumab as induction and maintenance therapy for Crohn's disease, *New England Journal of Medicine* **369(8)**, 711-721 (2013)

16. Bishop C et al.: Ustekinumab in paediatric Crohn's disease patients, *Journal of paediatric gastroenterology and nutrition* **63(3)**, 348-351 (2016)