II. Streszczenie w języku angielskim

Inflammatory bowel disease (IBD) is a term used primarily to refer to autoimmune diseases characterized by chronic inflammation in the gastrointestinal tract. For several years, we have seen a sudden increase in the incidence of two of the best-known IBD entities in the pediatric patient population: Crohn's disease (CD) and ulcerative colitis (UC). **[1]** This phenomenon is related to highly processed food and living environment, as well as an abnormal immune system response to the commensal microbiome. **[2]** Genetic predisposition may be important in the development of IBD, especially in the youngest patients. **[3]** Despite ongoing research, the etiology of inflammatory bowel disease is not fully understood yet. Current drugs used in the treatment of inflammatory bowel disease include 5-aminosalicylic acid preparations, glucocorticosteroids, immunosuppressive and immunomodulatory drugs, and, increasingly, biologic and small-molecule drugs. The primary therapeutic goal is to induce and maintain remission. In the pediatric population, treatment with glucocorticosteroids can cause long-term side effects such as stunted growth, osteopenia and pathological fractures, which is why it is very important to find effective and safe forms of treatment in pediatric patients with the most severe inflammatory bowel disease. **[4,5]**

People eligible for biologic therapy, represent a group of patients with a moderate to severe course of the disease in case of whom conventional drug therapy has failed. These patients are at high risk of surgical intervention, which can result in prolonged hospitalization and worsened quality of life. The wider use of biologic drugs as part of the management of inflammatory bowel disease has many benefits, both in terms of efficacy and safety of long-term therapy. However, in patients with severe disease, standard single-drug therapy with a biologic drug achieves clinical remission in only 40% of subjects after 1 year of treatment. **[6,7]**

Current reports from established Inflammatory Bowel Disease Treatment Centers, the possibility of combining two biologic drugs, may link with a good therapeutic effect and a low rate of side effects. Such a treatment regimen in patients of the Department of Gastroenterology, Hepatology of Nutritional Disorders and Pediatrics was performed with an evaluation of the efficacy and safety.

The primary objective of the dissertation is to analyze the efficacy and safety of combination biological therapy in pediatric patients diagnosed with moderate to severe inflammatory bowel disease. The doctoral dissertation entitled, "Retrospective evaluation of the efficacy and safety of dual biological therapy in inflammatory bowel disease in children" is a series of monothematic publications, two original papers and two review papers, including those

published in international scientific journals indexed in the PubMed database and listed in the Journal Citation Reports (JCR).

The first published article titled *„Dual biological therapy in inflammatory bowel disease"* summarizes the literature review of both adult and pediatric patients who received dual biological therapy. The paper includes information on the efficacy, safety and treatment regimens of combined biological therapy in inflammatory bowel disease. The second publication aimed to collect and systematize the available scientific data on the use of a combination of biologic drugs in children. The article **„Dual Biologic Therapy for the Treatment of Pediatric Inflammatory Bowel Disease: A Review of the Literature"** provides a review of the literature including case reports, a clinical case series and a retrospective study. The publication describes a comparison of the treatment regimens used, glucocorticosteroid-free remission, clinical improvement according to the pediatric disease activity scales (PCDAI and PUCAI), and endoscopic findings. A summary of the source material showed that dual biologic therapy offers the possibility of achieving clinical and endoscopic remission in patients refractory to standard drug therapy. The use of two biologic drugs with different mechanisms of action is an effective form of therapy, but due to the limited number of scientific reports, this therapeutic option requires further randomized studies on the safety of treatment. In the original paper **„Dual Biologic Therapy in Moderate to Severe Pediatric Inflammatory Bowel Disease: A Retrospective Study"**, a retrospective analysis of the medical records of fourteen patients undergoing treatment in a dual biological therapy regimen in the Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute was conducted. The publication focused on the early follow-up of patients qualified for dual biological therapy (induction of remission). 4 months after the implementation of treatment, it was taken into account as such: demographic data, the course of the disease in children, including the use of previous therapies and past surgeries, inflammatory markers (ESR, CRP), fecal calprotectin levels, pediatric scales of Crohn's disease activity (PCDAI), ulcerative colitis (PUCAI), and available endoscopic findings. The primary endpoint was clinical response after induction of remission. 10 children (73% out of 14) achieved clinical improvement on the pediatric PCDAI/PUCAI disease activity score four months after the addition of the second biologic drug. In addition, 7 (47%) patients achieved clinical remission after 4 months of therapy. The article titled **„Combination Biologic Therapy in Pediatric Inflammatory Bowel Disease: safety and efficacy over a minimum 12-month follow-up period"** evaluated the efficacy and safety of dual biologic drug therapy in 29

pediatric patients diagnosed with IBD at 12-month follow-up. The retrospective analysis included demographic data, duration of disease and previous treatment, comparison of endoscopic imaging before eligibility for dual biologic therapy and 12 months after treatment initiation, as well as evaluation of inflammatory exponents and fecal calprotectin determinations. The primary endpoint was the achievement of clinical remission 12 months after starting therapy. Secondary endpoints were achievement of clinical response without glucocorticosteroids, a 50% reduction in fecal calprotectin levels at 12-month follow-up, and assessment of endoscopic disease activity. Clinical remission as assessed by disease activity scales (wPCDAI/PUCAI) was achieved by 13 (45%) and 12 (41%) patients after 4 and 12 months of dual biological therapy, respectively. Clinical response was achieved by 16 (55%; 9 UC; 7 CD) and 12 (41% 7 UC; 5 CD) patients according to the (wPCDAI/PUCAI) scales, after 4 and 12 months of follow-up, respectively. Median fecal calprotectin decreased significantly between baseline and 12 months of follow-up. 10 patients (34%) showed endoscopic remission at follow-up colonoscopy. During the study, 5 patients (17%; 3 UC, 2 CD) experienced serious adverse events, including buttock abscess, renal dysfunction, dilated cardiomyopathy during COVID-19 infection, intestinal obstruction, and deep vein thrombosis.

Analysis of data concerning the use of dual biological therapy in children with diagnosed inflammatory bowel disease confirms that this is an effective treatment option for patients with moderate to severe disease, refractory to previous forms of therapy. The efficacy of this therapy has been proven in patients who have lost response or have not shown response to treatment with three or more biologic drugs.

The risk of adverse events, including serious adverse events, does not differ significantly from the risk during the use of biologic drugs in monotherapy.

Further prospective studies on the safety and efficacy of the combination of two biological drugs are necessary. The decision on qualification for therapy and the choice of treatment regimen should be considered individually for each patient.