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BIOLOGICAL THERAPY OF INFLAMMATORY BOWEL DISEASES

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A B S T R A C T

The term "inflammatory bowel disease" (IBD) covers a broad group of diseases, including acute and chronic enteritis and colitis of known and unknown etiology. In the literature, in accordance with ICD-10, the term IBD is understood as a narrower group of diseases combined into the class of IBD of non-infectious etiology, including Crohn's disease (CD) of the small and large intestine and ulcerative colitis (UC).

K E Y W O R D S

Therapy, method, diagnosis, treatment.

Introduction

Although the etiology of CD and UC remains unclear, there is no doubt that genetic, infectious, immunobiological and environmental factors play an important role in the development of IBD. With regard to environmental factors, stressful situations, medications, smoking and poor nutrition play a significant role in the genesis of CD and UC [2]. Among infectious causes, the role of various microbial agents and viruses (Mycobacterium paratuberculosis, Listeria monocytogenes, etc.) has been discussed at different times, but the evidence supporting the etiological role of these microorganisms is still not very convincing [3]. The place of Toll-like receptors in the genesis of IBD is discussed [4], the dysfunction of which may be one of the pathophysiological mechanisms contributing to the formation of inflammation.

MATERIALS AND METHODS

Hereditary predisposition plays a significant role in the development of IBD. Familial cases of the disease are registered in 10–20% of patients with IBD, but the familial predisposition is more obvious in CD. First-degree relatives have a 10–35 times higher risk of developing CD, and a 8–10 times higher risk of developing UC than in the general population. Among genetic factors, the role of the IBD1 gene, localized in one of the loci of the 16th chromosome, responsible for the predisposition to CD and called NOD2/CARD15, has been studied best. This gene is involved in the regulation of the immune response by binding to the nuclear factor NFkB, a transcription protein, which, in turn, initiates the production of inflammatory cytokines. The connection between the development of IBD and the human leukocyte antigen system (HLA system) is discussed; to a greater extent, this connection is observed in UC [5].

RESULTS AND DISCUSSION

Recent advances in immunology demonstrate that in a normal mucous membrane, after inactivation of a foreign antigen, the inflammatory response quickly subsides, but when the regulation of the inflammatory process is disrupted, a state of chronic inflammation develops [4], which is characterized by an imbalance of cytokines with a predominance of a group with a proinflammatory effect, such as IL-1, IL-2, IL-6, TNF-α, INF-γ, etc. [2]. Another link in the inflammatory cascade are adhesion molecules, which are represented by three superfamilies of molecules and are directly involved in maintaining inflammatory changes in the intestinal mucosa [3]. Treatment. For many years, the treatment of IBD was limited to the use of basic therapy drugs: aminosalicylates (sulfasalazine and 5-aminosalicylic acid derivatives), glucocorticosteroids (GCS), immunosuppressants. However, the insufficient effectiveness of existing basic therapy for IBD, the formation of refractory forms of the disease (35% of all IBD cases) and a deeper understanding of the pathogenesis underlying CD and UC, led to the development of a new treatment method - biological therapy based on the immunological theory of the inflammatory process [1; 7; 8]. Theoretically, any links in the inflammatory cascade can be selective targets or points of application of biological drugs. Today, there are five main methods of biological therapy: cell and gene therapy, methods using native biological drugs and products isolated from blood, the use of recombinant peptides or proteins, a method using antibodies, and methods of treatment based on the use of nuclear factor. The main goal of these treatment methods is to suppress effector signals at different levels and break the vicious circle of inflammation. The main advantage of biological therapy is its selectivity. There are already quite a lot of biological treatment methods today, but only some of them have proven their clinical effectiveness in large studies and are successfully used in practice. The most widely used methods in the treatment of IBD are those using monoclonal antibodies, recombinant human proteins with immunoregulatory effects [4].

The first drug from this group to enter clinical practice was Infliximab, a chimeric antibody to TNF-α. It contains 25% murine and 75% human immunoglobulin G1. Infliximab blocks soluble and membrane-bound TNF-α, which leads to activation of complement and cytolysis of inflammatory infiltrate cells through the mechanism of antibody-dependent cytotoxicity [1]. Infliximab has been used abroad since the 90s of the last century; it was registered in Russia in 2001. The effectiveness of this drug was confirmed by multicenter randomized placebo-controlled studies (ACCENT I and ACCENT II). The results of the studies showed a significantly higher frequency of clinical and endoscopic response (over 60%), as well as remission, among those receiving Infliximab compared to the placebo group.

Medicines based on antibodies to TNF-α have undergone a certain evolution in recent years. This concerns the ratio of human and mouse components in the structure of the molecule. Thus, the drug CDP-571 appeared, which is a humanized (consisting of only 5% mouse and 95% human protein) monoclonal antibodies to TNF. CDP-571 binds both dissolved and membrane-bound TNF-α, but does not cause lysis of inflammatory cells. CDP-571, unlike Infliximab, is an antibody of the immunoglobulin G4 class and is not able to fix complement or affect antibody-dependent cytotoxicity. Currently, 4 placebo-controlled studies of the effectiveness of this drug in CD have been conducted. These studies allowed us to draw the following conclusions. CDP-571 has a moderate effect in the treatment of patients with an active inflammatory process of the intestinal wall; an increase in the ESR level in the acute phase of the disease can be attributed to favorable prognostic factors for the long-

term outcome of therapy. The drug allows to reduce the dose of corticosteroids somewhat and can be considered as an alternative in case of intolerance to Infliximab. Based on the same molecule, a pegylated drug CDP-870 with prolonged action was created. This molecule consists of two parts: a fragment of a monoclonal antibody and a polyethyleneglycol molecule, which increases the half-life of the drug in the human body. CDP-870 differs from other drugs containing antibodies to TNF-α by its higher affinity and potency with a minimum concentration causing 50% neutralization of free TNF-α [1]. To date, only the results of the second phase of the study involving 292 patients with CD have been published. Preliminary results showed a moderate short-term effect of the substance on induction and maintenance of remission in patients with CD, with the effect being more pronounced with an increase in ESR. Results of the 3rd phase have not yet been published.

The possibility of treating IBD with IL-1 receptor antagonists, which have already been used in a small group of patients, is currently under clinical study. The possibility of using antibodies to IL-2 receptors in UC is being theoretically discussed. A small but significant decrease in the clinical activity of the disease in the first two weeks of treatment has been established [3]. The use of antibodies to T-lymphocyte subpopulations (CD4+) and IFN-γ inhibitors is considered justified, since they contribute to the formation of granulomas in CD. Antibodies to CD4+ lymphocytes have already been tested with good effect in experimental models of autoimmune diseases, but the results of the first clinical trials were contradictory. A drug based on monoclonal antibodies to CD3+ lymphocytes (Visilizumab) is undergoing clinical trials in patients with severe UC who have not responded to intravenous corticosteroids. Preliminary results from phase 1–2 trials showed that Visilizumab causes a reduction in the clinical and endoscopic UC intensity index by day 30 and is well tolerated [4].

CONCLUSION

In connection with the above, there is a need to develop and implement new, more effective strategies in the treatment of IBD, one of which is biological methods of treatment. Further, more detailed study of the clinical effectiveness of this group of drugs is required, based on the pharmacoeconomic aspects of this issue.

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