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BIOLOGICAL THERAPY IN PEDIATRIC RHEUMATOLOGY

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Abstract:

The article presents data on unique world experience in the use of biological agents in pediatric rheumatology. Treatment with genetically engineered biological drugs improves the quality of life of children with JA and their families, ensures normal growth and development of young patients, and changes the prognosis of this previously practically incurable chronic autoimmune disease.

Keywords: Children, Rheumatology, Biological Therapy

INTRODUCTION

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disease in children, which is characterized by inflammation of the synovial membrane of the joints, destruction of the cartilage and bone tissue of the joints, and the development of a wide range of extra-articular manifestations [1]. The chronic, steadily progressing course of JRA leads to the rapid development of disability in patients, a decrease in their quality of life, and social and psychological maladjustment [2, 3]

MATERIALS AND METHODS

The development and progression of JRA is determined by a complex combination of genetically determined and acquired defects in immunoregulatory mechanisms that trigger pathological activation of the immune system in response to potentially pathogenic, and often physiological stimuli [4, 5]. This leads to a rapid transformation of the physiological acute inflammatory response into chronic progressive inflammation, which is an integral feature of JRA. This disease is characterized by activation of both Th1 and Th2 types of immune response, manifested by hyperproduction of proinflammatory cytokines: interleukins (IL) 1, 6, 17, tumor necrosis factor (TNF) α, etc. [3]

RESULTS AND DISCUSSION

Currently, the term "biological drugs" (from the English biologics) is used in relation to drugs produced using biotechnologies and carrying out targeted (point-wise) blocking of key mechanisms of inflammation using antibodies or soluble receptors to cytokines, their receptors, as well as CD molecules, co-molecules, etc. [2]. Due to the large number of "target molecules" that can potentially suppress immune inflammation, a number of drugs from this group have been developed, and several more drugs are undergoing clinical trials [4].

The main biological drugs registered in the world for the treatment of rheumatoid arthritis include: infliximab, adalimumab, etanercept, cetrolizumab (TNF α inhibitors); rituximab (antibodies to CD 20 B lymphocytes); tocilizumab (anti-IL 6 receptor antibodies); abatacept (blocker of co-stimulation of T lymphocytes CD 80/86: CD 28); anakinra (recombinant antagonist of human IL-1 receptors). Biological drugs are characterized by a rapid and pronounced clinical effect and reliably proven inhibition of joint destruction [3]. A characteristic feature of biological agents is the potentiation of the effect in combination with basic anti-inflammatory drugs, primarily methotrexate. Due to its high effectiveness in rheumatoid arthritis, including in patients resistant to conventional therapy, biological therapy has now taken first place in the treatment of this disease.

The first biological agents that became widely used in clinical practice were TNF α inhibitors. They block the biological activity of this cytokine in the circulation and at the cellular level. These include chimeric (infliximab) and human (adalimumab) monoclonal antibodies to TNF α and soluble TNF α receptors - etanercept. Today they are considered as the most effective drugs for the treatment of JA [3]. TNF α is one of the key molecules in the pathogenesis of rheumatoid and juvenile arthritis. On the one hand, this cytokine plays an important role in the regulation of differentiation, growth and metabolism of various cells, and on the other hand, it acts as a mediator of inflammation in many human diseases [4]. The local effects of TNF α ensure the formation of a focus of local inflammation, activation of endothelial cells, and increased thrombus formation in microcirculatory vessels. Local edema promotes the drainage of the pathogen into regional lymph nodes, where normally there are all conditions for the development of a lymphocytic immune response [5].

To assess the results of the effectiveness of the therapy, the following indicators were used:

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1) the number of joints with signs of active inflammation (with exudation and/or pain and dysfunction);

2) ESR;

3) serum concentration of CRP;

4) the doctor's general assessment of disease activity (using a 100-mm visual analogue scale - VAS);

5) assessment by the patient or his parent of general health (using VAS);

6) assessment of health using the parent version of a special questionnaire CHAQ (Childhood Health Assessment Questionnaire); the minimum value of the CHAQ health status index is "0", the maximum is "3"; CHAQ index < 1.5 corresponds to minimal and moderate impairments, CHAQ index " 1.5 – severe [2].

The results of the study showed that infliximab had a pronounced anti-inflammatory effect, provided a decrease in the activity of articular syndrome and laboratory indicators of activity after the first administration in all patients [3]. However, it was later revealed that the drug is unequally effective in different variants of the disease. The best results were achieved with the use of infliximab in patients with articular variants of JRA: the drug induced the development of clinical and laboratory remission on average 1.5 months from the start of treatment in 69 (82%) patients with oligoarticular and in 41 (60 %) of a patient with a polyarticular variant of the disease [2]. In 25 (90%) children with a systemic variant of the disease, after 4–5 administrations of the drug, secondary ineffectiveness developed, which was the reason for discontinuation of treatment.

At the same time, it was found that infliximab prevented the progression of osteochondral destruction in all variants of the disease, regardless of the clinical effect, and in patients with a good therapeutic effect, the drug ensured complete restoration of function in the joints and improved quality of life , elimination of signs of disability [4].

The drug is officially registered for the indications "rheumatoid arthritis", "ankylosing spondylitis", "psoriatic arthritis" in adults. In children, infliximab is registered for the indication "Crohn's disease" from the age of 6 years. When prescribing infliximab, it is necessary to obtain the informed consent of parents and a child over 14 years of age, as well as the consent of the local ethical committee of the medical organization.

The results of many years of research into the effectiveness of various biological agents obtained by genetic engineering made it possible to develop an algorithm for biological therapy for this disease. In patients with oligo- and polyarthritis, as well as juvenile ankylosing spondylitis, it is advisable to prescribe TNF α inhibitors, in patients with arthritis and uveitis - human antibodies to TNF α - adalimumab. To achieve a rapid anti-inflammatory effect in patients with polyarthritis and juvenile ankylosing spondylitis with severe articular damage, high laboratory activity indicators, severe functional impairment and pain, it is advisable to prescribe infliximab or adalimumab, and in case of secondary ineffectiveness of infliximab, adalimumab. In severe systemic arthritis, TNF-α inhibitors are ineffective and their use is inappropriate

CONCLUSION

In these cases, if standard immunosuppressive therapy is ineffective, it is preferable to prescribe rituximab to patients with severe extra-articular manifestations and severe articular syndrome; patients with visceral manifestations, severe anemia, thrombocytosis and moderately severe articular syndrome (arthralgia, myalgia, oligo- and limited polyarthritis) - tocilizumab. Treatment with genetically engineered biological drugs improves the quality of life of children with JRA and their families, ensures normal growth and development of young patients and changes the prognosis of this previously practically incurable chronic autoimmune disease.

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