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EVALUATION OF THE EFFECTIVENESS OF GENETIC ENGINEERING BIOLOGICAL THERAPY IN CHILDREN WITH JUVENILE ARTHRITIS WITH A SYSTEMIC BEGINNING

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Abstract: The article presents the results of evaluating the effectiveness of a genetically engineered biological drug (tocilizumab) in children with juvenile arthritis with a systemic onset. Analysis of the results of the study showed that the use of a genetically engineered biological drug (tocilizumab) in the treatment of patients with juvenile arthritis with systemic onset contributes to a decrease in disease activity, regression of systemic signs and normalization of laboratory parameters in a significantly short time and improves the prognosis of the disease in these children.
Keywords: children, juvenile arthritis with systemic onset, tocilizumab.

Among the various variants of the course of juvenile arthritis, arthritis with systemic onset (JASCH) is characterized by a pronounced severity of the general inflammatory response, pronounced polysyndromicity, severe functional insufficiency in the acute period, and is distinguished by its various forms of course and outcomes, from favorable to extremely severe. The disease is characterized by an undulating course and damage to internal organs, the complexity of determining the period of remission of the disease [2, 8, 9, 10].

The protracted process of diagnosis and improper treatment at the initial stage leads to aggravation of the further course of the disease and response to therapy. The overall strategy for the treatment of systemic arthritis, aimed at the rapid and aggressive arrest of inflammatory activity, is the most important in therapy and may include various medical therapeutic agents. High disease activity and unfavorable prognosis in relation to deforming complications require the earliest possible appointment of basic therapy [1, 3, 4].

Recently, a lot of evidence has been accumulated about the leading role of inflammatory mediators, namely pro-inflammatory cytokines - interlekin-1 (IL-1) and interlekin-6 (IL-6), in the pathogenesis of this disease [2, 5, 6, 7]. Accumulated knowledge about the influence of pro-inflammatory cytokines distinguishes JAcCH with its pronounced activity of the laboratory inflammatory response and pronounced polysyndromicity from other JA variants. They cause a spectrum of various multi-organ extra-articular clinical manifestations [7, 10].

In addition, the local effects of IL-6, manifested in muscular-articular symptoms, are very diverse and are associated with its influence on the pathogenetic mechanisms of sinusitis and destructive joint damage [8, 9, 10].

A large evidence base created in the last decade has made it possible to revise the tactics of treating JAHF, according to which it is necessary to suppress the cytokine cascade at the earliest stages of pathology development through the use of basic immunobiological preparations.

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In this regard, the use of a recombinant humanized monoclonal antibody to the human interleukin-6 receptor (IL-6) from the IgG immunoglobulin subclass, which selectively binds and suppresses both soluble and membrane IL-6 receptors (sIL-6R and mIL-6R), in the form of the drug tocilizumab is currently the standard in the treatment of JASHF [5].

In addition, the effectiveness of NSAIDs and basal immunosuppressive therapy in JASHF, the short-term effectiveness of glucocorticoid drugs (GCS), and a large number of side effects have led to the widespread use of genetically engineered biological drugs (GEBDs) [9, 10].

Purpose of the study. To evaluate the effectiveness of genetically engineered biological therapy in children with juvenile arthritis with systemic onset.

Materials and research methods. We examined 32 patients with JASHF aged 1 to 18 years, hospitalized in the cardio-rheumatology department of the Republican Specialized Scientific and Practical Medical Center for Pediatrics from the beginning of 2017 to the present. The diagnosis was made according to the ILAR Edmonton criteria (2001).

All patients underwent general clinical, biochemical and instrumental research methods. Immunological studies included the determination of interleukin-6 (IL-6) and antibodies to modified citrullinated vimentin (anti-MCV/AMCV).

Out of 32 patients, in addition to complex treatment, 12 (31.2%) patients received a genetically engineered biological drug (GIBP) - tocilizumab (Actemra), which made up the 1st main group. The comparison group 2 consisted of 20 (68.8%) patients who received complex treatment, including immunosuppressant, corticosteroids and NSAIDs. Patients of the 1st group included in the study received tocilizumab therapy at a dose of 12 mg/kg of body weight (weighing < 30 kg) or 8 mg/kg (weighing 30 kg) intravenously every 4 weeks. Clinical, instrumental and laboratory assessment of the disease dynamics was carried out immediately before the start of therapy with tocilizumab and then every 3 months.

Statistical analysis of the obtained results was carried out using the software package "SPSS for Windows (2003) with the processing of material by groups using the methods of variation statistics, including the calculation of the arithmetic mean value (M), the arithmetic mean error (m), expressing the reliability of the obtained mean value of the studied trait, t-confidence coefficient (Student-Fisher difference significance test).

Results and discussion. The study of the timing of the onset of the disease showed that the earliest age of onset was 1.2 years, and the latest age was 10.8 years. At the same time, on average, the onset of the disease was noted at 5.4±3.2 years. According to foreign authors, the onset of the disease occurs at 1–5 years of age [1]. In the sexual aspect, boys (65.6%) predominated among all 32 examined patients with JASHF.

An analysis of the degree of disease activity in children revealed that the activity of the first degree was not recorded in any patient with JASHF. Grade II activity was detected in 56.2% of 18 patients, grade III activity - in 43.7% of 14 patients.

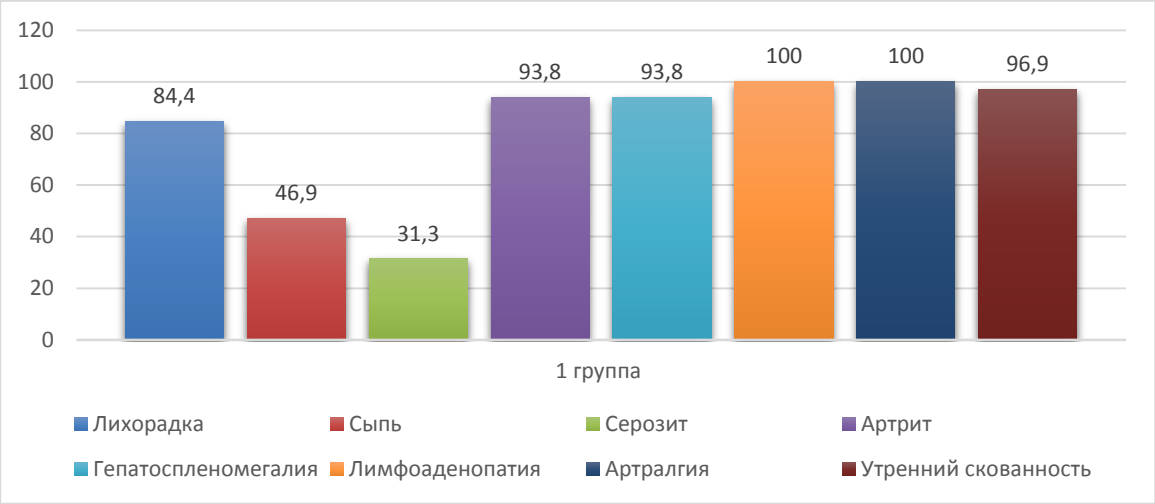

Fig.1. The frequency of clinical symptoms before treatment with GIBD in patients with JASHF.

The main clinical signs of the disease begin with an increase in body temperature, followed by joint pain, morning stiffness due to joint pain, swollen lymph nodes, enlarged liver and spleen, which are detected in the early stages of the disease. The main clinical manifestations of the disease in the examined children in both groups were fever (39-40ºC), the peak of which was in the daytime, transient maculopapular rash and arthritis. Other symptoms frequently included serositis (100%), generalized lymphadenopathy (100%), and hepatosplenomegaly (93.8%) (Figure 1).

The study of laboratory data during the acute phase showed the presence of varying degrees of severity of anemia in 84.4%, an increase in the number of leukocytes in 81.3% of patients. The most pronounced were an increase in ESR and an increase in the number of platelets, which were equally often recorded in 87.5% of patients. In 29 (90.6%) of 32 (100%) patients, the platelet count was higher than normal.

The presence of concomitant diseases also played a significant role in the course of the disease. Analysis of comorbidities revealed that among 32 patients, 26 (81.3%) were diagnosed with TORCH infections, 18 (56.3%) had chronic tonsillitis, 11 (34.4%) had gastroduodenitis, 8 (25) %) - minimal brain dysfunction, in 13 (40.6%) - autonomic dystonia syndrome, in 1 (3.1%) - community-acquired pneumonia, in 3 (9.4%) - urinary tract infection and in 4 (12, 5%) chronic cholecystitis.

Treatment of the patient was carried out with the consent of the parents or official representative.

Table 1

Drugs used at the start of treatment for systemic-onset juvenile arthritis

Name of the drug	**1 group with GIBP n-12**	**group 2 without GIBP n-20**
Ibuprofen	41.6%	15%
Diclofenac	33.3%	40%

Meloxicam	16.6%	20%
Naproxen	-	5%
Nimesulide	8.3%	20%
Methotrexate	91.6%	90%
Leflunomide	8.3%	10%
Prednisolone	100%	100%
Tocilizumab (Actemra)	100%	-

IL-6 in the presence of the soluble IL-6 receptor (pIL-6R) stimulates the production of vasculo-endothelial growth factor (VEGF) by synovial fibroblasts, thereby activating the synthesis of such chemokines by endotheliocytes, mononuclear cells and synovial fibroblasts, which in turn promote the migration of inflammatory cells into the joint cavity. As a result, under the influence of IL-6 there is an increase in osteoclastogenesis and bone resorption, which are of central importance in the progression of erosive damage to the joints in JA [5]. According to the recommendation of the American College of Rheumatology (ACR), IL-6 and IL-1 blockers are first-line drugs in the treatment of JASHF, which was proven by a randomized placebo control trial [2].

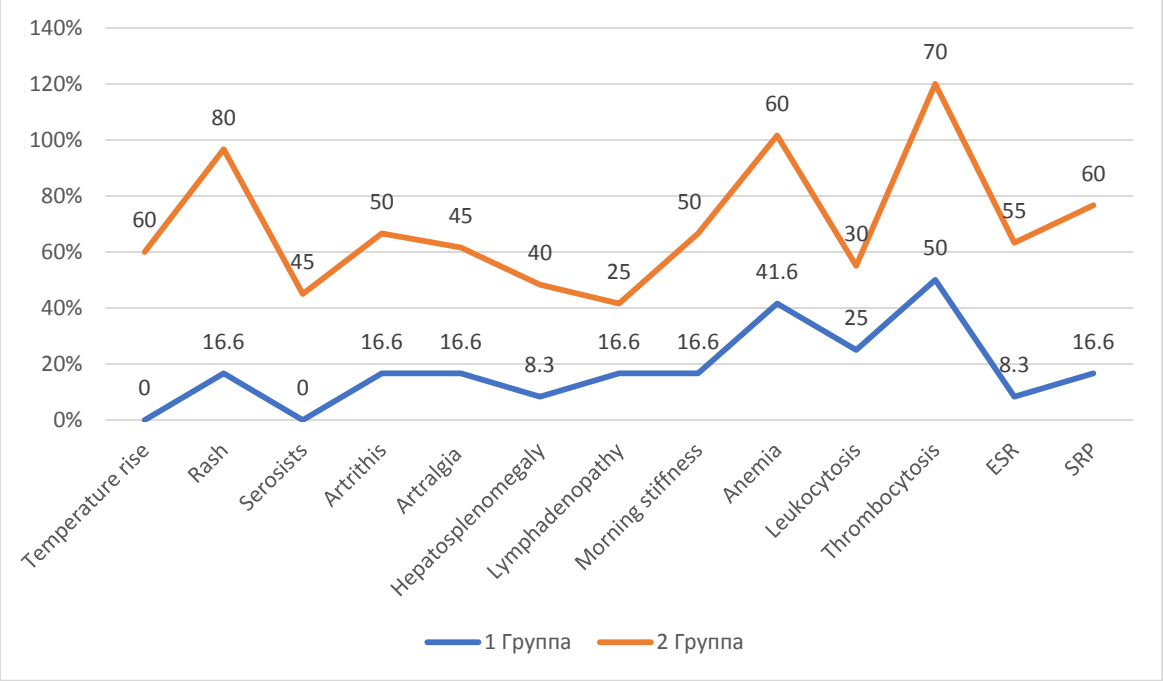

Fig.2. Dynamics of clinical and laboratory parameters in the compared groups 3 months after the use of GIBP

The main outcome of treatment was aimed at achieving the status of inactive disease in children with JASHF during therapy with tocilizumab. The timing and possibility of achieving the status of an inactive disease were assessed according to the criteria of C. Wallace [8], and the achievement of the status of "low disease activity" according to the criteria of A. Consolaro [9].

Additional outcomes during the study included changes in disease activity scores (number of active joints, hemoglobin, leukocytes, platelets; ESR; C-reactive protein), change in concomitant antirheumatic therapy from first tocilizumab infusion to last visit, lipid profile, and the occurrence of adverse events during therapy.

After 3 months, during treatment, there was a rapid regression of systemic manifestations of the disease, including articular syndrome in the 1st group of patients, and in the 2nd group, the improvement of these indicators occurred relatively more slowly ($p \leq 0.01$). During the first 3 months, no side effects were noted in group 1 of patients, and in patients without systemic symptoms in this group, the dose of GCS was reduced. However, in the 2nd group, due to the long-term regression of systemic manifestations and articular symptoms, the dose of GCS was reduced much more slowly than in the 1st group.

After 6 months of treatment in patients of group 1, all clinical signs of the disease disappeared, only such laboratory changes remained as anemia in 3 (25%) patients and thrombocytosis in 4 (33.3%) patients. In the 2nd group of clinical manifestations of JA, 8 (40%) patients had fever, 14 (70%) had skin rashes, 8 (40%) had symptoms of arthralgia and arthritis. Laboratory indicators indicated the presence of anemia in 10 (50%) patients, thrombocytosis in 11 (55%) patients, leukocytosis in 5 (25%) patients, accelerated ESR in 9 (45%) patients and an increase in CRP in 8 (40%) patients of the 2nd group. By this time, changes in the joints have decreased in patients of the 1st group, and the reduction in the dose of GCS was successful. However, in patients of the 2nd group, despite the treatment, deformities and limitation of movements in the joints occurred, which caused difficulties in reducing the dose of GCS and contributed to the recurrence of the disease.

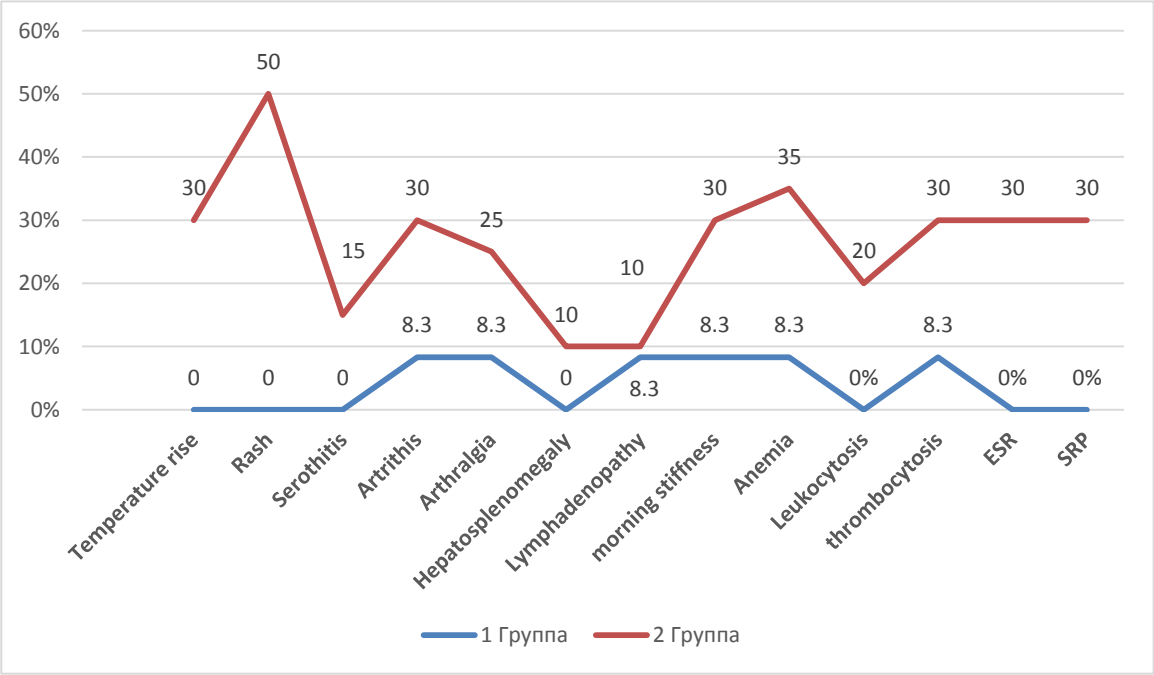

Fig.3. Dynamics of clinical and laboratory parameters in the compared groups 9 months after the use of GIBP

Evaluation of the effectiveness of tocilizumab therapy carried out 9 months after the start of treatment indicated the normalization of clinical symptoms and laboratory parameters in 91.6% of patients. The exception was 1 patient from group 1 with preserved changes in the joints. Among patients of the 2nd group, by the 9th month from the start of treatment, 30% retained such clinical manifestations as fever, arthritis and arthralgia, high levels of CRP, ESR and platelet count, which indicated a high activity of the disease in these patients. In children of the 1st group, no side effects of GEBA were observed during treatment, and glucocorticosteroids were successfully canceled in 75% of patients. In the 2nd group, side effects from drugs were observed in 2 patients with arterial hypertension, 3 patients with Cushing's syndrome, 1 patient with cataracts, 1 patient with tuberculosis, 1 patient with sepsis and 2 patients with macrophage activation syndrome.

Conclusion. Thus, the use of GEBAs in the treatment of patients with juvenile arthritis with systemic onset contributes to a decrease in disease activity, regression of systemic signs and normalization of laboratory parameters in a much shorter time and improves the prognosis of the disease in these children.

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