CHARACTERISTICS OF THE COURSE OF SYSTEMIC CONTINUING JUVENILE ARTHRITIS DURING GENETIC ENGINEERING BIOLOGICAL THERAPY IN CHILDREN

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Abstract*. At the Republican Scientific and Applied Pediatric Medical Center, 45 children aged 2 to 18 years with systemic rheumatoid arthritis were examined. The average age of the patients was 8.87±0.48 years, the majority of patients in both groups were of primary school age. The number of boys in both groups (1st group 59.3%, 2nd group 72.2%) occupied the bulk of the group.*

Purpose: to study the features of the systemic development of juvenile arthritis in children against the background of genetic engineering biological therapy.

Keywords*: juvenile rheumatoid arthritis with systemic onset, genetically engineered biological therapy (tocilizumab), CHAQ (Childhood Health Assessment Questionnaire; 0–3), remission.*

Relevance. Juvenile arthritis with systemic onset (JJA) is one of the most difficult diseases to diagnose and treat, characterized by a 25-50% risk of early disability due to destruction of joints and damage to internal organs (Kaleda M.I., Nikishina I.P., 2015; Valieva S.I., Glazyrina A.A., 2019).

The diagnosis of TBYRA is made by the presence of fever or arthritis, preceded by fever for 2 weeks, together with two or more symptoms of transient unstable erythematous rash, serositis, generalized lymphadenopathy, hepatomegaly and/or splenomegaly. The systemic form of JRA has the features of an articular syndrome. Often, articular syndrome appears simultaneously with extra-articular manifestations. However, fever, rash, lymphadenopathy, hepatosplenomegaly and polyserositis may occur early in the disease [4, 5, 6, 8]. The variety of clinical signs often leads to difficulties in diagnosing the systemic form of JRA and choosing the correct treatment tactics. The systemic form of JRA should be differentiated from sepsis, low-grade tumors and diffuse connective tissue diseases. Delay in diagnosis and treatment can lead to serious complications. Until recently, glucocorticoids (GCs) and intravenous immunoglobulins were used in combination with traditional immunosuppressive therapy at the onset of the systemic form of JRA in the absence of articular syndrome. Some patients respond well to such therapy and systemic manifestations are successfully controlled. However, a large number of patients with the systemic form of JRA note the ineffectiveness of traditional drugs, which prompts doctors to look for new ways to treat this disease.

Today, the solution to this problem is genetically engineered biological drugs. A characteristic feature of this group of drugs is the selective neutralization of some factors in the pathogenesis of JRA. TNF-alpha inhibitors are among the first biological drugs, however, according to international clinical studies, drugs of this class do not always achieve the desired result in children with systemic IRA [3, 6]. This is due to different pathogenetic mechanisms of

development of systemic and articular forms of JRA. It is currently believed that the development of the systemic form occurs primarily due to the overproduction of IL-6. In 2011, tocilizumab (Actemra) was registered in the United States, the European Union and Russia, the first drug for the treatment of systemic IRA that blocks the action of interleukin-6. It is the only drug approved for the treatment of systemic YRA. Tocilizumab (Actemra) is a recombinant monoclonal antibody against the human interleukin-6 receptor from the IgG1 subclass of immunoglobulins.

Despite the use of anti-inflammatory non-steroidal and glucocorticoid drugs in the treatment of patients with TBIA, it causes increased destructive changes in the joints, relapse of extra-articular symptoms and an increase in the level of disability (Kostik M.M., 2017; Horneff G., 2016; Berman M., 2021). For this reason, it seems relevant to study the features of the systemic development of juvenile arthritis against the background of genetic engineering biological therapy.

PURPOSE OF THE STUDY. Studying the features of the systemic development of juvenile arthritis in children against the background of genetic engineering biological therapy.

Materials and methods. At the Republican Specialized Children's Scientific and Applied Medical Center, 45 patients aged 2 to 18 years with systemic rheumatoid arthritis were examined. The average age of the patients was 8.87±0.48 years, the majority of patients in both groups were of primary school age. The number of boys in both groups (1st group 59.3%, 2nd group 72.2%) occupied the bulk of the group.

In order to study the course of the disease, the patients were divided into 2 groups. The 1st main group included 27 (60%) patients who received a genetically engineered biological drug (tocelizumab) as part of the complex treatment of children, and the 2nd comparison group. included 18 (40%) patients. In the complex treatment, the genetic engineer did not take a biological drug.

Before treatment, sick children underwent clinical, anamnestic, laboratory and instrumental studies. In addition, patients' functional status and level of pain/discomfort were assessed using the 30-item CHAQ (Childhood Health Assessment Questionnaire; 0–3) questionnaire. Examinations and questionnaires were carried out 3, 6, 9 months after treatment.

Statistical methods - IBM PC programs “Statistica 7.0”, “BIOSTAT” were used.

Results. A genetically engineered biological drug (tocilizumab) was administered to children weighing up to 30 kg at a dose of 12 mg/kg, and to patients weighing more than 30 kg - 8 mg/kg intravenously for 1 hour every 2-4 weeks. The average number of courses was 10 (8-10).

As a result, after 9 months there was a significant decrease in systemic symptoms. In group 1, rashes decreased from 29.6% to 3.7%, lymphadenopathy - from 81.5% to 7.4%, serositis - from 25.9% to 0%. In group 2, rashes decreased from 11.1% to 5.6%, lymphadenopathy from 55.5% to 33.3%, serositis from 22.2% to 11.1%.

Laboratory parameters in group 1 increased: SRO from 49.9 + 8.1 to 25.2 + 6.1, ECT from 24.7 + 3.8 to 10.1 + 1.21, LDH from 536.7 + 40, changed from 9 to 409.9+20.6. In group 2, these indicators increased from SRO 20.4 + 3.4 to 30.9 + 10.6, ECT from 20.7 + 3.8 to 19.06 + 3.8, LDH from 421 + 50, 9 to 471 changed to 0.3+54.2.

During instrumental examination of internal organs in patients receiving biologically active drugs, a significant improvement was expected. We observed such an improvement in the percentage of serositis in sick children.

According to the Jadas10 index, the dynamics of TBYA activity decreased from 19.6 points to 3.8 points in group 1 and from 19.6 points to 10.4 points in group 2.

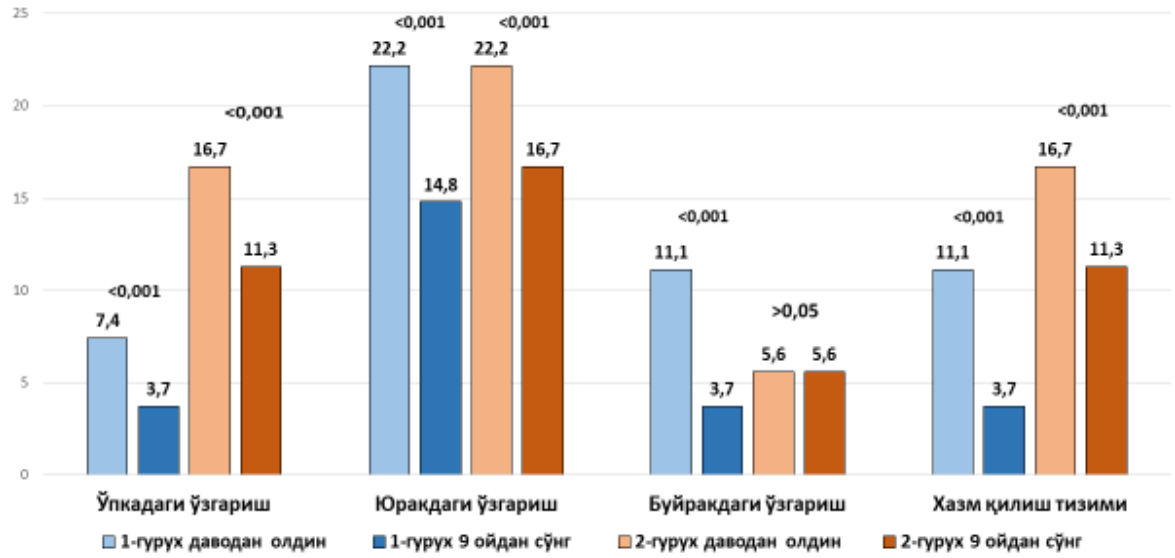
92.6% of patients in group 1 and 72.2% in group 2 had an inactive phase of the disease when examined according to K. Wallack's remission criteria.

ТБЮА болаларда лаборатор кўрсаткичлар динамикаси

Кўрсатгичлар	1 гурух			2 гурух			P1	P2
	Давогача	3 ой	9 ой	Давогача	3 ой	9 ой		
СРБ, мг/л	49,9+8,1	31,1+6,8	25,2+6,1 *(<0,001)	20,4+3,4	25,4+6,9	30,9+10,6 *(0,001)	<0,05	<0,05
СОЭ, мм/ч	24,7+3,8	16,6+2,5	10,1+1,21 *(<0,001)	20,7+3,84	19,0+3,9	19,06+3,8 *(>0,05)	<0,05	<0,001
Гемоглобин, г/л	108,8+2,7	111,8+2,5	117,7+2,31 *(<0,001)	105,0+3,7	106,6+4,9	111,6+3,5 *(<0,001)	<0,001	<0,001
Лейкоциты, тыс./мкл	12,9+1,51	10,78+1,0	8,3+0,92 *(<0,001)	10,1+1,3	11,9+ 1,6	10,3+1,1 *(>0,05)	<0,05	<0,001
Тромбоциты, тыс./мкл	537,2+30,7	437,2+30,7	305,9+17,9 *(<0,001)	446,6+31,9	425,6+59,2	419,5+40,3 *(<0,05)	>0,05	<0,001
ЛДГ (Ед/л)	536,7+40,9	483,6+38,3	409,9+20,6 *(<0,001)	421+50,9	462,8+43,6	471,3+54,2 *(<0,05)	>0,05	<0,001

Изоҳ: *-даволашдан олдин ва 9 ойдан кейинги фарқларнинг ишончлилиги
P1 – даводан 3 ой кейинги даврда 1 ва 2 гуруҳлар кўрсаткичлари ўртасидаги фарқларнинг ишончлилиги
P2 – даводан 9 ой кейинги даврда 1 ва 2 гуруҳлар кўрсаткичлари ўртасидаги фарқларнинг ишончлилиги

ГИБП фонида 9 ойдан кейинги ички аъзолардаги функционал ва инструментал ўзгаришлар динамикаси



Changes in the lungs
• Group 1 before treatment
Changes in heart
• Group 1 after 9 months
Changes in the kidney
• Group 2 before treatment
Digestive system
• Group 2 after 9 months

Summary. In the dynamics of treatment, 92.6% of patients with TBIA showed normalization of hemoglobin concentration, the number of leukocytes, neutrophils and platelets, and FRO concentration in the blood serum 9 months after the start of therapy, which indicated that the disease had reached inactive criteria.

In children with TBIA, against the background of biological therapy, there is a significant regression of functional and instrumental disorders of the respiratory, cardiovascular and digestive systems ($p < 0.01$).

In children with TBIA during biological therapy, the average CHAQ index dynamically improved after 9 months. Corresponds to minimal functional impairment and amounted to 0.04 (0.01-0.37) points.

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