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Clinical case of tocilizumab use in a patient with systemic juvenile idiopathic arthritis

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The article presents a case of successful use of a preparation of monoclonal antibodies to interleukin 6 receptors (tocilizumab) at a severe systemic juvenile idiopathic arthritis. Tocilizumab treatment promptly provided decrease of clinical and laboratory parameters of the disease activity, increase in the child's physical activity, systemic juvenile idiopathic arthritis remission development and allowed avoiding per os prescription of glucocorticoids.
Key words: *children, systemic juvenile idiopathic arthritis, tocilizumab.*

Systemic arthritis is a variant of juvenile idiopathic arthritis (sJIA) characterized by a wide range of extraarticular manifestations: pyretic fever, myopericarditis, pneumonitis, polyserositis [1]. Systemic JIA may appear at any age and is as frequent in boys as in girls. Despite the therapy involving non-steroidal anti-inflammatory drugs, glucocorticoids and immunosuppressants, destructive articular alterations and disability progress, extraarticular manifestations relapse in 50% of sJIA patients [1, 2]. It must be noted that glucocorticoids neither control the disease course nor prevent osteochondral destruction and incapacitation of patients, whereas long-term use thereof results in the development of severe and often irreversible consequences, such as Cushing's syndrome, dwarfism, delayed puberty, adrenal insufficiency, osteoporosis, cataract and hormone dependence [1-3]. Sometimes a long-term active inflammatory process, "cytokine storm" results in the development of a dangerous life-threatening complication – hemophagocytic syndrome – in sJIA patients [4, 5].
That is why practical application of new drugs for severe systemic juvenile idiopathic arthritis is one of the most important issues of the modern rheumatology. One such drug is tocilizumab – recombinant humanized monoclonal antibodies to the human interleukin 6 receptor (*Interleukin*, IL) – a cytokine playing a leading part in the development of extraarticular symptoms of the disease. The following clinical study bears evidence of validity thereof.
Patient Karina R., 9 years of age, diagnosed with "Juvenile arthritis with systemic onset" has been being observed at the rheumatology ward of the Scientific Center of Children's Health since September 2013 (9 years of age). The girl has been suffering since the age of 7 years (May 2012), when pyretic fever, body and extremity rash (maculopapular rash; migratory rash declining within a day; hand skin flaking), leg and shoulder pain appeared. The child was hospitalized to the district inpatient hospital. Clinical blood analysis performed in the framework of examination revealed erythrocyte sedimentation rate (ESR) increase up to 55 mm/h and leukocytosis (amount of leukocytes – $14x10^9$/l); enzyme immunoassay revealed positive antibodies to Lamblia and Yersinia. Diagnosis: "Exanthematic articular pseudotuberculosis, enterobiasis, intestinal giardiasis". The girl received etiotropic therapy. Maculopapular rash, fever and articular pains terminated in the setting of treatment. Low-grade fever, skin rashes (small papular and urticarial rashes present until 12:00 only) reappeared in autumn 2012. Feces analysis revealed helminth eggs (ascarids) twice. Hence, the girl received etiotropic therapy; the second feces analysis did not reveal helminth eggs.
Edema, skin hyperemia, tenderness to palpation and motion in the area of metatarsophalangeal articulations of left foot toes II-IV appeared for the first time on 01.02.2013. The district surgeon diagnosed the girl with phlegmon and prescribed treatment with antibacterial drugs and

antihistamines, as well as with Vishnevsky ointment for topical use. The therapy did not yield any effect. The child received antibacterial therapy courses several times within 4 months due to low-grade fever. Body temperature has become febrile since 30.05.2013 observable in the morning. The girl occasionally complained of pain in the left knee joint. The child was diagnosed with "Idiopathic fever" and hospitalized to the infectious diseases ward of the district inpatient hospital. At the inpatient hospital the patient had been receiving antibacterial therapy with ceftriaxone for 7 days, with azithromycin – for 4 days. No positive dynamics was observed in the child's condition in the setting of treatment; pyretic fever continued to persist. The patient started to complain of morning stiffness in hand joints, primarily in digital joints of fingers V. Pathologic alteration were worsening according to the laboratory parameters as well. Clinical blood analysis: anemia (hemoglobin – 85 g/l), thrombocytosis up to $784x10^9$/l, leukocytosis up to $16x10^9$/l, ESR increase up to 67 mm/h; immunoassay: serum C-reactive protein (CRP) concentration increase up to 14 mg/l. The child underwent computed examination of pelvic organs, thoracic and abdominal cavities, knee and hip joints, bone marrow and lymph node biopsy. The performed examinations revealed left knee joint synovitis, sacroileitis, hepatosplenomegaly, generalized lymphadenopathy and tuberculosis primary complex in the stage of calcination. On the basis of the clinical laboratory instrumental examination, the patient was diagnosed with "Juvenile arthritis with systemic onset". The prescribed therapy with non-steroidal anti-inflammatory drugs and antitubercular drugs proved ineffective.

Due to the process's remaining activity, the girl was for the first time forwarded to the rheumatology ward of the Scientific Center of Children's Health.

The child's condition at admission to the ward was considered severe. Daily body temperature increase up to febrile values, intense swelling of knee (pic. 1a), ankle, wrist, elbow and small hand and foot joints (pic. 2a) and characterized by severe pain and motion restriction were observed. Morning stiffness duration was 4 hours. The girl was usually unable to leave bed and attend to herself due to joint pains. Skin paleness and dark circles under eyes attracted attention at physical examination. Laboratory examination: clinical blood analysis revealed anemia, thrombocytosis, significant ESR increase; immunoassay: more than a tenfold serum CRP concentration increase (tb.). Given the disease's clinical presentation (long-term fever, rash, generalized articular syndrome, hepatosplenomegaly, lymphadenopathy), high laboratory parameters of disease activity (ESR and CRP), diagnosis "Systemic juvenile idiopathic arthritis" (according to ICD-10, M08.2 ""Juvenile arthritis with systemic onset") was confirmed.

The drug to be used to treat the patient was selected on the basis of the leading role of IL 6 in the genesis of extraarticular juvenile arthritis manifestations [6], hepatocytic synthesis of acute-phase inflammatory proteins (CRP, amyloid A, haptoglobin and fibrinogen) and anemia development due to hepatocytic hepcidin secretion. Hepcidin decreases intestinal absorption of iron and inhibits its release out of macrophages, which causes development of iron deficiency (erythropoiesis) [7-11]. In normal concentrations, IL 6 improves synthesis of adrenocorticotropic hormone and cortisol, production of growth hormone and procalcitonin [12]. In high concentrations, IL 6 blocks production of these hormones, which results in development of fatigue, sleepiness, depression, cognitive disorders and growth retardation in children with systemic juvenile idiopathic arthritis [13]. Development of amyloidosis – a lethal sJIA complication – is also associated with activity of this cytokine.

Tocilizumab (Actemra, F. Hoffmann-La Roche Ltd., Switzerland) is registered in the Russian Federation, Europe, the USA and Japan as a drug for treating rheumatoid arthritis, polyarticular and systemic juvenile idiopathic arthrites [13, 14]. Grounds for registering the drug for treating systemic juvenile idiopathic arthritis – positive results of a range of clinical trials aimed at assessing efficacy and safety of tocilizumab therapy in children with this variant of the disease [15-21].

Result s of tocilizumab trials demonstrated high efficacy and safety of the drug in children with sJIA; this allowed initiating tocilizumab treatment at the rheumatology ward of the Scientific

Center of Children's Health in the case of our patient. The drug was administered by drop infusion intravenously (dose – 8 mg/kg of body weight once per 2 weeks).

Generalized articular syndrome manifested itself in the patient with intense swelling of knee, ankle, wrist, elbow and small hand and foot joints and characterized by severe pain and motion restriction. Morning stiffness duration was 4 hours. The girl was prescribed methotrexate (dose – 15 mg/m^2 of body surface per week) in combination with tocilizumab therapy.

Analysis of tocilizumab and methotrexate therapeutic effect development rates demonstrated that fever terminated and the girl became more active after the first administration; morning stiffness duration decreased down to 30-40 minutes, pain became less intense, range of motions in knee (pic. 1b), wrist, ankle, elbow and small hand joints (pic. 2b) improved, the girl became able to attend to herself, laboratory parameters of disease activity decreased after 4 weeks (see tb.). After 4 months of observation the child's condition remained stable: the girl had no fever, rash and morning stiffness terminated, range of motions in knee, ankle, wrist, hip, elbow and small hand joint completely recovered, which is why the inactive disease stage was registered. No adverse phenomena were observed in the setting of tocilizumab treatment.

Thus, analysis of this clinical case demonstrates severe rapidly progressing course of systemic juvenile idiopathic arthritis characterized by pyretic fever, severe articular syndrome and intense functional incompetence.

Prescription of human monoclonal antibodies to IL 6 receptor secured decrease in clinical and laboratory parameters of disease activity, sJIA remission development and allowed avoiding *per os* prescription of glucocorticoids.

Lack of adverse phenomena in response to tocilizumab administration should be noted.

The obtained results demonstrate that the drug's choice was correct and reconfirms high tocilizumab efficacy for treating juvenile idiopathic arthritis.

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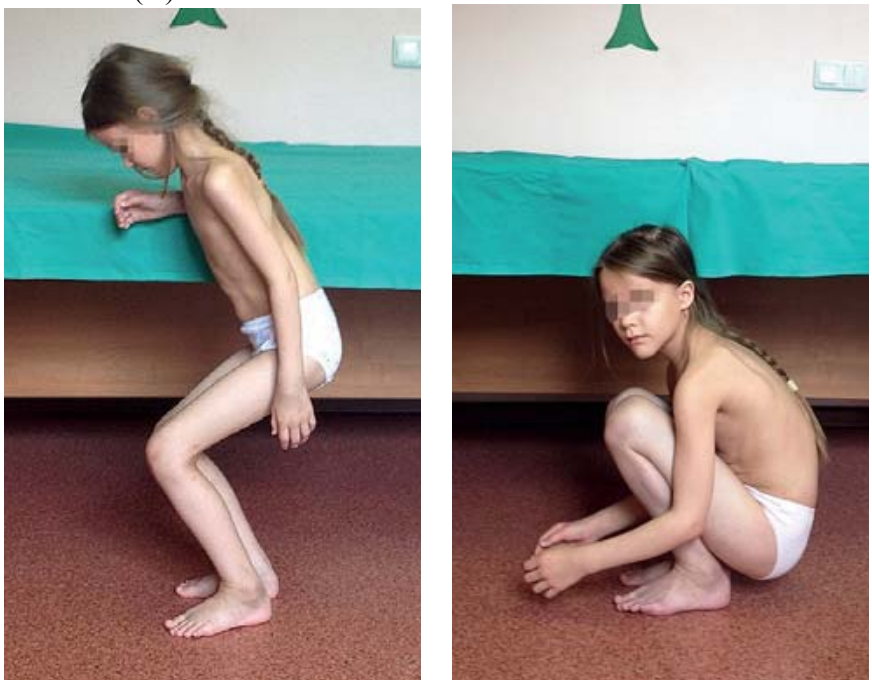
Pic. 1. Functional capacity of knee joints before treatment (A) and in the setting of tocilizumab treatment (B)



Pic. 2. Functional capacity of hand digital joints before treatment (A) and in the setting of tocilizumab treatment (B)

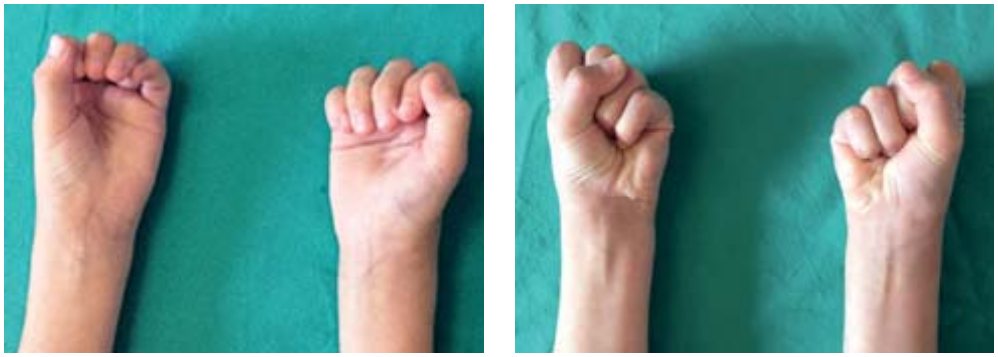


Table. Dynamics of clinical and laboratory parameters of systemic JIA activity in the setting of tocilizumab therapy in patient Karina R., 9 years of age.

Parameters	**Tocilizumab therapy duration**			
	No therapy	**1 day**	**4 weeks**	**20 weeks**
Body temperature (^{o}C)	39.0	36.7	36.6	36.7
Maculopapular rash	Y	Y	N	N
ESR (mm/h)	70	27	4	5
Hemoglobin (g/l)	85	120	127	123
Erythrocytes (x10^{12}/l)	3.71	4.4	5.04	5.34
Platelets (x10^{9}/l)	713	714	224	300
Leukocytes (x10^{9}/l)	11.46	10.91	6.52	7.3
CRP (mg/l) (norm – up to 5)	177	5.26	<1.0	<1.0
IgG (g/l) (norm – 5.72-14.74)	31.73	-	15.11	13.3
ACR_{pedi} criteria improvement (%)	-	-	90%	-