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

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The article presents a case of successful application of a monoclonal antibodies drug to interleukin 6 receptors (tocilizumab) at severe systemic juvenile idiopathic arthritis with the development of secondary hemophagocytic syndrome. Tocilizumab treatment secured a decrease in clinical and laboratory parameters of the disease activity, life quality improvement, systemic juvenile idiopathic arthritis and hemophagocytic syndrome remission and allowed avoiding the per os prescription of glucocorticoids.

Keywords: *children, systemic juvenile idiopathic arthritis, hemophagocytic syndrome, tocilizumab.*

Systemic arthritis is a variant of juvenile idiopathic arthritis (sJIA), which takes its course with a wide range of extra-articular manifestations: pyretic fever, myopericarditis, pneumonitis and polyserositis [1]. Destructive articular alterations progress, extra-articular manifestations relapse and incapacitation aggravates steadily in 50% of patients with sJIA despite the therapy conducted with non-steroid anti-inflammatory drugs and glucocorticoids. It should be noted that glucocorticoids do not control the disease course or prevent osteochondrous destruction and incapacitation of patients from progressing, while protracted application of them results in the development of severe and often irreversible consequence, in particular, of Cushing's syndrome, dwarfism, sexual development delay, adrenal failure, osteoporosis, cataract and hormone dependence [1-3]. Protracted active inflammatory process – “cytokine storm” – in patients with sJIA leads to the development of a life-threatening complication – hemophagocytic syndrome – in a range of cases [4, 5].

That is why one of the important issues of modern rheumatology is the introduction of new drugs for treating systemic juvenile arthritis in practice. Tocilizumab is recombinant

humanized monoclonal antibodies to human interleukin (IL) 6 receptor, cytokine, which plays the key role in the development of extra-articular disease symptoms; this is indicated by the following clinical observation.

Patient A., 2 years of age, has been ill since June 2012. The girl contracted the disease at the age of 1 year 4 months, when pyretic fever up to 39°C and maculopapular rash appeared 2 weeks after a viral infection. The child was hospitalized to the local inpatient hospital, where leukocytosis up to $28 \times 10^9/l$, thrombocytopenia up to $32 \times 10^9/l$ and ESR acceleration to 120mm/h were revealed by the clinical blood analysis at examination. Biochemical blood analysis: increase in the serum level of aspartate aminotransferase (AST) up to 250 norms, of alanine aminotransferase (ALT) – up to 10 norms. Diagnosis established: “Kawasaki disease. Disseminated intravascular coagulation. Sepsis”. The child received various combinations of antibacterial drugs, normal human immunoglobulin for intravenous administration, antiaggregants and anticoagulants. Replacement transfusion of blood components was conducted due to the pronounced thrombocytopenia. The condition improved in the setting of the conducted treatment, so the girl was discharged from the hospital.

In the beginning of August 2012 edema and tenderness developed in the girl's right knee, ankle joints and right foot's small joints. The girl stopped leaning on the leg and refused to walk. The child's parents consulted the local surgeon and were forwarded to hospitalization. Fever up to 39°C and maculopapular rash all over the body reappeared several days after the inpatient treatment had started. Intensity of rash decreased with temperature reduction and became pale. Clinical blood analysis: leukocytes – $4.5 \times 10^9/l$, platelets – $450 \times 10^9/l$, ESR – 55mm/h. Biochemical blood analysis revealed the persistence of the increased serum levels of AST (up to 4 norms) and ALT (up to 5 norms). Diagnosis established: “Juvenile arthritis with systemic onset”; the initial treatment included non-steroid anti-inflammatory drugs, dexamethasone, normal human immunoglobulin for intravenous administration and methylprednisolone pulse-therapy. The treatment helped to arrest the articular syndrome, although fever and high laboratory activity parameters continued to persist.

Due to the process's persisting activity, the girl was transferred to the rheumatology department of the Scientific Center of Children's Health 5 months after the disease onset (2012).

The child's condition at admission to the department was considered severe. Daily temperature rises to low-grade fever were observed. There were no acute inflammatory alterations in joints or morning stiffness. Skin pallor and dark shadows beneath the eyes attracted attention. The examination (tb.) clinical blood analysis revealed tendency to leukopenia, thrombocytopenia, significant ESR increase and hypochromic anemia. Immunological blood analysis: more than tenfold increase in the C-reactive protein's serum concentration and more

than fifteen-fold increase in the ferritin serum level. Biochemical blood analysis revealed a considerable increase in the level of hepatic transaminases: ALT – up to 1,086 ea/l, AST – up to 695 ea/l, lactate dehydrogenase – up to 790 ea/l. Periodic syndromes, autoimmune hepatitis, hemoblastoses and neoplastic processes were ruled out. Trepanobiopsy revealed an active secondary hemophagocytic syndrome. Given the disease's clinical presentation and results of the conducted trials, the diagnosis “juvenile idiopathic arthritis with systemic onset” (according to the ICD-10, M08.2) did not give rise to any doubt.

Table. Dynamics of clinical and laboratory parameters of activity of systemic juvenile idiopathic arthritis in the setting of tocilizumab therapy in patient A., 2 years of age

Parameters	Before the beginning of pulse therapy with methylprednisolone and IVIG	Tocilizumab therapy duration				
		setting	day 1	4 weeks	26 weeks	52 weeks
Body temperature (°C)	39.4	39.0	36.7	36.6	36.6	36.6
Maculopapular rash	present	present	present	none	none	none
CHAQ functional incompetence index, points	2.25	2.2	1.7	0.25	0	0
ESR (mm/h)	65	70	55	3	5	2
Hemoglobin (g/l)	90	85	90	115	112	124
Erythrocytes ($\times 10^{12}/l$)	3.57	3.48	3.8	4.4	4.25	4.5
Platelets ($\times 10^9/l$)	305	541	520	375	358	335
Leukocytes ($\times 10^9/l$)	3.61	17.46	10.8	5.26	5.7	5.2
CRP (mg/l), norm (up to 5)	120	13	10	<1.0	<1.0	<1.0
IgG (g/l), norm (5.72-14.74)	15.38	14.8	-	10.8	14.2	11.8
Height, cm	86	86	86	86	87	88
Weight, kg	10	10	10	10.5	11	12
Improvement percentage according to the ACR _{pedi}	-	-	-	90%	Inactive disease	Disease remission

Note. IVIG – intravenous immunoglobulins; CHAQ allows evaluating functional status of children with juvenile arthritis; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; ACR_{pedi} – pediatric criteria of the American College of Rheumatology

The child was prescribed life-saving methylprednisolone pulse therapy in the dosage of 15mg/kg per administration with gradual dosage reduction; she also received therapy with normal human immunoglobulin for intravenous administration in the dosage of 2g/kg. The

condition improved and fever cut off in the setting of therapy. However, temperature rises up to 39°C and maculopapular body rash reappeared when an attempt to reduce the dosage of intravenous glucocorticosteroids had been made (pic. 1, a-c). According to the control clinical and immunological blood analyses, pathologic process activity did not decrease (see tb.). Given the disease's aggressive course signs (fever, rash, high immunologic activity, secondary hemophagocytic syndrome's development, impossibility to withdraw intravenous glucocorticosteroids), there were indications to the prescription of glucocorticoids for peroral intake in the dosage of 2mg/kg per day according to all world protocols. Insufficient efficacy of intravenous methylprednisolone on the one hand and dependence of the process's activity on its dosage on the other indicated that peroral intake would most probably be insufficiently efficient and provoke uncontrollable hormone dependence. Other important reasons for rejecting prednisolone's peroral intake were the child's age, pronounced Cushing's syndrome, risk of development of dwarfism and other severe glucocorticoid intake complications in the girl. That is why it was decided to abstain from the peroral prednisolone prescription and begin therapy using a genetically engineered biologic drug of recombinant humanized monoclonal antibodies to IL 6 receptor – tocilizumab.

Pic. 1 (a-c). Maculopapular rash on the body of the patient with systemic juvenile idiopathic arthritis



The drug's choice was determined by the key role of IL 6 in the genesis of extra-articular manifestations of juvenile arthritis [6, 7], synthesis of acute-phase inflammation proteins (C-reactive protein, amyloid A, haptoglobin and fibrinogen) by hepatocytes and anemia development due to the hepcidin secretion by hepatocytes. Hepcidin decreases intestinal absorption of iron and inhibits its release from macrophages, thus causing development of deficiency of iron for erythropoiesis [8-12]. IL 6 in normal concentrations intensifies synthesis of adrenocorticotrophic hormone and cortisol and production of growth hormone and prolactin.

[12, 13]. On the contrary, IL 6 in increased concentrations block the production of these hormones, thus causing development of fatigue, sleepiness, depression, cognitive disorders and development delay in children with juvenile arthritis [12-14]. Development of amyloidosis – a fatal sJIA complication – is also associated with the 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 arthritis [15-17].

The reason for registering the drug for treating systemic juvenile arthritis was positive results of a range of clinical studies aimed at assessing efficacy and safety of tocilizumab therapy in children with systemic arthritis [18-29].

The international 5-year-long multicenter randomized double-blind placebo-controlled study of tocilizumab efficacy and safety in patients with systemic juvenile arthritis (TENDER) is now in progress [27, 28]. Study results obtained by observation weeks 12 and 52 have been published. The study involved children of 2-17 years of age with the diagnosis “Systemic arthritis” established according to the criteria of the International League of Associations for Rheumatology (ILAR) with persisting disease’s activity signs for the previous 6 months, insufficient glucocorticoid therapy efficacy, non-steroid anti-inflammatory drugs, fever and active arthritis. The study consisted of 2 phases: 12-week-long double-blind randomized placebo-controlled and non-blind phases (total study duration – 5 years) [27, 28]. In the first phase the patients randomized into the first group were treated with tocilizumab (n=75), the patients of the second group – with placebo (n=37). The non-blind phase involved children who had not dropped out from the first study phase. In this study phase all patients received tocilizumab in a non-blind manner. In all phases the drug was introduced intravenously by drop infusion in the dosage of 8mg/kg of body weight every 2 weeks in patients with body weight ≥ 30 kg and in the dosage of 12mg/kg of body weight in patients with body weight ≤ 30 kg. Treatment efficacy was evaluated by pediatric criteria of the American College of Rheumatology (ACR_{pedi}).

Thus, the study involved 112 children with sJIA. All the children had previously been treated with immunosuppressive agent, glucocorticoids; most children had been receiving genetically engineered biologic drugs (anakinra – 54 patients, TNF α blockers – 81 children). The patients were characterized by a high degree of disease’s activity: ESR of 57 ± 34 mm/h, CRP concentration of 166 ± 349 mg/l, 19 ± 16 joints with active arthritis and malfunction and fever over 37.5°C for 14 days prior to screening were observed in 62 (55%) out of 112 children.

30% improvement according to the ACR_{pedi} criteria and lack of fever (primary end point) in the end of the double-blind phase were registered in 64 (85%) out of 75 children treated with

tocilizumab and only in 9 (24%) of the children, who received placebo. 50, 70 and 90% improvement according to the ACR_{pedi} criteria were observed in 85, 71 and 37% out of 75 children treated with tocilizumab, respectively, and in 11, 8 and 5% out of the 37 placebo group children ($p < 0.001$) [27, 28].

The finishing non-blind phase involved 110 children: 88 of them continued treatment with tocilizumab by observation week 52. 30% improvement according to the ACR_{pedi} criteria and lack of fever after 52 weeks and lack of fever were observed in 77 (88%) of children. 70 and 90% improvement according to the ACR_{pedi} criteria was registered in 78 (89%) and 57 (65%) of children, respectively. Number of joints with active arthritis reduced down to 3 ± 7 , the number of joints with malfunction – down to 7.5 ± 11.7 ; number of children with fever over 37.5°C reduced down to 8 (9%); CHAQ functional incompetence index reduced from 1.7 ± 0.9 to 0.7 ± 0.8 ; disease activity evaluation by the visual analog scale and in the opinion of the patients' doctors and parents reduced from 64.9 ± 22.3 and 58.7 ± 24.4 to 9.7 ± 12.8 and 12.6 ± 18.5 , respectively.

It should be noted that the daily glucocorticoid dosage was reduced from 0.3 ± 0.2 to 0.06 ± 0.08 mg/kg per day; it was possible to withdraw glucocorticoids in 48% of patients.

Tocilizumab therapy safety analysis showed that 33 severe unfavorable phenomena were registered in 25 patients. 13 of them were considered to be associated with tocilizumab treatment. They included increase in transaminases (in 2 patients), angioedema (in 1), urticarial (in 1), hemophagocytic syndrome (in 1), pulmonary hypertension (in 1), gastroenteritis (in 1), septic arthritis (in 1), otitis media (in 1), panniculitis (in 1), pharyngotonsillitis (in 1), infection of upper airways (in 1) and chickenpox (in 1). 15 cases of severe infectious unfavorable phenomena were registered; 6 of them were associated with tocilizumab therapy. All unfavorable phenomena resolved and the patients continued to take part in the study. In the process of the non-blind phase 12 children dropped out from the study due to the development of severe unfavorable phenomena, 4 – due to the lack of effect. One patient died of pressure pneumothorax not associated with tocilizumab treatment.

Thus, the drug's study results demonstrated its high efficacy and safety in children with sJIA; this allowed initiating tocilizumab treatment of our patient at the RAMS SCCH rheumatology department.

The drug was administered intravenously by drop infusion in the dosage of 12mg/kg of body weight once in 2 weeks. The drug's prescription was approved by the Academic Senate, Local Ethic and Formulary Committees of the Scientific Center of Children's Health. The child's parents signed an informed consent to the tocilizumab application.

Tocilizumab's therapeutic effect development rate analysis showed that fever cut off after the very first administration, the girl became more active; we managed to completely withdraw

glucocorticosteroids for intravenous administrations without withdrawal syndrome after 1 week; skin rash cut off completely (pic. 2, a-c) and laboratory parameters of the disease's activity normalized (see tb.) by observation week 4. Inactive disease status was registered in the patient after 1 month of therapy; remission – after 7 months. The girl has been receiving intravenous tocilizumab infusions in the dosage of 12mg/kg of body weight once in 2 weeks for 1 year. The disease's remission has remained for the whole observation period. The girl grew by 2cm and gained 2kg within 1 year of therapy (see tb.).

Pic. 2 (a-c). Appearance of the child with systemic juvenile idiopathic arthritis 4 months after the therapy beginning



In the setting of tocilizumab therapy, neutropenia cases were registered in the first weeks after infusions. 2 acute respiratory viral infection episodes with bronchoobstructive syndrome, which did not require hospitalization to inpatient department, were observed.

Thus, analysis of the given clinical case demonstrates severe and quickly progressing course of systemic juvenile arthritis characterized by pyretic fever, secondary hemophagocytic syndrome development, low quality of life and pronounced hormone dependence. Prescription of human monoclonal antibodies to IL 6 receptor secured decrease in clinical and laboratory parameters of the disease's activity, sJIA and hemophagocytic syndrome's remission development and allowed avoiding the *per os* prescription of glucocorticoids.

It is necessary to note the lack of severe unfavorable phenomena in response to the administration of tocilizumab. The obtained results indicate that the drug's choice was correct and reaffirm high efficacy of tocilizumab for treating systemic juvenile arthritis.

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