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Clinical case: use of canakinumab in a patient with systemic juvenile idiopathic arthritis resistant to immunosuppressants and genetically engineered biopharmaceuticals

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The article presents a case of successful use of an interleukin-1 monoclonal antibody drug (canakinumab) for severe systemic juvenile idiopathic arthritis refractory to treatment with classic immunosuppressants and genetically engineered biopharmaceuticals with a different mode of action. Canakinumab treatment shortly provided reduction in clinical and laboratory parameters of the disease activity, life quality improvement, development of an inactive disease stage and allowed reducing the prednisolone dose by 90% and avoiding intravenous and intraarticular administration of glucocorticoids.
Keywords: *systemic juvenile idiopathic arthritis, canakinumab, children.*

Juvenile idiopathic arthritis (JIA) is a severe chronic consistently progressing disease on the basis of activation of both cell-mediated and humoral immunity. Immune inflammation leads to the development of chronic synovitis and extraarticular manifestations, which often result in multiple organ failure and destruction of cartilaginous and osseous joint tissues. Such alterations lead to incapacitation and sometimes to death of the patients [1].
Control over JIA course may be achieved only with pathogenetic therapy and consists in suppression of inflammatory synovitis activity, maximum recovery of articular function, deceleration of progression of destructive joint alterations, control over systemic manifestations of the disease, termination of pain and reduction in psychological disease-associated restrictions. Antirheumatic therapy must ultimately lead to remission or at least a very low activity of the disease [2-4].
That is why introduction of new drugs for treating severe systemic juvenile arthritis into practice is one of the most important issues of modern rheumatology. One such drug is canakinumab – recombinant humanized monoclonal antibodies blocking interleukin (IL) 1β, which plays the crucial role in the development of extraarticular symptoms of the disease [5, 6].
The following clinical case demonstrates efficacy of canakinumab.
The boy developed the disease in December 2010, at the age of 5 years. The onset was characterized by pyretic fever, maculopapular rash, lymphadenopathy, hepatomegaly, pain and movement restriction in knee and ankle joints and high laboratory values of activity parameters (erythrocyte sedimentation rate [ESR] – 42 mm/h; C-reactive protein [CRP] - +++++). After infectious diseases, neoplasms and hemoblastoses were ruled out, specialists at the local inpatient hospital established diagnosis "Juvenile arthritis with systemic onset". The boy was prescribed prednisolone – 1 mg/kg per day (17.5 mg), methotrexate – 15 mg/m^2 per week (10 mg/week) intramuscularly, diclofenac – 50 mg/day; the boy underwent a course of therapy with normal human immunoglobulin. Fever, rash and inflammatory joint alterations terminated and laboratory parameters of the disease activity normalized in the setting of the treatment. The

child was discharged from the inpatient hospital and recommended to continue the therapy at home gradually reducing the prednisolone dose. The disease exacerbated in May 2011, when the prednisolone dose dropped to 2.5 tablets (12.5 mg): pyretic fever, abundant skin rash, morning stiffness of up to 2 hours, inflammatory alterations of knee, ankle and proximal interphalangeal joints (fingers 2 and 3 of both hands), pain and movement restriction therein developed again. The child was rehospitalized to the local inpatient hospital; the examination revealed high laboratory parameters of the disease activity (ESR – 55 mm/h, CRP - +++++). Due to the disease exacerbation, it was decided to perform pulse therapy with methotrexate in the dose of 50 mg/m^2 per week intravenously (35 mg/week). The child received 4 methotrexate injections at the hospital without positive effect. Due to the absence of positive dynamics in the setting of the therapy, the child was transferred to the rheumatology department of the Scientific Center of Children's Health (SCCH) in July 2011.

The child was admitted to the department at the age of 5.5 years, six months after the disease onset. The child's condition at admission to the department was estimated as severe. Daily multiple body temperature rises up to fever and maculopapular rashes on skin and extremities were observed. Articular syndrome progressed; inflammatory alterations of knee, ankle and proximal interphalangeal joints (fingers 2-4 of both hands) were observed. Joint movement was restricted and painful. The child complained of morning stiffness of up to 2 hours. Skin pallor and dark circles under eyes came under notice during the examination. Clinical blood analysis revealed leukocytosis of up to 22 x 10^9/l, thrombocytosis of up to 700 x 10^9/l, considerable ESR increase up to 40 mm/h and hypochromic anemia (hemoglobin level reduced down to 77 g/l). Immunological blood analysis – a more than 14-fold increase in the serum CRP concentration (75 mg/l). Periodic syndromes, hemoblastoses and neoplastic processes were ruled out. Taking into consideration clinical pattern of the disease and results of the performed tests, diagnosis "Juvenile idiopathic arthritis with systemic onset" (according to ICD-10, M08.2) did not raise any doubt.

Given the symptoms of aggressive course of the disease (fever, rash, high immunologic activity), increase in the dose of glucocorticoids for oral intake up to 1-2 mg/kg per day could be prescribed according to all the international protocols. However, taking into consideration the child's age, high risk of dwarfism and other severe glucocorticoid-induced complications (osteoporosis, obesity, delayed puberty, psychosis, hormone dependence and hormone resistance) [7], we decided against increasing the prednisolone dose and to start therapy with a genetically engineered biopharmaceutical based on recombinant humanized monoclonal antibodies to IL6 receptor – tocilizumab (according to sJIA treatment protocol) [8].

The patient received the drug in the dose of 12 mg/kg of body weight once per 2 weeks intravenously. Tocilizumab's therapeutic effect development rate analysis demonstrated that the first injection of the drug resulted in termination of pyretic fever, reduction in laboratory parameters of the disease activity and pain intensity; the boy became more active; however, maculopapular rash, low-grade fever and inflammatory joint alterations persisted.

The boy developed symptoms of intestinal infection (nausea, emesis, diarrhea) 4 days after the first tocilizumab infusion; leukocytosis became worse. Hence, we started antibacterial therapy with amikacin. Fever relapsed the following day; examination revealed double reduction in the amount of leukocytes and platelets and 5-fold ESR reduction, increase in ferritin over 2,000 ng/ml and in transaminases up to the triple normal value. On the basis of clinical-laboratory data we diagnosed macrophage activation syndrome, started urgent pulse therapy with methylprednisolone in the dose of 12 mg/kg per administration and continued antibacterial therapy with positive effect. Fever and infectious disease symptoms terminated and laboratory parameters normalized (concentration of transaminases and ferritin) in the setting of the treatment.

We continued therapy with tocilizumab in the dose of 12 mg/kg per administration once in 2 weeks in combination with methotrexate in the dose of 15 mg/m^2 per week intramuscularly; this helped to achieve the non-active disease stage and start reducing the prednisolone dose.

When the prednisolone dose was reduced down to 7.5 mg/day in January 2012, systemic manifestations of the disease, such as pyretic fever, rash, hepatosplenomegaly, generalized lymphadenopathy and inflammatory joint alterations relapsed again. The child was rehospitalized to the rheumatology department of the SCCH.

The condition at admission to the department was estimated as severe. Daily pyretic fever, maculopapular rashes on skin and extremities, progression of articular syndrome affecting knee, hip, wrist and proximal interphalangeal joints of all fingers of both hands were observed. Clinical blood analysis did not reveal any deviation of the amount of leukocytes and platelets and ESR from the age norm; immunological blood analysis did not reveal CRP concentration increase. Taking into consideration development of resistance to tocilizumab therapy, marked hormone dependence and high risk of severe glucocorticoid therapy-induced complications in the event of the prednisolone dose increase, we decide to prescribe rituximab to the patient.

Rituximab – chimeric high-affinity monoclonal antibodies to CD20 receptors on the surface of B lymphocytes. We have been using rituximab in patients with sJIA at our department since 2006 [9]. To this patient, rituximab was prescribed in the dose of 375 mg/m^2 of body surface per administration for 4 subsequent weeks. Prescription of the drug was approved by the local Ethics Committee of the SCCH. The child's parents signed an informed consent to the use of the drug.

The child's condition aggravated before rituximab therapy: pyretic fever of up to 4 episodes per day, prolonged (for 4-5 hours) morning stiffness, asthenia, intense joint pains were observed; the child could not leave the bed. Generalized articular syndrome, flexion contractures in knee and elbow joints and marked movement restriction in all groups of joints persisted. We registered high laboratory parameters of the disease activity. Infusion of methylprednisolone in the dose of 100 mg was performed before each administration of rituximab. No side effects due to administration of the drug were registered.

However, the therapy resulted in only a short-term effect; the patient's condition was gradually aggravating, pyretic fever relapsed again, hepatosplenomegaly, generalized lymphadenopathy persisted, asthenia, arthralgiae, morning stiffness and articular syndrome activity were becoming worse. Due to severe condition and increasing incapacitation, the methotrexate dose was increased up to 25 mg/m^2 per week and therapy with cyclosporine in the dose of 4 mg/kg per day was initiated; given high risk of macrophage activation syndrome, we performed pulse therapy with methylprednisolone in the dose of 10 mg/kg per day for 3 days.

Frequency of body temperature rises (1-2 times per day), pain syndrome intensity and inflammatory alterations of knee and ankle joints decreased in the setting of the combined immunosuppressive therapy.

However, when the boy was readmitted to the rheumatology department in June 2012 the disease activity manifested with persisting pyretic fever, asthenia, arthralgiae, marked functional restriction and stiffness of joints remained in place. Laboratory examination revealed leukocytosis of up to 30 x 10^9/l, thrombocytosis of up to 800 x 10^9/l, hypochromic anemia, 30-fold serum CRP concentration increase, immunoglobulin G concentration reduction and increase in serum creatinine and urea concentrations up to the double normal values. Despite the high disease activity, we decided against prescribing glucocorticoids again due to the aforementioned severe side effects induced by such therapy. We performed a second rituximab therapy course due to activity of the inflammatory process. Development of hypogammaglobulinemia served as a reason to perform replacement therapy with normal human immunoglobulin, of nephrotoxicity – to withdraw cyclosporine.

Rituximab's effect development rate analysis demonstrated that positive dynamics in the child's condition 4 weeks after the second course: the number of body temperature rises decreased down to 1 per day, morning stiffness duration, intensity of arthralgiae and exudative joint alterations reduced and the patient's total activity improved. However, the child's condition was not improving in the following 4 months: pyretic fever, inflammatory joint alterations and high laboratory parameters of the disease activity persisted.

The child's condition at admission to the rheumatology department in October 2012 was estimated as severe due to pyretic fever, chronic intoxication and generalized articular syndrome; physical examination revealed rash, marked muscular and general hypotrophy, exudative alterations of knee, ankle, wrist, elbow joints and small joints of hands, acute restriction and pain at movement in all joints, including hip (flexion, 70^{o} extension, rotation) and maxillotemporal joints and cervical spine, fusiform deformity of fingers, edema in ankle region and of heel tendons. Functional activity restriction, flexion contracture in knee and elbow joints were observed; the child could not touch his ears, shoulders and shoulder blades, did not walk, squat, clench fists or attend to himself (pic. 1a-f). Clinical blood analysis revealed hypochromic anemia (Hb – 76 g/l), leukocytosis (32 x 10^{9}/l), thrombocytosis (770 x 10^{9}/l) and the ESR increase up to 65 mm/h. Immunological blood analysis – serum CRP concentration increase up to 178 mg/l (N – up to 5).

Taking into consideration early disease onset and symptoms of aggressive course of sJIA (extraarticular manifestations, generalized articular syndrome high immunologic activity, hormone dependence, inefficacy of the previously performed glucocorticoid, immunosuppressive and biological therapies), the child could have been prescribed the prednisolone dose increase or a therapy with a genetically engineered biopharmaceutical of a different mechanism of action. Canakinumab (IL1 inhibitor) was registered in the Russian Federation in that period for treating autoinflammatory diseases.

It has recently been proven that 2 cytokines – IL6 and IL1 – play the crucial role in sJIA pathogenesis. Efficacy and safety of anti-IL1-therapy for treating sJIA has been proven [10-15]. Canakinumab – a recombinant human monoclonal antibody blocking IL1β – was registered in the Russian Federation in 2013 for children over 2 years of age with sJIA. International multicenter double blind placebo-controlled studies served as the motivation for the drug's registration [15].

The first study assessed efficacy of a singular injection of the drug in comparison with a placebo. The study involved 84 2-19-year-old patients with active sJIA course (fever, arthritis, CRP increase). The average disease duration was 2 years; 58% of the patients had previously been treated with biological agents, 37% - with anakinra; 65% of the children continued to receive methotrexate as concomitant therapy, 72% - glucocorticoids in the dose of up to 1 g/kg per day. The group of canakinumab-treated patients involved 43 children, the placebo group – 41 children. 15 days after the first injection of the drug/placebo, absence of fever and 30% improvement according to criteria of the American College of Rheumatology (ACR) were registered in 84% of the patients treated with canakinumab and only in 10% of the placebo group patients; absence of fever and 90% improvement according to the ACR criteria – in 42 and 0%, respectively; non-active disease stage – in 33 and 0% of the patients, respectively ($p < 0.001$). The same difference between the groups remained in place 29 days after. The patients involved in that study were also involved in the second study of canakinumab efficacy and safety.

The study involved 177 children with active sJIA and was divided into 2 stages. The first stage consisted in an open prospective study with reduction in the dose glucocorticoids. All 128 patients had been treated with canakinumab for 12-32 weeks. The dose of glucocorticoids could be reduced in the event of no fever and 50% of better improvement according to the ACR criteria. The average prednisolone dose was reduced from 0.34 to 0.05 mg/kg per day in 57 (45%) patients; glucocorticoids were completely withdrawn in 42 (33%) patients.

The second stage of the study was double blind placebo-controlled with therapy withdrawal and registration of the interval between the last injection of the drug/placebo and an exacerbation. Canakinumab therapy was resumed in all the patients, who developed exacerbation of the disease. The rate of exacerbations was significantly higher ($p = 0.003$) in the group of the placebo-treated patients than in the canakinumab group.

Safety profile of canakinumab was comparable with safety profile of the placebo. The first study registered 2 cases of severe side effects in each group, 1 case of macrophage activation syndrome in each group, 2 cases of severe infectious side effects in the canakinumab group and 1

such case in the placebo group. The number of side effects in the canakinumab group in the second study with therapy withdrawal was 2.34, in the placebo group – 2.54 per 100 patient-days.

Thus, results of canakinumab studies demonstrated high efficacy and safety of the drug for children with sJIA, which is why we could initiate canakinumab treatment of our patient at the rheumatology department of the SCCH. Prescription of the drug was approved by the local Ethics Committee of the SCCH. The child's parents signed an informed consent to the use of the drug.

The drug was injected intravenously subcutaneously in the dose of 4 mg/kg of body weight once per 4 weeks.

Canakinumab's therapeutic effect development rate analysis demonstrated that the first injection of the drug resulted in termination of fever and rash on the following day (pic. 2a-f); the boy became more active; we were able to withdraw nonsteroidal anti-inflammatory drugs; laboratory parameters of the disease activity normalizer after 4 weeks; inflammatory joint alterations terminated and the movement range therein recovered by the 8th week of observation. Non-active disease stage was registered by the 3rd administration of the drug, after 12 weeks of therapy.

The patient has been having remission of the disease for 1.5 years in the setting of canakinumab therapy; we were able to reduce the prednisolone dose down to 2.5 mg/day. No severe side effects have been registered throughout the observation period; the rate of acute respiratory infections has not increased.

Thus, analysis of this clinical case demonstrates a severe galloping course of systemic juvenile arthritis characterized by pyretic fever, rash, arthritis, high laboratory values of activity parameters, development of secondary resistance to tocilizumab and insufficient efficacy of rituximab. Prescription of human monoclonal antibodies to IL1 provided reduction in clinical and laboratory parameters of the disease activity, development of the non-active disease stage and helped to reduce the dose of glucocorticoids.

We ought to mention the absence of severe canakinumab-induced side effects. The obtained results indicate that the drug's choice was correct and reconfirm high efficacy of canakinumab for treating systemic juvenile idiopathic arthritis.

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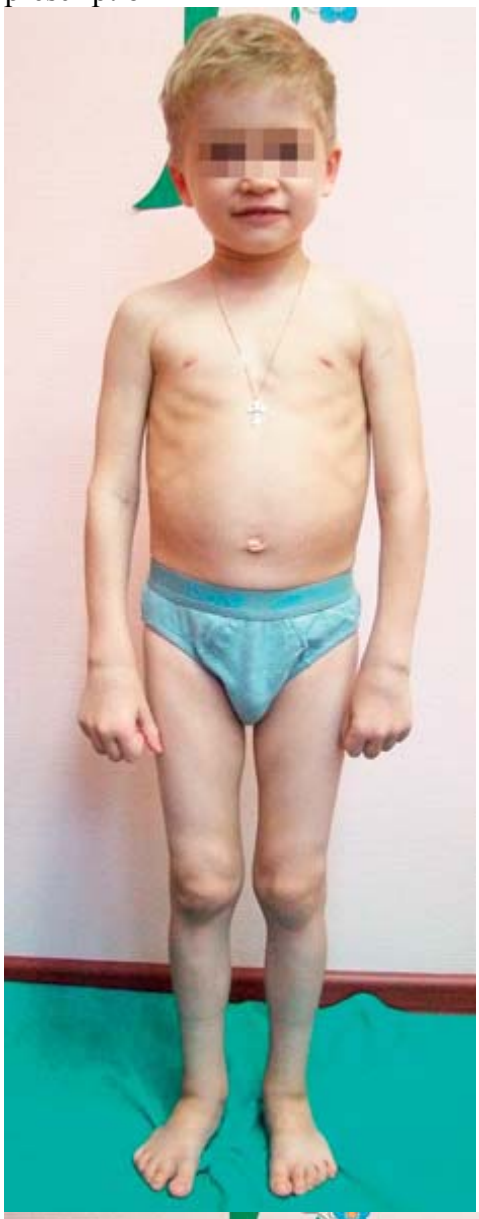
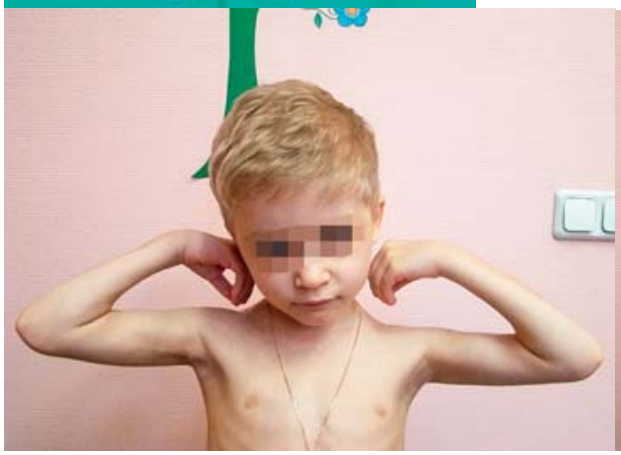
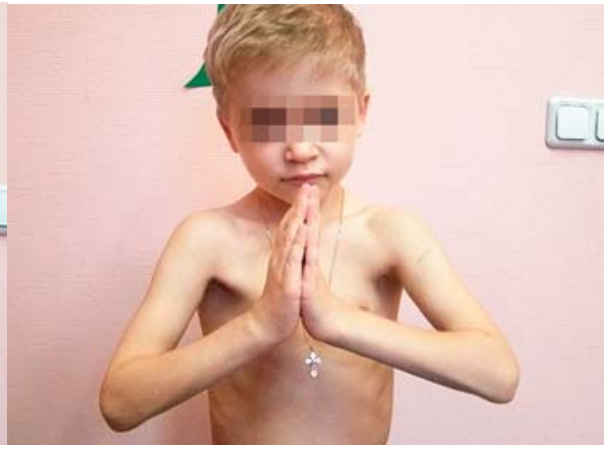
Table. Dynamics of clinical and laboratory parameters of systemic juvenile idiopathic arthritis activity in the setting of canakinumab therapy in an 8-year-old patient

Parameters	**Canakinumab therapy duration**					
	0 days	**1 day**	**4 weeks**	**8 weeks**	**12 weeks**	**1.5 years**
Body temperature (^{o}C)	38.8	36.6	36.6	36.6	36.7	36.8
Rash	+	none	none	none	none	none
Morning stiffness duration (minutes)	240	none	none	none	none	none
Number of joints with active arthritis	31	17	9	0	0	0
CHAQ functional insufficiency index (score)	2.5	-	1.25	0.5	0	0
ESR (mm/h)	65	35	8	4	2	2
Hemoglobin (g/l)	76	84	104	118	124	128
Erythrocytes (x 10^{12}/l)	3.7	3.8	4.02	5.2	5.1	4.9
Platelets (x 10^{9}/l)	770	580	390	330	280	310
Leukocytes (x 10^{9}/l)	28.4	18.5	11.4	9.7	8.8	5.7
CRP (mg/l) (norm – up to 5)	178	85	4.5	< 1.0	< 1.0	< 1.0
Improvement according to the ACR_{pedi} criteria (%)	-	-	70%	90% Non-active disease	100% Non-active disease	100% Remission
Prednisolone dose (mg/kg per day)	0.4	0.4	0.4	0.4	0.4	0.09

Pic. 1. The patient's appearance before canakinumab prescription (a); functional capacity of elbow (b, f), wrist (c, d, f) and knee (e) joints and small joints of hands (f) before canakinumab prescription







Pic. 2. The patient's appearance after 1.5 years of canakinumab therapy (a); functional capacity of elbow (b, f), wrist (c, d, f) and knee (e) joints and small joints of hands (f) after 1.5 years of canakinumab therapy