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

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*The article presents a case of successful use of therapeutic monoclonal antibodies to interleukin 1 (canakinumab) at severe systemic juvenile idiopathic arthritis. Canakinumab treatment promptly provided reduction in clinical and laboratory disease activity indicators, increase in life quality, development of inactive disease stage and allowed avoiding prescription of glucocorticoids.*
***Keywords:*** *systemic juvenile idiopathic arthritis, canakinumab, children.*

Systemic arthritis is the severest variant of juvenile idiopathic arthritis (sJIA); its course is characterized by a wide range of extraarticular manifestations: pyretic fever, myopericarditis, pneumonitis and polyserositis [1]. The disease is characterized by such laboratory alterations, as anemia, thrombocytosis, leukocytosis, increase in erythrocyte sedimentation rate (ESR) and serum concentration of C-reactive protein (CRP) [2]. Destructive arthritis resulting in functional incompetence, progressive incapacitation and reduction in life quality of patients develops in more than 1/3 of the patients [1, 2]. Destructive articular alterations progress, extraarticular manifestations recurs and incapacitation grade steadily increases in more than 50% of patients with sJIA despite therapy using non-steroid anti-inflammatory drugs and glucocorticoids. It should be noted that glucocorticoids do not control the disease course, do not prevent progression of osteochondrous destruction and incapacitation of patients; long-term application of them results in the development of severe and often irreversible consequences – in particular, of Cushing's syndrome, dwarfism, delayed puberty, adrenal insufficiency, osteoporosis, cataract and hormone dependence [1-3]. Long-term active inflammatory process and cytokine storm in 10% of patients with sJIA results in the development of such a severe life-threatening complication as hemophagocytic syndrome [4].
That is why introduction of new drugs for sever systemic juvenile arthritis into practice is one of the crucial issues of modern rheumatology, e.g., canakinumab – recombinant humanized monoclonal antibodies blocking interleukin (IL) 1β, which play the leading role in the development of extraarticular symptoms of the disease [5].
The following clinical observation demonstrates efficacy of canakinumab.
Veronica F. has been ill since April 2013 (2 years 2 months of age). Pyretic fever, maculopapular rash, pericarditis, lymphadenopathy, hepatomegaly, pain and restriction of movements in cervical spine and high laboratory activity parameters (ESR – 58 mm/h, serum SRP concentration – 64 mg/l) were observed in the onset. Diagnosis of juvenile arthritis with systemic onset was established at the local inpatient hospital after ruling out possibility of infectious diseases, neoplasms and hemoblastoses. The girl was prescribed to take nimesulide; however, despite the conducted therapy all the symptoms persisted, which is why the girl was urgently hospitalized to the rheumatology department at the Scientific Center of Children's Health in August 2013.
The child's condition at admission was appraised as severe. Repeated body temperature rises to fever and maculopapular rash on the body and limbs were observed on a daily basis. Articular

syndrome progressed; inflammatory alterations in the right ankle joint, left foot joints and cervical spine were observed. Joint movements were restricted and painful; the head posture was forced to bend left during the day. The child experience morning stiffness of up to 90 minutes. Skin pallor and dark shadows beneath the eyes attracted attention. The examination (tb.) revealed leukocytosis, thrombocytosis, considerable ESR acceleration and hypochromic anemia in clinical blood analysis; >40 times increase in serum CRP concentration and >30 times increase in immunoglobulins (Ig) G and M and ferritin – in immunological blood analysis (see tb.). Periodic syndromes, hemoblastoses and neoplastic processes were ruled out. Given the disease's clinical presentation and the examination results, diagnosis of juvenile idiopathic arthritis with systemic onset (according to ICD-10: M08.2) did not cause doubt.

**Table.** Dynamics of clinical and laboratory parameters of systemic juvenile idiopathic arthritis activity in the setting of therapy in patient Veronica F., 2.5 years of age.

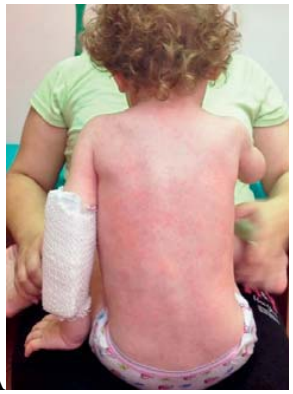
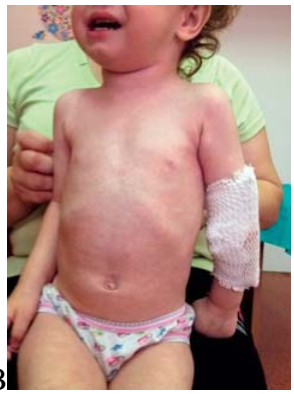
| **Parameters** | **Duration of tocilizumab therapy** | | **Duration of canakinumab therapy** | | | |
|---|---|---|---|---|---|---|
| | **Initial** | **2 weeks** | **Initial** | **1 day** | **2 weeks** | **4 weeks** |
| Body temperature ($^{o}$C) | 39.4 | 37.5 | 38.8 | 36.6 | 36.6 | 36.6 |
| Rash | + | + | + | None | None | None |
| Duration of morning stiffness (minutes) | 90 | 20 | 60 | None | None | None |
| Number of joints with active arthritis | 3 | 3 | 3 | 3 | 3 | 0 |
| Functional incompetence index according to CHAQ questionnaire (points) | 1.5 | 1.25 | 1.5 | - | 0.75 | 0.5 |
| ESR (mm/h) | 79 | 15 | 54 | 48 | 15 | 2 |
| Hemoglobin (g/l) | 82 | 96 | 92 | 96 | 111 | 121 |
| Erythrocytes (x$10^{12}$/l) | 3.78 | 4.35 | 4.2 | 4.3 | 5.02 | 5.2 |
| Platelets (x$10^{9}$/l) | 894 | 414 | 780 | 690 | 420 | 330 |
| Leukocytes (x$10^{9}$/l) | 53 | 15.9 | 21.4 | 16.5 | 13.4 | 12.7 |
| CRP (mg/l), norm - ≤5 | 238 | 30 | 139 | 100 | 1.8 | <1.0 |
| IgG (g/l), norm – 4.53-9.16 | 9.47 | 8.7 | 9.3 | - | - | 8.5 |
| Ferritin (ng/ml), norm – 10-60 | 2206 | 128 | 390 | 211 | 55 | 45 |
| Improvement percentage according to the $ACR_{pedi}$ criteria | - | 30% | - | 30% | 70% | 90% Inactive disease |

Given the signs of aggressive course of the disease (fever, rash, high immunological activity), oral glucocorticoids were to be prescribed in the dose of 1-2 mg/kg per day according to all world protocols. However, given the child's age, high risk of development of dwarfism and other severe complications resulting from the glucocorticoid therapy, such as osteoporosis, obesity, delayed puberty, psychosis, hormone dependence and hormone resistance, it was decided not to prescribe prednisolone and start therapy with a genetically engineered biological preparation of recombinant humanized monoclonal antibodies to receptor IL 6 – tocilizumab – according to the sJIA treatment protocol [6].

The patient intravenously received the drug in the dose of 12 mg/kg of body weight once in 2 weeks. Analysis of tocilizumab's therapeutic effect development showed, that the first administration of the drug resulted in termination of pyretic fever, decrease in laboratory parameters of disease activity and higher activity of the girl; however, maculopapular rash, low-grade fever and inflammatory alterations of joints persisted.

Infusion reaction developed during the second administration of tocilizumab (cough, hyperthermia, rigor, cyanosis). The drug's infusion was terminated. The condition terminated after administration of an antihistamine drug, non-steroid anti-inflammatory drug and intravenous infusion of methylprednisolone.
Tocilizumab therapy was not restored due to the development of an allergic reaction and high risk of development of anaphylactic shock.
Pyretic fever recurred up to 3 times per day, rashes intensified (pic. 1 A, B), laboratory parameters of the disease activity increased and pain syndrome intensified in the setting of tocilizumab withdrawal.

**Pic. 1.**
A. Maculopapular rash on back.
B. Maculopapular rash on chest, abdomen and thighs.

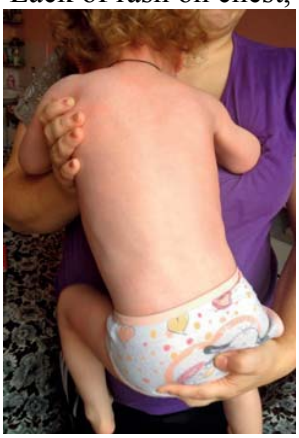
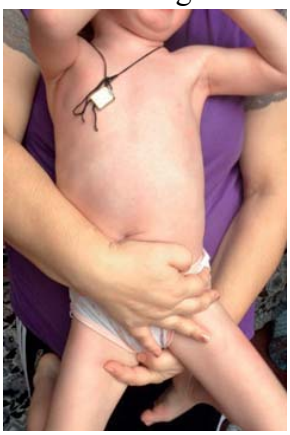
A  B 

Despite high activity of the disease, we decided to refrain from prescription of glucocorticoids, given the aforementioned severe undesirable effects of glucocorticoid therapy.
It has recently been proved that 2 cytokines – IL 6 and IL 1 play the leading role in sJIA pathogenesis. Efficacy and safety of anti-IL1-therapy for sJIA treatment has been proved as well [7-12]. Canakinumab – recombinant humanized monoclonal antibody blocking IL 1β – was registered in the Russian Federation in 2013 for prescription at sJIA to children over 2 years of age. The ground for the drug's registration was based on the international multicenter double-blind placebo-controlled trials [12].
The first trial evaluated efficacy of a singular injection of the drug in comparison with a placebo. The trial involved 84 patients with active sJIA (fever, arthritis, CRP increase) of 2-19 years of age. Average duration of the disease was ca. 2 years; 58% of patients had previously been treated with biological agents, 37% - with anakinra; 65% of children continued to take methotrexate as concomitant therapy, 72% - glucocorticoids in the dose of not more than 1 g/kg per day. The group of patients treated with canakinumab involved 43 children, the placebo group – 41 children. Lack of fever and 30% improvement according to the criteria of the American College of Rheumatology (ACR) was registered in 84% of patients treated with canakinumab and only in 10% of the placebo group children 15 days after the first injection of the drug/placebo; lack of fever and 90% improvement according to the ACR criteria – in 42 and 0%, inactive disease stage – in 33 and 0%, respectively ($p<0.001$). The difference between groups preserved after 29 days. Patients of that trial were involved in the second trial, which examined efficacy and safety of canakinumab.
The second trial involved 177 children with active sJIA. Design of that trial was divided into 2 parts. The first part was an open prospective trial with the reduction in the dose of glucocorticoids. All 128 patients receiving glucocorticoids had been treated with canakinumab for 12-32 weeks. It was allowed to reduce the dose of glucocorticoids in absence of fever and ≥50% improvement according to the ACR criteria. We managed to reduce the average dose of

prednisolone from 0.34 to 0.05 mg/kg per day in 57 (45%) patients and to withdraw glucocorticoids completely in 42 (33%) patients.
The second part of the trial was double-blind and placebo-controlled, with therapy withdrawal and registration of duration of the period between the last injection of the drug/placebo and exacerbation. Canakinumab therapy was restored in all patients with exacerbation of the disease. Rate of exacerbations was significantly higher in the group of patients treated with placebo (p=0.003) in comparison with the group treated with canakinumab.
Safety profile of canakinumab was comparable to safety profile of placebo. In the first trial, 2 cases of severe undesirable phenomena and 2 cases of hemophagocytic syndrome were registered in both groups; 2 infectious cases were registered in the group treated with canakinumab, 1 case – in the placebo group. In the second trial, the number of undesirable phenomena in the groups treated with canakinumab was 2.34, in the placebo group – 2.54 per 100 patient-years.
Thus, results of the canakinumab trials demonstrated high efficacy and safety of the drug in children with sJIA; this allowed initiating canakinumab treatment in the SCCH rheumatology department in the case of our patient.
The drug was administered intravenously subcutaneously in the dose of 4 mg/kg of body weight once in 4 weeks.
Analysis of canakinumab's therapeutic effect development showed that fever and rash (pic. 2 A, B) terminated, the girl became more active and it was possible to withdraw non-steroid anti-inflammatory drugs on the day following the first administration of the drug; laboratory parameters of the disease activity normalized after 2 weeks; inflammatory alterations of joints terminated completely and range of motions recovered by the 4$^{th}$ week of observation. By the second administration of the drug (after 4 weeks of therapy) we registered the inactive disease stage in the patient.

**Pic. 2.**

A. Lack of rash on back.
B. Lack of rash on chest, abdomen and thighs.

A  B 

No undesirable phenomena were registered within 1 month of therapy in the setting of canakinumab therapy.
Thus, analysis of the given clinical case demonstrates severe and rapidly progressing course of systemic juvenile arthritis characterized by pyretic fever, rash, arthritis, high laboratory parameters of activity and tocilizumab intolerance. Prescription of human monoclonal antibodies to IL 1 provided reduction in clinical and laboratory parameters of the disease activity, development of the inactive disease stage and allowed avoiding prescription of glucocorticoids.
Lack of severe undesirable phenomena in response to administration of canakinumab should be noted. The obtained results indicate correctness of the drug's selection and reconfirm high efficacy of canakinumab for the treatment of systemic juvenile arthritis.

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