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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 using genetically engineered biopharmaceutical tocilizumab in a child with systemic juvenile idiopathic arthritis. On the initial stage, the treatment was characterized by resistance to high doses of glucocorticoids and cytostatic drugs. Successful termination of visceral and articular manifestations of systemic juvenile idiopathic arthritis and normalization of laboratory indicators of disease activity in the setting of use of interleukin 6 receptor blocker were described. We observed stable improvement of the child's condition during a year-long follow-up in the setting of the selected anti-inflammatory therapy pattern.
Keywords: *juvenile idiopathic arthritis, systemic variant, genetically engineered biopharmaceuticals, tocilizumab.*

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Introduction

Clinical recommendations of the Union of Pediatricians of Russia define juvenile arthritis as arthritis of unidentified cause that lasts over six weeks and develops in a child under 16, if other articular pathologies are excluded [1]. In the structure of rheumatic diseases in children under 16, the most prevalent diseases belong to a large heterogeneous group of inflammatory articular diseases, jointly referred to as juvenile idiopathic arthritis (JIA) and posing a high risk of disability [2, 3].

JUVENILE IDIOPATHIC ARTHRITIS CLASSIFICATION

Despite detailed studies of JIA pathogenesis, epidemiology, diagnosis and therapy, issues related to the practicable classification of this disease have remained unsolved for decades. Of all the existing classifications (ACR, EULAR, ILAR), the most frequently used one is that of the International League of Associations for Rheumatology (ILAR), which was adopted in Durban in 1997, and later amended in Edmonton in 2001 [2, 4]. This classification is widely used in international studies and scientific papers, as it provides a list of clear inclusion and exclusion criteria that enable an accurate determination of the type of the disease [5]. In their everyday clinical practice, Russian doctors still use the Russian classification of juvenile rheumatoid arthritis [6]; statistical accounting and reports are based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision.

DIAGNOSIS OF SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

In all these classifications, systemic juvenile idiopathic arthritis (sJIA) is deemed a separate type of JIA. SJIA was first described by a physician in 1897 when English physician G.F. Still described a clinical syndrome that included arthritis, fever, splenomegaly, and lymphadenopathy (Still's disease) [7]. Today, sJIA is diagnosed per the ILAR classificatory criteria, if a child under 16 has the following symptoms:

• arthritis in one or more joints and/or preceding or concomitant fever lasting at least 2 weeks, documented every day for three days with one (or more) of the following signs:

▪ evanescent, non-fixed erythematous rash;

▪ serositis;

▪ generalized lymphadenopathy;

▪ hepatomegaly and/or splenomegaly [5].

One of the key features of various sJIA forms is the emergence of constant articular syndrome relative to extraarticular manifestations [8, 9]. If articular syndrome manifests itself later than visceral lesions, this is allergoseptic JIA. This type of JIA was described much later. It was first mentioned in German and French papers in mid-20th century and was then named differently: Subsepsis allergic, Wissler's syndrome, Wissler-Fanconi syndrome [9]. The syndrome was characterized by intermittent fever, exanthema, leukocytosis, and arthritis [10-12].

The Russian JIA classification refers to it as allergoseptic syndrome and lists it along with Stills' disease. Aside from some clinical nuances, their key difference was the time of emergence and the degree of progression in comparison to present visceral lesions. International classifications use other names for these clinical types, which allows making clinical and epidemiological comparisons [13].

PATHOGENESIS OF SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

So far, sJIA is considered a form of JIA. However, new data on its pathogenesis, clinical picture, therapeutic peculiarities, and possible complications justify the theory that sJIA is an independent nosological item [13]. For instance, sJIA is characterized by cellular response involving T_{x1} and T_{x2} cells, where type 1 helper lymphocytes dominate; this is where this type differs from other JIA types [5]. Besides, sJIA pathogenesis features a peculiar cytokine response [14, 15]. Whilst the level of interferon γ falls, the concentration of a number of cytokines skyrockets. These cytokines are: tumor necrosis factor (TNF) α, interleukins (IL) 1, 6, and 8, monocyte chemoattractant protein 1, and E-selectin [16, 17].

IL 1 and IL 6 play a special role in sJIA pathogenesis. Increased concentration of IL 1β is associated with such symptoms as fever, anorexia, weight loss, and pain; it potentates the development of local vasculitis events and thrombosis [18]. It may be the case that an increased concentration of IL 1ß plays a crucial role in mechanisms that increase the concentration of IL 6, which in its turn is crucial for sJIA-associated systemic inflammatory response and articular inflammations. Increased IL6 level in peripheral blood and synovial fluid are seen as a factor of direct correlation with disease activity, feverish response level, and acute phase protein content, i.e. the content of C-reactive protein, serum amyloid A, fibrinogen, and ferritin [19]. Besides, IL6 activates osteoclasts, which leads to osteoporosis, structural damage and loss of integrity in cartilage tissue [20].

IL 4 and 18, myeloid release proteins 8 and 14 as well as macrophage migration inhibitory factor are also on the list of cytokines crucial for sJIA development [21]. In general, the immunity disorders associated with sJIA allow analyzing this disease as belonging to the group of autoinflammatory diseases. This fact was highlighted at the 4th International Congress on the Systemic Autoinflammatory Diseases (Bethesda, the United States, 2005), where sJIA was classified as a multifactor autoinflammatory disease [22, 23].

TREATMENT OF PATIENTS WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

SJIA has always been extremely hard to treat. Over the history of healthcare, different methods and drugs, with varying efficiency, were combined with traditional immunosuppressive therapy. These included non-steroidal anti-inflammatory drugs, glucocorticoids (GC), high-molecular immunoglobulin [24, 25]. Pulse GC therapy still remains one of the most efficient treatment methods [26].

Given that autoinflammatory mechanisms resulting from innate immunity response are predominant in sJIA pathogenesis, sJIA treatment features peculiar approaches to application of genetically engineered biological drugs (GEBD). One peculiarity is that baseline drugs for immunosuppressive therapy and first-line GEBD (inhibitors of TNF α) are not efficient in case of sJIA. As the key cytokines of autoinflammatory innate immunity responses are IL1 and IL6, the inhibition thereof ensures a sustainable therapeutic effect and stops the progression of this severe disease, a fact proven by multiple international and Russian trials as well as by clinical experience [27-29].

Clinical Case

The following clinical case demonstrates different approaches to sJIA treatment and provides an evaluation of their efficiency.

Patient A, aged 5 years 9 months, hospitalized to an inpatient unit in April 2013 with complaints of fever (febrile body temperature of 39-40ºC), had cutaneous rashes, experienced pain in the lower extremities and the neck, had severe asthenia and poor appetite.

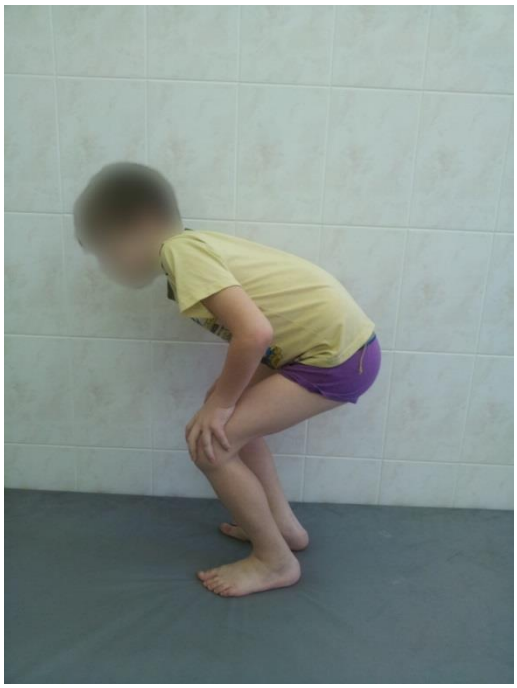
Medical history: Born in the 1st pregnancy accompanied by anemia; threatened miscarriage in the 28th week; chronic intrauterine fetal hypoxia; delivery at term. Early postnatal life without complications. The child was vaccinated at the maternity home. Bottle-fed right from the birth. Past medical history: acute respiratory infections twice to thrice a year, no childhood infections.

From the history of disease, we knew that he had been sick since late March, when the body temperature rose to subfebrile levels (37.5 to 37.7 °C). Had febrile morbidity (up to 38°C) since April 2, 2013; was treated outpatiently with successive antiviral courses, was administered antibiotics (semi-synthetic penicillins) and received antipyretics situationally. Body temperature would decrease to normal levels and increase back again repeatedly during a single day. Along with hectic fever, there appeared maculopapular rash on the thighs, albeit non-plentiful; that was why the child received generation I antihistamines to no effect. Rash was evanescent, its instances worsened, and there appeared newer and newer rashes against the backdrop of fever episodes. Over the next three days, there appeared plentiful facial rash with continuing hectic fever episodes (body temperature exceeded 40 ºC repeatedly within a day); motion-induced pain in the extremities (myalgia, arthralgia).

As the clinical picture indicated continuing hyperthermia, the patient was hospitalized to an infection hospital, where he was examined per an algorithm designed for feverish patients. This examination did not identify any crucial infectious causes. There persisted febrile morbidity (up to 40 ºC), "evanescent" maculopapular rash that sometimes merged, disappeared on its own and then emerged again regardless of drugs taken. The child complained of articular pain in the lower extremities, pain in the neck and arm joints. The child could not stand up on his feet and had intense asthenia. The blood sample taken at the infection hospital identified leukocytosis (12.4-32.0 x 10^9 per liter, whereas the normal range is 4.9-11.3 x 10^9 per liter) with stab shift (8-19%, whereas the normal range is 1-5%), neutrophilia (62-78%, whereas the normal range is 32-55%), and a sharp increase of ESR (up to 50 mm/h, whereas the norm is 4-12 mm/h). At the infection hospital, the child underwent a comprehensive antibacterial therapy with III generation cephalosporins and aminoglycosides, to no effect. As the child stayed at the hospital, the doctors prescribed prednisolone (parenteral administration) in a dose of 3 mg/kg of body weight for 5

days, after which the body temperature normalized, the child came to be able to stand up on the feed again, regained his appetite, and had rashes reduced. Body temperature rose to 39.1ºC again on the next day after GC treatment was terminated. Abdominal ultrasonography identified hepatosplenomegaly. The boy was transferred to a pediatric inpatient hospital (Mirotvortsev Clinical Hospital of Saratov State Medical University).

Pic. *Articular syndrome manifestations in Patient A at the onset of the disease*



When hospitalized to the pediatric hospital, the child's parameters were as follows: fever (up to 39-40.2ºC), the child did not walk, had evanescent, bright pink, maculopapular cutaneous rash that emerged on the setting of temperature responses; myalgia and arthralgia. From the 3rd week of inpatient monitoring, articular syndrome debuted and involved tarsal-metatarsal joints on both sides, left-knee and right-ankle joints as well as smaller joints of hands and feet (see Pic.). The clinical blood test identified hyperleukocytosis (up to 60 x 10^9 per liter), hyperthrombocytosis (up to 942 x 10^9 per liter, whereas the normal range is 180-320 x 10^9 per liter), whilst hemoglobin concentration was reduced to 70g/l (the normal range is 120-140 g/l), ESR was reduced to 66 mm/h, and the CRP content was increased to 150 mg/l (the normal is up to 5 mg/l). Periodic syndromes, hemoblastosis, and neoplastic processes were excluded based on the examination results. Sternal puncture was performed repeatedly; the child was examined by a hematologist multiple times. Thoracic CT, abdominal and cerebral MRI did not identify space-occupying lesions or lymphoproliferative processes. There were described manifestations of moderate splenomegaly, an enlargement of lymphatic nodes in the chest cavity. After septic process and cancer were excluded, the established diagnosis was as follows: juvenile rheumatoid arthritis with systemic onset. Comprehensive therapy was carried out, including pulse methyl-prednisolone therapy (20 mg/kg a day, 300 mg i/v), pulse therapy with megadoses of methotrexate (50 mg/m² a week i/v, no. 7), massive antibacterial, symptomatic, detoxification therapy; no positive effects. Fever persisted, articular syndrome grew ever stronger, rashes persisted, laboratory activity of disease indicators remained high. In the light of the above occurring at the specialized pediatric rheumatology unit of the Scientific Center of Children's Health (Moscow) and due account of the disease course, high inflammatory activity, little effect of pulse methotrexate therapy and GC, the progression of articular syndrome, and systemic manifestations of the disease, the child was prescribed tocilizumab, an IL6 receptor inhibitor (Actemra by Hoffman-La Roche Ltd., Switzerland), which was administered in a dose of 12 mg/kg per administration once every two weeks.

Tocilizumab therapy was clinically efficient, was the patient's body temperature normalized after the first infusion. Table 1 demonstrates the dynamics of laboratory parameter normalization. Articular syndrome reversal was slower, and the syndrome was reversed completely by the 2nd month of tocilizumab treatment.

Table 1. *Dynamic of Clinical and Laboratory Parameters of Disease Activity in Patient A During Treatment*

Parameters	Pulse methyl-prednisolone therapy		After pulse therapy with high doses of methotrexate	Treatment with tocilizumab				
	Before	After		After the 1st infusion	After the 2nd infusion	4 weeks	26 weeks	52 weeks
Body temperature, °C	39-40	39-40	39-40	N	N	N	N	N
Presence of rashes	+	+	+	-	-	-	-	-
Articular syndrome	+	+	+	+	±	-	-	-
Erythrocytes, x 10^{12}/l	3.57	3.52	3.28	4.00	4.71	4.5	4.5	4.4
Hemoglobin, g/l	97	99	77	82	105	112	115	122
Leukocytes, x 10^9/l	18.9	37.9	15.4	8.99	8.82	7.01	6.55	6.0
Thrombocytes, x 10^9/l	459	827	706	820	369	332	298	310
ESR in mm/h	51	35	59	36	5	3	3	5
C-reactive protein, mg/l	146	150	120.4	22.5	5.1	1.3	1.05	<1
Improvement per ACR_{pedi} criteria	-	-	-	-	-	70%	Inactive disease	Remission

In accordance with the modern views on choosing the optimal therapy for JIA-affected patients, it is believed that such therapy should be chosen based on cytokine parameters, which may vary at different stages of the disease and determine the response to this or that drug [30]. In this case, cytokine data were collected in-process (Table 2). In the setting of convincing positive dynamics, we noted a significant decrease in IL6 concentration in peripheral blood, which confirmed the need for continued treatment.

Table 2. *Cytokine status parameters of Patient A after 10 weeks of tocilizumab treatment*

Parameter	Patient's data, pg/ml	Normal value(s), pg/ml
IL 1β	1.5	3.6 (1.1-11.3)
IL 4	2.0	1.89 (1.0-2.78)
IL 6	16.9	1.7 (0.8-8.7)
Interferon γ	77.5	21.8 (12.2-26.5)

As the patient was followed-up for 18 months whilst treated with tocilizumab, no significant adverse effects (infusion response, cytopenia, transferasemia) were noted. Tolerance to the drug was satisfactory. The child continues to undergo tocilizumab treatment, receiving 8 mg/kg once every four weeks. No significant clinical symptoms of sJIA.

Discussion

The first scientific papers that allowed for an optimistic outlook on the effect of GEBD on the IL 6 activity and thus helped significantly improve sJIA treatment were published as a result of the studies by S. Yokota et al. [31]. It was noted that GEBD significantly decreased the patients' dependence on GC, thus decreasing the risk of potential severe complications of the disease as well as therapy-associated complications.

An important milestone in the history of sJIA treatment was the development and real clinical application of a drug capable of binding to, and blocking IL 6 receptors. This drug, tocilizumab, is a recombinant humanized monoclonal antibody to human IL 6 receptor. It can bind selectively and suppress to both soluble and membrane receptors of interleukin.

Official treatment protocols of many countries now list tocilizumab along with IL 1 inhibitors as one of the drugs of choice when it comes to treating systemic juvenile idiopathic arthritis [34]. According to the approved Standards of Medical Care For Children With Juvenile Arthritis With Systemic Onset (Orders of Ministry of Health of the Russian Federation no. 668н dd. November 7, 2012, and no. 777н dd. November 9, 2012), tocilizumab, an IL6 receptor blocker, is the only genetically engineered biological drug that should be prescribed to sJIA patients when standard therapy (nonsteroid anti-inflammatory drugs and GC) proves ineffective.

These official recommendations were largely based on the results of years-long international clinical trials, the largest of which was TENDER [27, 35]. In this trial, the researchers evaluated the efficiency of tocilizumab when administered to sJIA patients (n = 112), who had been treated with "standard" therapeutic methods for at least 6 months to no effect. It should be noted that prior to that trial, most patients had underwent unsuccessful treatment with other GEBD drugs (TNF α inhibitors and IL1 blockers). By the start of the treatment, 58% of the patients had fever and 36% had rash. The main efficiency criterion was the number of patients who by the 12th week of treatment had no fever and achieved at least a 30% improvement per the American College of Rheumatology criteria (ACR_{pedi}). By that time, 85% of the study participants achieved the specified level of positive response, cf. 24% in the placebo-controlled group. Besides, more than 70% of tocilizumab-treated children had a 70% improvement, and more than 35% of them had a 90% improvement per the ACR_{pedi} criteria, whereas in the placebo group, such an improvement was the case for 8% and 5% of the patients, respectively.

In the second part of the study, a year after the open phase had begun, 48% of the patients had no sign of disease activity; 80% had reached a 70% improvement, whilst a bit less than 60% had reached a 90% improvement per the ACR_{pedi} criteria. More than a half of patients treated with tocilizumab had their GC treatment terminated; for those who had to continue to take GC, the GC dose was lowered from 0.3 to 0.06 mg/kg. In two years, 88% of the patients still followed up had preserved their 70% improvement per the ACR_{pedi} criteria, whilst the remission status was reached in every third patient. The research described a number of adverse events, mostly infections, headache, and diarrhea. Infusion responses were identified in 16% of tocilizumab-treated patients, cf. 5% in the placebo-controlled group. Other notable adverse events recorded in this study include neutropenia of varying intensity, which is a peculiarity of tocilizumab when used to treat sJIA [36].

As for Russian clinical trials, the Scientific Center of Children's Health presented in 2013 a retrospective analysis of the efficiency and safety of tocilizumab when used to treat sJIA-affected patients. The analysis was based on a 12-month follow-up. The study involved 75 sJIA-affected patients. In 6 months of treatment, 64% reached the inactive phase, 73% did so in a year. Possible adverse events include neutropenia and leukopenia as well as transferasemia. Based on the study results, the authors have pointed out how efficient tocilizumab was. Its effects were strongly positive even in patients with the most severe sJIA forms and refractoriness not only to conventional cytostatics and GC but also to other GEBD groups like TNF α inhibitors and anti-B-cell therapy).

According to the studies carried out by St. Petersburg Pediatric Medical University, the follow-up results of 33 sJIA-affected patients were used as a basis for developing clinical-laboratory criteria allowing to identify patients at high or low risk, who could take tocilizumab once every two or four weeks, respectively, while preserving its efficiency and safety [38].
Nasonova Research Institute of Rheumatology has followed up 49 sJIA-affected tocilizumab-treated children. The authors have evaluated how various factors affect the results of tocilizumab treatment. The factors included the age of manifestation of the main sJIA symptoms, how long treatment has lasted prior to the application of IL 6 receptor inhibitor, including the use of other GEBD as specified in the medical history. The intensity of articular and visceral manifestations of the disease are also among such factors. Based on the evaluation results, the scientists have analyzes the safety of prolonged use of this drug, the reasons for treatment termination, and opportunities for reinitiation of treatment. It was noted that tocilizumab is an efficient anti-sJIA drug. It was recommended to monitor the patients' status on a regular basis and to stick to reasonable approaches when adjusting the treatment course. Besides, there was identified a list of adverse factors of disease course. The presence of such factors allows considering the earliest introduction of IL6 receptor blocker therapy [28, 30].

Conclusion

The clinical case under discussion proves the efficiency of tocilizumab for program sJIA therapy and confirms that it is possible to reach the remission and to lower the activity of the disease. Use of this drug requires strict adherence to the rules and regimen of administration. It also necessitates a mandatory dynamic laboratory control of clinical and biochemical blood test indicators. A dynamic evaluation of the patient's clinical status is also a must.

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Conflict of interest

Y.M. Spivakovskiy received royalties for preparing this article.
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