Experience of using drug tocilizumab in a boy with systemic juvenile idiopathic arthritis

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The article presents a case of complicated diagnostics of systemic juvenile idiopathic (rheumatoid) arthritis (JIA) starting with a fever of unclear genesis. Efficacy of interleukin 6 inhibitor tocilizumab for treating the systemic JIA resistant to glucocorticosteroid and methotrexate therapy is shown.

Juvenile idiopathic arthritis (JIA) is the most widespread rheumatic disease developing in children under 16 years of age. The severest is the systemic JIA (sJIA) characterized by such extraarticular manifestations as fever, rash, leukocytosis, thrombocytosis, hepatosplenomegaly and polyserositis. Persistent articular syndrome in the event of this JIA variant may develop considerably later than extraarticular manifestations; this significantly complicates the disease diagnostics. In that case, sJIA diagnosis requires ruling out a range of pathological conditions characterized by severe fever. Systemic JIA ought to be differentiated from sepsis, oncohematological diseases, systemic connective tissue affections, inflammatory intestinal diseases and auto-inflammatory syndromes [1-3].

Before the era of genetically engineered drugs, sJIA therapy was a complicated issue due to the need in systemic application of glucocorticoids in combination with baseline anti-rheumatic drugs. Durable effect was achieved only in few patients. Reduction in glucocorticoid dosage resulted in the disease exacerbation in most patients; prolonged intake caused development of such complications as Itsenko-Cushing syndrome, growth lag, gastric ulcer, arterial hypertension, osteoporosis etc. [4].

Inhibitors of anti-inflammatory cytokines – interleukins (IL) 1 and 6 – are used for treating systemic JIA. It is well known that such extraarticular manifestations of sJIA as fever, rash, lymphadenopathy, weight loss etc. are associated with synthesis intensification and activity of IL 1 and 6. Tocilizumab is the first recombinant humanized antibody to human IL6 receptor of immunoglobulin (Ig) subclass G1. The drug selectively binds with soluble and membranous IL6 receptors, the expression level of which correlates with general clinical activity in the event of sJIA. Tocilizumab efficacy (both as monotherapy and in combination with methotrexate) has been proven in controlled studies of children with systemic JIA [5-14].

We are presenting a clinical case illustrating difficulty of systemic JIA diagnostics and tocilizumab therapy efficacy.

Artyom P. of 5 years of age was admitted to the pediatric rheumatologic department at the university pediatric clinical hospital of the First Sechenov MSMU with complaints of fever up to 38°C and pains in the right hip joint.

Anamnesis states that the boy was born of the 4th pregnancy (of the 1st – son, 16 years of age, healthy; 2nd-3rd pregnancies – therapeutic abortions), the course of which was characterized by toxemia and threat of miscarriage on the early stages. Term delivery (2nd delivery), no abnormalities. Child’s birth weight – 3,150 g, length – 51 cm. Early psychomotor development was age-adequate. Previous diseases: the child was being observed at the maternity hospital with
regard to suspicion of mucoviscidosis due to stool analysis alterations; monthly acute respiratory infections. Obstructive bronchitis at 1 year of age. The child has been being observed with regard to atopic bronchial asthma and has been receiving inhalation glucocorticoids from 3 years of age. The most recent episode of bronchial asthma was registered in May 2013. No pediatric infections. Allergic anamnesis: pollinosis. The boy was vaccinated according to the individual schedule. Mantoux test in 2008 – 10 mm papule, 2009, 2011 – 9 mm papule, 2013 – hyperemia, 12 mm. Hereditary anamnesis: rheumatoid arthritis in paternal grandmother and aunt.

The boy has had the disease since the beginning of December 2012. The onset was characterized by subfebrile fever and weakness. Within a week, the fever acquired a hectic character; erratic menocelis and pains in leg joints developed on its peak. The child refused to walk. The boy was hospitalized to the local inpatient hospital. The following phenomena were observed at admission: fever up to 40 °C, skin menocelis, arthralgiae, intense regional lymphadenopathy and rigidity of cervical muscles regarded as a meningeal symptom. Supposedly, it was caused by pains in cervical spine. The child was transferred to the contagious isolation ward to rule out meningitis. Microbiological liquor analysis did not reveal microflora growth: glucose – 3.52 mmol/l, protein – 0.52 g/l, cytosis – 25 per mcl; all the listed parameters were within normal values. Meningitis was ruled out. The boy was undergoing antibacterial therapy with cefazolin, ceftriaxone and treatment with nonsteroid anti-inflammatory drugs to no effect. The boy was consulted by a cardiologist, who suspected onset of the systemic JIA. The boy was transferred to the cardiology department. His condition at admission was considered severe due to pyretic fever. Body weight – 16.4 kg, height – 105 cm. Linear eruptions on internal antebrachial surface and intense regional lymphadenopathy were observed on the peak of fever. Motion of all articular groups was painless and to a full extent. No pathology of respiratory tract organs was revealed. Moderate tachycardia (heart rate of 90-120 bpm), muffled heart tones, respiratory arrhythmia, singular extrasystoles and systolic noise in secondary aortic area were observed with regard to the cardiovascular system.

Clinical blood analysis: moderate hypochromic anemia (hemoglobin – 110 g/l, number of erythrocytes – 3.9x10⁹/mm³); leukocytosis – up to 35.9x10³/mm³; left deviation (stab neutrophils – 12%, segmented neutrophils – 72%); thrombocytosis – up to 635x10³/mm³; erythrocyte sedimentation rate (ESR) increased up to 55 mm/h. Blood serum: hypoalbuminemia (albumin content – 39%), serum alpha-1-acid glycoprotein increased up to 3.99 g/l (with norm being up to 1.2 g/l). Analysis of hemostasis system revealed increase in serum fibrinogen level up to 9.79 g/l (with norm being up to 4 g/l), antithrombin III level – up to 152 (with norm being up to 120%), plasminogen level – up to 160% (with norm being up to 120%), D-dimer level – up to 577 mcg/l (with norm being up to 240 mcg/l). Other parameters were within normal values.

According to the morphological and histological analysis of marrow biopsy material, hemoblastoses were ruled out. According to the microbiological and immune-enzyme analysis, viral infections, including herpetic, Epstein-Barr, cytomegalovirus, enterovirus, mycoplasmal, chlamydial, toxoplasmal and intestinal group infections, were ruled out. Ultrasound examination of abdominal cavity organs revealed moderate hepatosplenomegaly. Thus, diagnosis sJIA was established to a child on the basis of clinical symptoms (fever, skin eruptions, lymphadenopathy, arthralgiae, moderate hepatosplenomegaly) and laboratory data (hypochromic anemia, leukocytosis, thrombocytosis, increased ESR). The patient was prescribed diclofenac sodium (37.5 mg/day), prednisolone (1 mg/kg per day (15 mg/day) perorally), methotrexate (10 mg/week, intramuscularly), normal human IgG -and IgM-containing immunoglobulin infusion (3 ml/kg (150 ml)) and antibacterial therapy. Condition improved in the setting of the treatment; however, unstable subfebrile fever (up to 37.7 °C) and arthralgiae in shoulder and elbow joints persisted.

The child has been observed at the university pediatric clinical hospital of the First Sechenov MSMU since March 2013. The patient’s condition was considered satisfactory at admission. Body weight – 19.9 kg, height – 115 cm. Body temperature – 36.7 °C. Physical examination...
revealed a moderate medicamentous Itsenko-Cushing syndrome, lymphadenopathy, restricted hip joint opening (especially on the right). Clinical blood analysis: moderate hypochromic anemia (hemoglobin – 115 g/l), leukocytosis – up to 24x10³/mm³, ESR increased up to 36 mm/hour. Other peripheral blood parameters were within normal values. Immunological examination revealed increase in the serum C-reactive protein level up to 4.55 mg/dl (with norm being up to 0.8 mg/dl).

Magnetic resonance imaging of hip joints revealed a small amount of liquid in articular cavities; this indicated arthritis in the moderate activity stage. Daily prednisolone dosage was reduced by 1.25 mg. Disease exacerbation developed during the therapy using this dosage; it manifested itself with fever up to 38.5 °C, maculopapular linear eruptions in axillary areas and internal hip surface. Distinct articular syndrome in the form of an active arthritis of the right knee and ankle joints with function impairment develop in the patient for the first time; pains and motion restriction appeared in cervical spine and shoulder joints. Pulse therapy with methyl prednisolone was conducted according to schemes #1 (250 mg) and #2 (125 mg) in order to arrest the exacerbation. Given high activity of the disease and inefficacy of the therapy performed, tocilizumab (Actemra, Chugai Pharma Manufacturing Co., Japan) treatment (8mg/kg of body weight per administration (200 mg per administration)) has been begun since 08.04.2013. Prednisolone dosage totaled 13.75 mg/day by that time; methotrexate dosage was increased up to 15 mg/week.

Extraarticular manifestations arrested in the setting of the therapy performed: fever, rash and articular syndrome – after 4 weeks of treatment (after the 3rd drug infusion); number of peripheral blood leukocytes and ESR (7 mm/h) normalized as well. The boy had been receiving intravenous tocilizumab infusions once in 2 weeks. No undesirable reactions to infusions were observed. In the setting of the therapy, the child gained weight and grew by 3 cm within 6 months: body weight – 20.3 kg, height – 107 cm. Manifestations of medicamentous Itsenko-Cushing syndrome reduced considerably. At the moment, minimal opening restriction persists in the right hip joint. Laboratory parameters of the disease activity are within normal values; hypochromic anemia persists (hemoglobin – 106 g/l, color index – 0.69).

By October 2013, daily prednisolone dose was reduced down to 2.5 mg/day. The child continues to receive methotrexate intravenously in the dose of 15 mg/week. The presented case demonstrates severe course of the sJIA, torpid to treatment with glucocorticoids and methotrexate, and efficacy of IL6 inhibitor tocilizumab for this variant of the disease.

REFERENCES


