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The effectiveness of TNF α inhibitor adalimumab in a patient with chronic uveitis in the onset of juvenile idiopathic arthritis

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The article presents a clinical case of successful use of monoclonal antibodies to TNF α — adalimumab — as the drug of choice for treatment of continuously recurrent chronic bilateral uveitis, complicated with cataract, which had emerged at the onset of juvenile idiopathic arthritis long before the articular syndrome, in the absence of humoral activity in a child, who got the disease at the age of 12. The initiation of the therapy with adamumab induced uveitis remission after 12 weeks after the initialization.
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Introduction

Juvenile idiopathic arthritis (JIA) is a systemic chronic disease, which develops in children under 16 years of age.
JIA is characterized by predominant destructive joint disease, as well as by the pathology of other organs and tissues with the formation of multiple organ failure of varying level of manifestation [1].
Interconnected, immunopathological and inflammatory processes and reactions underlie the origin and, usually, progressive development of JIA; these processes and reactions are presented in a particular clinical picture, lower quality of life, and, often, in heavy disablement of the patients [2].
JIA is one of the most common and most disabling rheumatic diseases in children. The incidence of JIA is from 16 to 20 cases per 100 thousand children under 16 years of age. The prevalence of JIA in different countries is 0,05-0,6%. The prevalence of JIA in children under 18 years of age on the territory of the Russian Federation is 62,3 per 100 thousand children, primary disease incidence — 16,2 per 100 thousand. Quite an unfavorable situation, concerning JIA, is observed in adolescents: the prevalence is 116,4 per 100 thousand (for comparison — in children under the age of 14 it is equal to 45,8 per 100 thousand), and primary disease incidence — 28,3 per 100 thousand (for comparison — in children up to 14 years of age it is 12,6 per 100 thousand) [3].
Development of eye pathology, including uveitis, can precede the articular syndrome in juvenile arthritis in some cases [3]. Uveitis develops in 12-24% of children with JIA [4].
The most common eye disease is common in girls with oligoarticular JIA. The heaviest extraarticular manifestation of JIA is uveitis, which can be both acute, sub-acute and chronic. The most common form of uveitis is acute iridocyclitis with well marked clinical symptoms — injection of the sclera and conjunctiva, photophobia, lacrimation and pain in the eyeball. However, uveitis in JIA quite often has a sluggish chronicity, and patients go to an ophthalmologist when they already have decrement in visual acuity. Ophthalmoscopy detects corneal dystrophy, angiogenesis in the iris, formed spikes, resulting in deformation of the pupil and reduction of its reaction to light. Develops cataract — cataract.

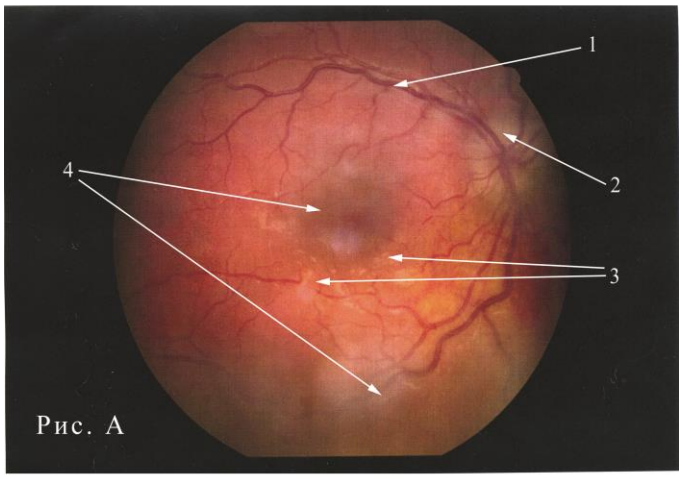
The importance of timely treatment of pathogenetic uveitis, associated with JIA, is proved by the fact, that without the adequate treatment, visual acuity eventually decreases down to full blindness, with possible development of glaucoma.
Reduced visual acuity due to the development of uveitis complications, which leads to disability in children, can reach 12% [5], so the treatment of uveitis in JIA should be quite aggressive and start immediately after the diagnosis. Local therapy, carried out by ophthalmologists, is often not effective enough, consequently, the patients require prescription of immunosuppressive drugs and genetically engineered biological preparations.

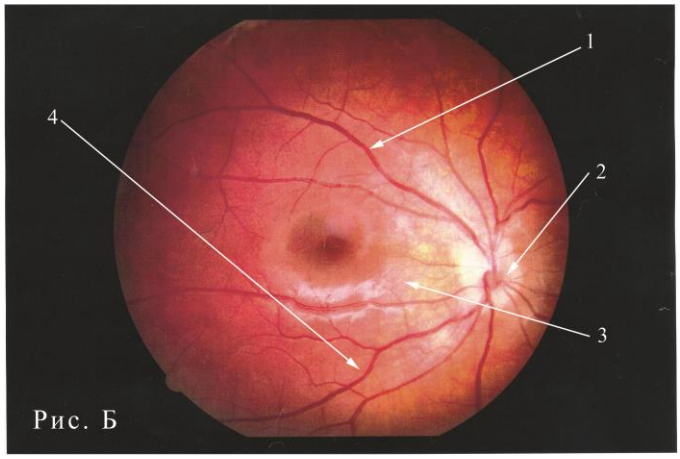
A clinical example

Patient K., born in 2002, for the first time applied to the regional children's hospital (Ulyanovsk) on the 06/30/2014 for verification of the diagnosis and treatment.
Past medical history: a child from the 2nd pregnancy, which was proceeding on the background of gestosis in I and II trimester; threats of interruption in the I trimester; 2 term births. The birth weight was 3400 g, the body length was 52 cm. The neonatal period was without complications. The girl was not behind in physical and mental development, comparing to her peers. She was vaccinated according to the calendar of preventive vaccinations.
Past diseases: acute respiratory infection (infrequently), chicken pox; a surgery for adenoid stage 3 in 2011. Allergic anamnesis is not burdened. Blood transfusions have not been carried out. Heredity is not burdened. Tuberculosis is denied among the entourage.
The disease history: the patient was ill since 2012, when the first symptoms eyes disorders appeared —redness, decrement of visual activity (short-term). The patient was not taken to the hospital for examination, neither did she visit an ophthalmologist in the regional children's clinical hospital. She was examined by an ophthalmologist at the place of residence in the district hospital, symptomatic treatment was carried out with short-term effect. At the end of April 2014, for no apparent reason, rashes appeared on her face and hands without fever, which were regarded as an allergic rash by the district hospital. The patient was assigned prednisolone at 1 mg/kg for 5 days. The treatment stopped the dermatitis symptoms. At the beginning of May 2014 there was redness of the conjunctival mucous membrane, sclera injection, pain in the right eye, decrement of visual activity in the right eye. From 07.05.14 to 16.05.14 the patient was examined in the Republican Ophthalmological Clinic of Saransk (the Republic of Mordovia). A CT scan of the brain was conducted: no pathology was revealed. The patient was screened for chlamydia, toxoplasma, helminth, herpes simplex virus – the result (IgM) was negative. Very high (189,8 IU/ml; result is considered positive when concentration is more than 15 IU/ml) IgG titer to cytomegalovirus and herpes simplex virus (22,7 U; result is considered positive when concentration is more than 1.1 IU) was detected. According to the ultrasound examination of eyes, opacities in the vitreous in both eyes more on the right, the fields of vision were within normal values. Instillations of dexamethasone, levofloxacin, cyclopentolate, diclofenac, parenteral antibacterial therapy, electrophoresis with calcium were assigned. The patient was discharged with a diagnosis of "Iridocyclitis of the right eye, papilledema on two sides (more on the right)" (fig. 1). Given the papilledema symptoms, the patient was examined by a neurologist of the RCCH (Ulyanovsk): there were no data detected in favour of neurological disorders. Ophthalmologist diagnosed "Iridocyclitis of the right eye in remission; papilledema of stage 2 on the right, of stage 1 on the left, in regression". In order to exclude uveitis associated with JIA, the girl was hospitalized to the Department of Cardiorheumatology of the RCCH.
The child's condition on hospitalization was assessed as satisfactory. The skin was clean, pale pink. Peripheral lymph nodes were not enlarged. Acute inflammatory changes in the joints were not detected, the active and passive movements of the joints were normal.
A full examination was carried out at the department.
The patient consulted an oculist. Visual acuity of the right eye — 0,7, left eye — 0,9-1,0.
The right eye: 3 spikes at 5, 18, 11 o'clock. Objectively: both eyes were calm, full mobility, the position of the eyeballs was normal, the anterior eye was of medium depth, the iris was structural, the optical medium was transparent. The fundus of the eye: the optic disc was rose-pink, the borders were unclear, the veins were enlarged; the ratio of arteria to veins was 2: 3, macular reflex were

distinct, periphery was without pathology. The right eye: optic disc protruded into vitreous body; the left eye: the borders were slightly effaced.

Fig. 1. A picture of the eye fundus in the onset of patient K.'s disease, aged 12 years, with JIA-associated uveitis.
Note. A — the right eye: 1 — expansion and tortuosity of the veins; 2 — peripapillary albedo retinae, papillitis, prominence of the optic nerve; 3 — albedo retinae, soft exudates; 4 — turbidity in the vitreous body. B — the left eye: 1 — expansion and tortuosity of the veins; 2 — less pronounced peripapillary albedo retinae, prominence of the optic nerve, the boundaries are distinct; 3 — less pronounced albedo retinae; 4 — unmarked turbidity in the vitreous.





The patient was consulted by a phthisiatrician: any contact with tuberculosis patients was denied by the parents. The patient was registered with tuberculosis infection since 12.04.13, The Mantoux tuberculin skin test from 1.07.14: + 2mm. Diaskin-test from 01.07.14 was negative.
The patient was examined by a tubosteologist: there was no data in favour of tuberculosis of bones.
The patient was examined by a phthisiophthalmologist: the remission of right eye uveitis was detected.
The results of X-ray examination of the chest organs revealed no pathology.
According to the results of X-rays of the cervical spine with functional tests, there was instability of the cervical spine at the levels C_{II}-C_{III}, C_{IV}-C_V, C_V-C_{VI}.
According to the results of X-rays of hands: periarticular osteoporosis.
The laboratory indicators of activity were in normal range (hemoglobulin 145 g/l at normal values of 120-160, the number of leukocytes $6{,}6\times10^9$/l at normal values of 4,0-9,0, thrombocytes — 344×10^9/l at normal values of 180-320, ESR 3 mm/hr at normal values of 5-15, serum CRP level of 0,5 mg/l at normal values of 0-5,0); antinuclear factor, rheumatoid factor, antibodies to DNA were negative.
In August-September 2014, the girl was examined in the Republican Children's Clinical Hospital (Moscow), where she was diagnosed with "Uveitis of unknown etiology. Visus OD = 0,8 OS = 0,9". An anti-inflammatory treatment was carried out − application adrenaline and dexamethasone instillation.
In October, November, December 2014 uveitis was recurring continuously. The child was treated at the ophthalmology department of the RCCH. The effect of treatment was short-term and associated with the application of local glucocorticoids and nonsteroidal anti-inflammatory drugs. When the course treatment was completed, the aggravation of uveitis developed again. In October 2014, the patient got persistent decrement in visual acuity in her right eye. On the admission to the Department, the visual acuity in her right eye was equal to 0,7 without any spectacle correction, the visual acuity in the left eye was 0,9-1, binocular vision. Both eyes were very calm, with full mobility, the position of the eyeballs was normal, adnexa was retained, keratoderma was transparent, single old precipitates were identified on the corneal endothelium, the anterior eye was of medium depth, iris was structural and unchanged in color and pattern, the newly formed blood vessels were not detected, the pupil on the left was round, 3,5 mm in diameter, pupillary light reflex was lively, the pupil of the right — iris

adhesion at 5, 7, 11 h, deposition of pigment on the anterior capsule of the lens. In both eyes there were determined floater in the vitreous opacities.
The fundus of the eye: the optic disc rose-pink color, contours effaced, veins moderately expanded, the ratio of arteries to veins 2:3,5, periphery without features. By palpable the tonicity was normal (fig. 1).
Since October 2015, articular syndrome has developed in the patient. Pain and stiffness in the knee and ankle joints has appeared.
In connection with the recurrence of uveitis, the child was sent to the Moscow Scientific Research Institute of Eye Diseases Helmholtz (Moscow), where uveitis in acute stage and papillitis were confirmed.
The girl was also consulted at the Scientific Research Institute of Rheumatology (Moscow). Given marked inflammatory changes in the metacarpophalangeal, knee and ankle joints with limitation of motion, the diagnosis was the following: "chronic juvenile arthritis, polyarticular version with an eye lesion, 2 stage activity, 2nd functional class. Chronic uveitis. Aggravation." As a basic therapy, methotrexate at a dose of 15mg/m^2 of body surface per week was appointed, with further decision on initiation of the GIBP therapy.
In March 2015, the patient was re-examined and treated in the RCCH. Laboratory indicators were within the normal limits. According to the MRI of the right knee joint, areas of bone marrow infiltration in metaphysis and medial condyle of the femur and tibia epiphysis, signs of synovitis were revealed (fig. 2).

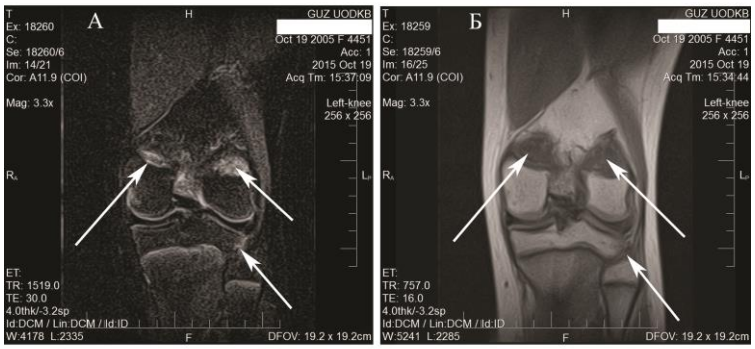


Fig. 2. MRI of the right knee joint of patient K., aged 12, with JIA-associated uveitis.

Note. 2A — coronal projection in T_2-sequence with fat suppression (STIR) in distal metaphysis, medial femoral condyle, lateral tibial epiphysis fracture — bone marrow infiltration zone. 2B — coronal projection in T_2-sequence in the distal metaphysis, medial femoral condyle, lateral tibial epiphysis fracture — bone marrow infiltration zone. Arrows indicate bone marrow infiltration and edema.

The child continued to receive methotrexate at a dose of 15 mg/m^2 of body surface per week.
The child was again hospitalized in the Scientific Research Institute of Rheumatology for examination and correction of the therapy.
The results of the research revealed exacerbation of articular syndrome and uveitis. Given the continuously recurring course of uveitis, resistance to methotrexate therapy, it was decided to appoint a human monoclonal antibody to TNF α of adalimumab for subcutaneous administration at a dose of 40 mg once a week.
The patient started to receive adalimumab in July 2015.
In the course of the treatment, the articular syndrome was completely stopped, and in September 2015 remission of uveitis was pronounced (table).

Table. **The dynamics of the picture of the fundus of the eye in patients K. in the course of the treatment**

Indicators	**Before treatment**		**In the course of treatment with adalimumab**	
	October 2014		**September 2015**	
	The right eye	**The left eye**	**The right eye**	**The left eye**
Visual acuity	0,8	0,9	1,0	1,0
Eye position	Dev 0, the position is normal, movements are in full scale	Normal, movements are in full scale	Dev 0, movements are in full scale	Normal, movements are in full scale
Conjunctiva	Unchanged, calm	Unchanged, calm	Unchanged, calm	Unchanged, calm
Keratoderma	With precipitates and sweated endothelium	With single precipitates and sweated endothelium (less than in OD)	Single elements of endotheliopathy	Single elements of endotheliopathy
Anterior chamber	Uniform, medium, moisture is transparent, with cells 1,0+	Uniform, medium, moisture is transparent, with single cells 0,5+	Uniform, medium depth	Uniform, medium depth
Iris, pupil	Structural, the pupil is in the center, posterior synechiae at 4, 8, 11 h	Structural, the pupil is in the center	Calm, posterior synechiae at 4, 8, 11 h	Calm, the pupil is rounded
Crystalline lens	Transparent, iridocapsular synechiae	Transparent	stiffness of the posterior capsule	stiffness of the posterior capsule
Vitreous body	With fresh cells	With fresh cells	Small cells (a small number)	Small cells (a small number)
Eye fundus	Optic disk is rose-pink, protrudes, the boundaries effaced, vascular pathway and caliber are not violated, macula corresponds the age, no focal symptoms detected	Optic disk is rose-pink, protrudes, less than OD, the boundaries effaced, vascular pathway and caliber are not violated, macula corresponds the age, no focal symptoms detected	Optic disk is rose-pink, protrudes, less than OD, the boundaries are distinct, vessels are unchanged, macula — reflexes are signified, periphery — without pathologies	Optic disk is rose-pink, protrudes, less than OD, the boundaries are distinct, vessels are unchanged, macula — reflexes are signified, periphery — without pathologies

Discussion

A significant number of patients with JIA in the start period of uveitis are already receiving immunosuppressors because of the activity of the articular syndrome. However, in some cases uveitis can be primary and the only manifestation of rheumatic process.

The development of uveitis in our patient did not correlate with arthritis activity, which is congruent to the literature [6, 7]. The treatment of the ophthalmologists included active local therapy of uveitis with glucocorticoids and eye drops containing NSAID. As a basic therapy, methotrexate was appointed subcutaneously. Despite the treatment, uveitis continued recurring during 3 months, which

led to a decrease in visual acuity. According to the literature, the effectiveness of methotrexate and glucocorticoids in uveitis at mono- or combined administration does not exceed 48-71% [5, 8, 9].
The patient required the correction of the treatment to achieve the remission of uveitis. The chosen drug, in this case, was the GIBP adalimumab, which, in many clinical researches, has proved itself as an effective tool in JIA treatment, including cases with ophthalmological manifestations [6-8].
The analysis of effectiveness of adamumab has shown after only 3 months of treatment, that our patient K. with JIA achieved remission of uveitis and the status of inactive disease. Currently, the girl continues to receive adalimumab at a dose of 40mg subcutaneously once in two weeks in combination with methotrexate at a dose of 15 mg per week. The patient tolerates the drug well, without adverse effects. The visual acuity in both eyes was restored (see table.).
Adalimumab — a representative of inhibitors group (blocking agents) TNF α — is currently one of the major biological preparations for treating JIA without systemic manifestations. It is consists of recombinant homogeneous antibodies, peptide sequence of which is identical to the human IgG_1. The preparation is obtained by recombinant DNA technology and it has high affinity to p75- and p55-receptors of soluble and membrane associated TNF α. Adalimumab may cause activation of the complement system, which leads to cell lysis, which has TNF α located on its surface. Adalimumab is injected subcutaneously, 1 time in 2 weeks (its half-life is 2 weeks), which determines the possibility of its convenient application for the majority of patients on an outpatient basis [1, 3]. In the Russian Federation, adalimumab is recorded in children with JIA from the age of 4. Adalimumab can be used both in combination of with methotrexate and as monotherapy [1].
In clinical researches, it was demonstrated that adalimumab is effective in children with JIA, including cases with concomitant uveitis [6-8]. Despite strong evidence of high effectiveness of the drug, the data obtained from clinical researches and practical application of adalimumab in Europe and the United States, own domestic experience in using one or another method of treatment is of the greatest interest [10]. The results of Russian clinical researches of effectivity and safety of adalimumab in patients with JIA and arthritis with eye disease, refractory to treatment by classical immunosuppressors, demonstrate its high effectiveness and safety as the drug of the first choice [5, 8].

Conclusion

At the present time, there is a modern range of tools at rheumatologists' disposal to control the pathological process in children with JIA. It is necessary to start early the systemic therapy for children with ophthalmological manifestations of JIA, and it should be corrected by rheumatologists and ophthalmologists, who are being in close contact. The emergence of GIBP in the arsenal of pediatric rheumatologist has changed the prognosis of such a severe disease like JIA.
Our clinical observation demonstrates the high effectiveness of TNF α adalimumab inhibitor, which allowed achieving success after a previous long-lasting ineffective treatment with basic preparations of local and systemic action.
The induction of remission of uveitis after 12 weeks of the therapy in our patient allows considering adalimumab to be promising in the treatment of JIA-associated uveitis with chronic and continuously recurrent course, resistant to treatment in children.

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Conflict of interest

The authors of this article have confirmed the absence of conflict of interest worth reporting.

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