

Clinical observation

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The Experience of Using Adalimumab for the Treatment of Juvenile Ankylosing Spondylitis

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This article presents a case with an early onset of severe juvenile spondylitis defeating the eye; refractory to treatment by classical immunosuppressant. Successful use of biological agent adalimumab is described. Acute inflammation was stopped in the affected joints by the 4th weeks of therapy with complete recovering a range of motion; remission of uveitis was observed by the 8th week; laboratory values of a disease activity such as ESR and serum CRP returned to normal.

Key words: *children, juvenile ankylosing spondylitis, uveitis, adalimumab.*

Juvenile idiopathic arthritis is arthritis of unknown reason, lasting more than 6 weeks, developing in children only under the age of 16, excluding other pathologies of joints. By the criteria of International League of Rheumatology Associations (ILAR) a number of options are identified for juvenile idiopathic arthritis. One of them is **entezit** arthritis, which according to the classification of the European League against Rheumatism (EULAR) corresponds to the juvenile ankylosing spondylitis. Juvenile ankylosing spondylitis (JAS) is a chronic inflammatory disease of the peripheral joints, tendons, ligaments and the spine, starting before the age of 16 and is characterized by predominant disease of males, also having the tendency to familial aggregation and association with HLA-B27. Treatment of JAS is a complex problem of child rheumatology. Medicines that are traditionally used for the treatment of juvenile arthritis are not effective or ineffective for JAS [1]. The majority of immunosuppressive drugs does not have a selective effect on the immune system and does not eliminate the link in the pathogenic chain of juvenile spondylitis. The consequence is a steady progression of the disease, the rapid development of joint destruction, patients' disability and a

significant reduction in their quality of life. In some cases, the use of immunosuppressive drugs is accompanied by the development of severe adverse events. Thus, the introduction of new medicines for the treatment of JAS is very important. The last are tumor necrosis factor blockers (TNF α), obtained by genetic engineering. In JAS eyes damage manifests as uveitis [2]. This location of rheumatoid inflammation is associated with a common origin of the mesenchyme tissues of the joints and the vascular tract of the eye. The course of uveitis may be acute, sub acute and chronic [2, 3]. In acute uveitis an injection of the sclera and conjunctiva, photophobia, lacrimation and pain in the eyeball are developing. The process is characterized by lesions of the iris and cilia body, forming iridous cyclitis, in some cases pan uveitis. The development of iridous cyclitis is accompanied by precipitation of protein in the anterior chamber of the eye, clouding the cornea with the deposition of precipitates. The most common uveitis in juvenile spondylitis is acute and sub acute. With the progression of uveitis, corneal dystrophy, cataract (cataract), adhesions are formed, leading to the deformation of the pupil and reduction its response to light. Uveitis tends to be bilateral leading to a significant decrease in visual acuity and blindness. The most difficult cases are cases of uveitis that come prior to the development of joint syndrome [3, 4].

In some cases, local treatment of uveitis by dexamethasone drops or injections; drops with anti-inflammatory drugs and mydriatic drugs; oral cyclosporine and corticosteroids are not able to prevent the further loss of the vision. Moreover, the long-term treatment with glucocorticoids leads to severe, often irreversible side effects (in particular short stature, delayed puberty and adrenal insufficiency). Given the above, the implementation of new drugs is relevant for the treatment of juvenile spondylitis defeating the eye. These drugs might be biological agents obtained by genetic engineering, as evidenced by clinical observation presented below.

Patient Y, 17 years old (he was born in 1995) has been observed in the Rheumatology department of the Scientific Center of Children's Health since March 2005. The boy was born from the pregnancy, proceeding with the toxicity in the first half. The delivery was urgent. Weight at birth was 3400 g, length was 51 cm; neonatal period was uneventful. The boy was attached to the chest on the first day. He was breastfed until the age of 2. Early physical and psychomotor development corresponded with age. Till 2 years, vaccination had been carried out on the calendar. ARI used to be 1-2 times a year in the past medical history. The boy's parents are basically healthy. Heredity of rheumatic diseases is not burdened. The child became ill at the age of 2 years old, when without apparent precipitating factors he had had the swelling and soreness in the left knee. The parents made an appointment with the surgeon and the boy was admitted to local hospital. After the inspection "Juvenile Rheumatoid Arthritis" was diagnosed. The boy was appointed to antibiotic therapy with penicillin and prednisone orally at a dose of 0.5 mg / kg body weight per day. The therapy with prednisolone rapidly improved the child's condition, fully stopped acute inflammation in the joints and decreased pain. After 6 months from the initiation, prednisone has been completely withdrawn followed

by the aggravation of the articular syndrome. At the age of three, the boy suffered a severe intestinal infection, accompanied by conjunctivitis and urethritis when the diagnosis of Reiter's disease was made. An examination of the child identified chlamydia antigen in epithelial cells of the conjunctiva and urethra. The prednisone at a dose of 0.5 mg / kg body weight per day and macrolide antibiotic therapy was newly appointed.

In four months of treatment prednisone was discontinued. Hydroxychloroquine therapy was assigned the effect of which was not observed. Since 5 years old the child has not been observed by a rheumatologist, because his parents decided to treat him with non-traditional methods such as homeopathy, bio resonance therapy and the healers' services. While treated with alternative therapies, articular syndrome has become generalized and poly articular, the disease has steadily progressed causing febrile fever.

In March 2005 the child was admitted to the local hospital and giving the severity of the condition, was transferred to the rheumatology department scientific center of Health Care RAMS.

On admission the boy was accepted as extremely grave: he could not move independently, was exhausted; sharp shortage of weight drew attention (20%). He was with the fever about febrile digits daily. Marked lacrimation, photophobia, and blephar spasm were noted; sclera and conjunctiva were injected.

Articular Syndrome had poly articular character: exudative-proliferative changes in the knee and ankle joints with a sharp curtailment of their functions were marked. Cultivation and rotation in the hip joints were complicated. The "sausage like" toes deformation was marked. There were multiple enthes pathologies.

The clinical analysis of blood revealed increased numbers of platelets to $650 \times 10^9 / l$, ESR 55 mm / h. The immunological analysis of blood serum revealed an increased concentration of CRP up to 12.5 mg% (normal up to 0.8 mg %).

Immunogenic study found B27 antigen class I major histocompatibility complex.

Computed tomography of ilea sacral joints revealed bilateral sacra ileitis.

The boy was consulted by an ophthalmologist: diagnosis of bilateral uveitis in a stage of severe exacerbation was confirmed.

Based on history, clinical examination, the results of instrumental and laboratory methods the boy was diagnosed with "Juvenile ankylosing spondylitis, bilateral iridocyclitis," according to the ICD-X (M08.1).

Considering the early onset and rapidly progressive course of disease with development of disability; in order to prevent further destructive changes in joints, to relief symptoms of uveitis and to support life indications the boy had been introduced chimeric monoclonal antibody to tumor necrosis factor α - infliximab. Prior to initiation of therapy with infliximab the consent of the local ethical committee, approval of the Academic Council of Scientific center of Health Care Medical Sciences, and parental consent have been obtained.

Methotrexate as fond therapy has been appointed at a standard dose of 15 mg/m² of body surface per week. Given the severity of the uveitis, the threat of vision loss, ophthalmologist assigned cyclosporine at a dose of 4.4 mg / kg body weight per day.

Therapy improved the boy's condition significantly and rapidly: after the first infusion of infliximab the pain and stiffness in the joints were fully stopped, the child had no fever any longer. Swelling of the affected joints was also significantly reduced, the range of motion in them increased.

After the third administration of infliximab inflammatory changes in joints were completely cropped, a range of motion in them was restored and the boy began to move independently.

Laboratory indices of disease activity were also normalized in the child such as the serum level of CRP, ESR, and platelet count. The boy was re-consulted by an ophthalmologist who marked that inflammatory activity of uveitis was reduced.

Later the child was under constant surveillance in the rheumatology department of the Scientific Center of children's health RAMS, and Moscow Scientific Research Institute of Ophthalmology named after Helmholtz.

The treatment with infliximab, methotrexate and cyclosporine developed clinical and laboratory remission of ankylosing spondylitis. Inflammatory changes in the joints disappeared; the child was able to take care of himself completely.

Remission of the articular syndrome had persisted for 2 years.

In spite of the remission of arthritis, during the whole observation period (from May 2005 to 2007) of a boy with a frequency of 1 every 2-3 months, uveitis had recurred: there was an injection of the sclera and conjunctiva with expressed photophobia, lacrimation, pain in the eyeballs, decreased visual acuity; and subsequently the boy had developed bilateral cataracts. Local therapy of uveitis was being carried out constantly. In 2006 the boy had removed lens on the right-sided cataract in Moscow Scientific Research Institute of Ophthalmology named after Helmholtz. For further surgical treatment uveitis remission was necessary, but stable remission couldn't have been achieved for a year and a half.

Analysis of the child testified the need for correction therapy for uveitis remission.

In this case, all indications were present for the use of oral glucocorticoids.

However, retro bulbar administration of glucocorticoids didn't give even a short-term positive effect, and therefore it was concluded that oral administration of prednisolone will likely be insufficiently effective, and at the same time - have an uncontrollable teenager due to the development of drug-dependent Cushing's syndrome.

All the above gave a reason to refrain from oral administration of prednisolone therapy and start another of TNF α -blocker adalimumab (Humira, Abbott, Germany).

Adalimumab is different from infliximab in that way that it is a fully human monoclonal antibody that lows immunogenicity and reduces the incidence of allergic reactions.

Adalimumab is approved for use in the U.S. (FDA; December, 2002) and Western Europe (EMA; September, 2003). In Russia, the product has been registered at the beginning of 2007 as, indicated for a "juvenile idiopathic arthritis in children and adolescents from the age of 13". In July 2010 Adalimumab was approved for usage in 67 countries around the world. The main indication for adalimumab is a heavy and moderately severe rheumatoid arthritis. The drug is also used for the

treatment of ankylosing spondylitis, psoriasis, and psoriatic arthritis. The study of efficacy and safety of adalimumab in patients who had been previously treated with other drugs anti FNO is of interest. Thus, out of 899 patients with rheumatoid arthritis had been treated with infliximab before and / or etanercept, out of 56.7% 20 reported improvement, 32.2% - 50 and 12.5% - 70 patients reported improvement according to the criteria of the American College of Rheumatology . According to the criteria of the European League against Rheumatism 20.3% of patients reported good results, while 73.8% had satisfactory response [5]. The results of these studies showed no significant difference in the effectiveness and frequency of side effects between patients who had not previously received anti FNO drugs and those who had been treated with infliximab or etanercept [5-9].

Adalimumab has been successfully used for the treatment of ankylosing spondylitis [10]. The study included 46 patients. During the first phase (double-blind, randomized study, lasting 12 weeks) the effectiveness of adalimumab was compared with placebo. Out of 46 patients 22 were receiving adalimumab and 24 - placebo. As a result, 54.5% of patients treated with adalimumab improved by 40% by using criteria for ASAS (Assessment in Ankylosing Spondylitis), and 12.5% with placebo ($p = 0.004$). During the second 52-open phase week, all patients had been receiving adalimumab, and the good effect of therapy was maintained throughout the observation period.

In juvenile idiopathic arthritis eye disease develops manifested as uveitis while rheumatoid uveitis takes 15% of all cases of uveitis in childhood [11-14]. In biological fluids of patients with uveitis elevated levels of tumor necrosis factor α were defined. It is believed that this is a key mediator of inflammation in uveitis. In experimental autoimmune uveitis inflammation was blocked through an inhibition of tumor necrosis factor α by a receptor blocker p55 TNF α . However, in a randomized, placebo-controlled study the effectiveness of etanercept for the treatment of juvenile idiopathic arthritis with uveitis had no significant difference observed between the effect of TNF α blockers and placebo.

In June 2006, P. Tynjala presented the results of a pilot study of efficacy and tolerability of adalimumab in children with juvenile idiopathic arthritis with uveitis [15]. The study included 21 children with juvenile idiopathic arthritis and anterior uveitis in age from 6 to 19 years, mean age - 13.5 years. Disease duration ranged from 2.5 to 14.6 years and averaged 10.1 years. At the time of the study one third of patients had only a worsening of uveitis, one third - just the aggravation of arthritis and one third - a worsening of uveitis and arthritis. In 18 out of 21 children (86%) bilateral uveitis were diagnosed. Before the start of the study 18 out of 21 children received disease-modifying drugs, 12 of them (57%) - methotrexate, 95% of patients prior to treatment with adalimumab were treated with anti FNO α drugs: infliximab - 8 children, etanercept - 2, both drugs - 10. Prior to this anti cytokine therapy was appointed 38 months before the study (from 16 to 67 months). One patient had never been treated by any biological agents. The duration of adalimumab therapy was 17.5 months (range 4.5 to 31.2 months). Uveitis activity was assessed by the number of cells of the anterior chamber in the field of a view.

Improvement was recorded as the reduction of inflammation, at least to one degree; the deterioration was recorded as an inflammation increase, at least one degree, a decrease in visual acuity and development of complications.

The results showed that the decrease in the activity of uveitis was noted in 11 (53%) patients, 4 patients (19%) had no changes, 6 (28%) had an increased activity of uveitis. The average number of relapses per year decreased from 1.9 to 1.4 ($p = 0.093$), especially in girls ($p = 0.074$). Thus, a positive trend during the uveitis was observed in half of patients treated with adalimumab. Serious side effects have not been reported. 5 (24%) patients had a local skin reaction. Adalimumab therapy was discontinued in 7 patients: 6 - due to lack of efficacy of the treatment, 1 - in connection with the development of uveitis remission. The results obtained are encouraging and suggest that adalimumab may be a promising treatment for refractory uveitis.

L.B. Vazquez-Cobian with coauthors used adalimumab for uveitis of various etiologies [16]. The study was with 14 children, including 11 girls, mean age - 11.5 years (range, 4 to 9 years). 5 patients were diagnosed with idiopathic uveitis, 9 - rheumatoid. 5 children had articular syndrome, type mono arthritis, and 4 - polyarthritis. In 51% of patients the elevated serum levels of antinuclear factor were determined. All children did not respond to standard therapy or had evidence of active arthritis. In all cases of idiopathic uveitis other causes of disease were excluded. Adalimumab was administered subcutaneously at a dose of 40 mg/m² of body surface per week, the maximum dose was 40 mg per week. Children with a body surface less than 0.5 m² a dose of adalimumab 40 mg every 1 to 2 weeks was administered. Duration of adalimumab's treatment was $18,1 \pm 2,3$ months. The effectiveness of treatment was evaluated monthly by the dynamics of choroid inflammation, intraocular pressure and visual activity. The side effects and toxicity of the drug were also monitored.

The results of research showed that 80.8% of patients with cellular inflammation in the anterior chamber had an eye inflammation decreased. In 17 out of 26 affected eyes (65.3%), adalimumab therapy led to a reduction in inflammatory activity. In 4 patients (15.4%) no changes were observed. Only 1 child had increased inflammation. In 8 patients adalimumab induced a complete remission of uveitis. Improvement of visual activity was observed in 10 out of 26 eyes (7 patients); visual acuity remained unchanged in 9 eyes. Only in one child visual activity worsened during therapy. ($p < 0.0025$)

In 11 out of 14 children (78.5%) the dose of topical steroids (drops) was reduced. 4 of 14 patients completely abandoned drops (28.5%). Corticosteroids for oral administration were canceled for 2 out of 3 children; one child's dose of glucocorticoids was reduced. No serious side effects and toxic reactions were reported. The only complaint of the patients had been pain at the injection sites. The study for evaluation the effectiveness of adalimumab in children with rheumatoid uveitis, previously treated with TNF blockers α was conducted [17]. The study included 20 patients with juvenile idiopathic arthritis-associated uveitis, 17 of them (85%) with poly articular JIA variant, 19 (95%) had previously received drugs anti FNO; average age was 13.4 years; mean duration of the course

of uveitis 8.7 years; mean duration of adalimumab treatment of 18.7 months. As the results of the study, 7 (35%) reported some decrease in the activity of uveitis, 12 (60%) had no change and 1 (5%) had exacerbation of uveitis. Patients with remission of uveitis were younger and had shorter duration of illness. The results of this study indicate that adalimumab is a potential medicine for uveitis in children with JIA who had not previously responded to other therapy of anti FNO drugs [18].

A study of the comparative effectiveness of treatments for anti FNO uveitis in children is worth your attention [19]. Results of the study revealed significant differences in the effectiveness of adalimumab and infliximab for the treatment of uveitis in children with JIA compared with etanercept.

All the above was the basis for assigning adalimumab for patient Y at a dose of 40 mg from August 14, 2008 under the scheme 1 every 2 weeks. Purpose of the drug was approved by the local Ethics Committee of the Scientific Center of Medical Sciences of children's health. The child's parents signed informed consent for use of the drug. The boy was held five subcutaneous injections of adalimumab 40 mg. Treatment of drug induced remission of uveitis in a child. Combined immunosuppressive therapy with methotrexate at a dose of 15 mg/m² body surface per week and cyclosporine at a dose of 4.4 mg / kg body weight per day was continued at the previous doses. Adalimumab injections were performed on a regular basis at a local clinic.

Prior to the appointment of the drug the boy pointed marked photophobia, lacrimation, and pain in the eyeball. At ophthalmologic examination diagnosed a bilateral uveitis, hypo tonic, OD - complicated cataracts, OS – aphakia. On examination, visual acuity of the right eye is absent (complicated cataract), there is decreased vision of the left eye (0.02). There were signs of inflammatory changes of the anterior eye in the form of conjunctiva injection of the mixed and injected. Right: the pupil of irregular shape, multiple adhesions, swelling of the iris, the lens cloudy, with a reflex of the fundus not. Left: the cornea is cloudy, opalescent, and on the corneal endothelium there are multiple precipitates, in the vitreous there are floating opacities (Fig. 1A, B).

Analysis of the effect of adalimumab showed that after the second injection, the boy decreased conjunctiva injection and photophobia. After 8 weeks of therapy (4 adalimumab injections) iris edema disappeared and the number of precipitates narrowed down. After two months of therapy the child was marked with pharmacological remission of bilateral uveitis: signs of inflammatory changes of the anterior eye were fully stopped, precipitates were not detected (Fig. 2A, B), visual acuity in the left eye improved to 0.05.

Conclusion

The analysis presented by the observation shows a very severe course of continuous recurrent uveitis. The disease debuted with patsy articular joint damage, therapy with methotrexate and cyclosporine was not effective enough. Treatment of chimeric monoclonal antibody to tumor necrosis factor α - infliximab induced remission of articular symptoms, providing the normalization of laboratory parameters. However, the child continued having a high activity of

uveitis, which continually recurred, leading to a decrease visual acuity. This was the basis for cancellation of infliximab and the appointment of the second inhibitor of tumor necrosis factor α - human antibodies - adalimumab. Treatment with adalimumab induced remission of uveitis in the boy. High therapeutic effect of adalimumab allowed refraining from the use of gluco corticosteroids. Adverse effects on the administration of the drug were not obvious. Thus, these results suggest that in case of intolerance or secondary infliximab failure switching to a second inhibitor - human antibody to tumor necrosis factor α - adalimumab provides recovery of therapeutic effect and induces remission in severe uveitis.

Fig. 1A-B Patient Y, 17 years old, disease duration 15 years.

Prior to adalimumab therapy

Fig. 1 A. Conjunctiva injection of the right eye with uveitis before the appointment of adalimumab



Fig. 1 B. Precipitates in the anterior chamber of the right eye with uveitis before the appointment of adalimumab

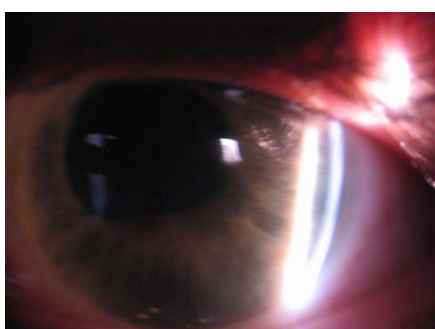
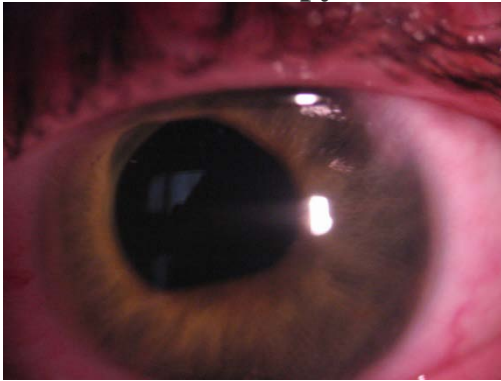


Figure 2 A-B Patient Y, 17 years old. After 8 weeks of treatment with adalimumab

Fig. 2 A. Conjunctiva injection of the right eye with uveitis on adalimumab therapy



Fig. 2 B Precipitates in the anterior chamber of the right eye with uveitis on adalimumab therapy



References:

1. Cassidy J., Petty R., eds. 6th ed. *Textbook of paediatric rheumatology*. Elsevier Saunders. 2010.
2. Benezra D., Cohen E., Maftzir G. Uveitis in children and adolescents. *Br. J. Ophthalmol.* 2006; 89 (4): 444–48.
3. Foster C. Diagnosis and treatment of juvenile idiopathic arthritis associated uveitis. *Current. Opin. Ophthalmol.* 2003; 14 (6): 395–98.
4. Dana M., Merayo Lloves J., Schaumberg D., Foster C.S. Visual outcomes prognosticators in juvenile rheumatoid arthritis associated uveitis. *Ophthalmology.* 1997; 104 (2): 236–44.

5. Furst D., Schiff M., Fleischmann R. et al. Adahmumab, a fully human anti tumor necrosis factor a monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis results of STAR (Safety Trial of Adahmumab in Rheumatoid Arthritis). *J. Rheumatol.* 2003; 30 (12): 2563–571.
6. Keystone E., Kavanaugh A., Sharp J. et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human antitumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum.* 2004; 50 (5): 1400–411.
7. Mease P., Gladman D., Ritchhn C. et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis results of a double blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 2005; 52 (10): 3279–289.
8. Van der Heijde D., Salonen D., Weissman B N. et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res. Ther.* 2009; 11 (4): 127.
9. Rudwaleit M., Claudepierre P. J. et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *Rheumatol.* 2009; 36 (4): 801–808.
10. Rudwaleit M., Claudepierre P., Kron M. et al. Effectiveness of adalimumab in treating patients with ankylosing spondylitis associated with enthesitis and peripheral arthritis. *Arthritis Res. Ther.* 2010; 12 (2): 43.
11. E.I. Alekseeva, A.M. Alekseeva, T.M. Bzarova etc. The effectiveness of infliximab treatment resistant forms of juvenile rheumatoid arthritis. *Issues of modern pediatrics.* 2006, 5 (2): 20.

12. Barrera P., Boerbooms A.M., Janssen E.M. et al. Circulating soluble tumor necrosis factor receptors, interleukin 2 receptors, tumor necrosis factor alpha, and interleukin 6 levels in rheumatoid arthritis. Longitudinal evaluation during methotrexate and azathioprine therapy. *Arthritis Rheum.* 1993; 36 (8): 1070–1079.
13. Kalden J. Emerging role of antitumor necrosis factor therapy in rheumatic disease. *Arthritis Research.* 2002; 4 (Suppl. 2): 34–40.
14. Lahdenne P., Vahasalo P., Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. *Annals of Rheumatic Disease.* 2003; 62 (3): 245–47.
15. Tynjala P., Kotaniemi K., Lindahl P. et al. Adalimumab in the treatment of juvenile idiopathic arthritis associated uveitis — a pilot study. 8th Annual European League Against Rheumatism. *Barcelona.* 2007. Abstract THU0483.
16. Vazquez Cobian L.B., Flynn T., Lehman T.J. Adalimumab therapy for childhood uveitis. *J. Pediatr.* 2006; 149 (4): 572–75.
17. Heiligenhaus A., Horneff G., Greiner K. et al. Inhibitors of tumour necrosis factor-alpha for the treatment of arthritis and uveitis in childhood. *Klin Monatsbl Augenheilkd.* 2007; 224 (6): 526–31.
18. Foeldvari I., Nielsen S., Kümmerle-Deschner J. et al. Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. *Nat Clin Pract Rheumatol.* 2007; 3 (11): 608–609.
19. Brocq O., Albert C., Roux C. et al. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy experience with 18 patients. *Joint Bone Spine.* 2004; 71: 601–3.