

L.A. Balykova¹, N.V. Ivyanskaya², T.N. Arzamaskina², E.V. Makarkina¹, Y.V. Lavskaya¹

1 Ogaryov Mordovia State University, Saransk, Russian Federation

2 Mordovia republican children's clinical hospital #2, Saransk, Russian Federation

Experience of adalimumab use in a patient with juvenile oligoarthritis and uveitis

Author affiliation:

Larisa Alexandrovna Balykova, PhD, Professor, head of the pediatrics department at the Ogaryov Mordovia State University

Address: 15, R. Luxemburg Str., Saransk, 430032, **tel.:** +7 (927) 276-10-64, **e-mail:** larisabalykova@yandex.ru

Article received: 23.08.2013, accepted for publication: 18.11.2013.

The article presents a case of a severe progressive course of a juvenile arthritis refractory to the standard antirheumatic therapy. Due to oligosymptomatic disease onset and low adherence of the patient to treatment, the disease was characterized by development of polyarticular joint syndrome with destructive changes (aseptic whirlbone necrosis) and formation of uveitis complicated by a cataract and patient's incapacitation. Prescription of adalimumab allowed reducing activity of the inflammatory process, considerably improving function of the affected joints, terminating pain syndrome and stiffness and inducing remission of uveitis.

Keywords: juvenile idiopathic arthritis, uveitis, adalimumab.

One of the relevant issues of modern pediatrics and pediatric rheumatology is juvenile idiopathic arthritis (JIA) – a multifactorial disease with complicated immunoaggressive pathogenesis characterized by progressive course and development of articular destruction and a wide spectrum of extraarticular manifestations. Functional incompetence of joints progresses and incapacitation develops within the first year of disease in half of the patients with symptoms of unfavorable outcome (disease onset at the age of 0-5 years characterized by oligoarthritis and uveitis or polyarthritis, systemic onset, continuous recurrent disease course characterized by development of anatomical alterations, high laboratory rate of activity, rheumatoid factor in blood serum) [1]. Ability of activated T lymphocytes to stimulate synthesis of a wide range of anti-inflammatory mediators, the primary of them being tumor necrosis factor (TNF) α , which supports development of a chronic inflammation and destruction of cartilaginous and bone tissue, plays the fundamental role in inflammation development at JIA [2, 3].

Increase in concentration of TNF- α and soluble TNF- α -receptors in joint cavity and blood serum corresponding with the disease activity is observed in patients with rheumatoid arthritis (RA) and JIA [4, 5]. By activating transcription factor NF- κ B, TNF- α causes proliferation of synovial tissue, migration of immunocompetent cells to the inflammation nidus, synthesis of other anti-inflammatory cytokines and intensification of osteoclastogenesis [6]. It has been proved that TNF α induces expression of adhesion molecules (ICAM) and E-selectin, which facilitate further infiltration of the synovial membrane by immune system's cells [7], and increases generation of metalloproteinases – enzymes taking part in destruction of cartilages and bones [8, 9].

Given the aforementioned, the key role TNF in RA pathogenesis and its significance as a target of antirheumatic therapy is beyond any doubt [10, 11]. That is why TNF inhibitors are the first line drugs for treating severe RA forms refractory to the standard baseline therapy and the most widely used genetically engineered biologic drugs (GEBDs) among children and adults [12-14].

In Russia, the approved drugs of this group for treating JIA are human monoclonal antibodies to TNF- α – adalimumab (from 4 years of age) and soluble receptors to TNF – etanercept (from 2 years of age) [15]. By binding with TNF- α , adalimumab prevents its interaction with the corresponding receptor; thus, it prevents development of the subsequent cytokine-mediated inflammation by reducing generation of interleukins (IL) 1 and 6, suppressing functional activity

of neutrophils and eosinophils, restricting migration of leukocytes, expression of adhesion molecules and tissue degradation by aggressive synoviocytes and chondrocytes [16, 17].

The drug's efficacy for JIA was proved in a trial by the Pediatric Rheumatology International Trials Organization (PRINTO) under the guidance of D.J. Lovell [18]. The trial involved 171 patients with polyarticular JIA who either did not take methotrexate or had a negative response to it. Those who "responded" to the drug after 4 months of open phase involving subcutaneous administration of adalimumab (24 mg/m², up to 40 mg, once per two weeks) were randomized into the 32-week-long placebo-controlled double-blind phase. The percentage of patients with the developed disease exacerbation was significantly higher in the double-blind phase than in the placebo group who continued taking adalimumab (71 to 43% among the methotrexate-naïve patients, $p=0.03$; 65 to 37% among the patients taking methotrexate, $p=0.02$). After 104 weeks of treatment in the extended open phase, a 50% improvement in the ACR_{pedi} criteria was achieved in 86% of 128 patients, a 70% improvement – in 77%, a 100% improvement – in 40% of patients. Similar results were obtained by drug efficacy trials in Russia and Japan [19, 20].

Adalimumab treatment features a similar range of undesirable manifestations as the other TNF inhibitors, although the risk of infectious complications and tuberculosis activation in the setting of adalimumab is lower than at infliximab treatment and in view of the fact that long-term adalimumab treatment in adults and children is characterized by a rather sound safety profile [21, 22]. Experience of adalimumab use (Humira, Abbott Laboratories Ltd., the Netherlands) allows us to conclude that, unlike the first TNF inhibitor – infliximab – and other drugs of this group, it is completely identical to human antibodies and, as a result, features lower immunogenicity; in particular, it is better tolerated and cause transfusion reactions less frequently [23]; it is highly effective both in combination with baseline antirheumatic drugs (methotrexate) and as a monotherapy for RA [24, 25]; it has been invariably efficient for years of use (a long-term randomized clinical trial in a large group of patients demonstrated a 7-year-long preservation of the achieved effect) [26]; it controls not only activity of the joint syndrome at JIA, but also the course of rheumatoid uveitis [27], which is extremely important for pediatric patients in view of an unfavorable prognosis of the latter and has been confirmed at the leading pediatric rheumatologic center of Russia numerous times [28-30].

We would like to set forth our observation of a successful use of Humira in a child with extended juvenile oligoarthritis (according to the ILAR) and uveitis.

Patient M.S., 8 years of age, diagnosed with "HLA-B27-associated juvenile polyarthritis with eye lesion (chronic uveitis: sluggish OD, subactive OS, partial complicated cataract), active phase, activity – II, radiographic stage – III, valvular dysfunction – III" has been observed by a pediatric rheumatologist.

The boy of the second pregnancy taking its course in the setting of risk of miscarriage (in the 1st trimester), mother's nephropathy and chronic intrauterine fetal hypoxia. Born in the second term labor; birth weight – 3,850 g, length – 53 cm, cried immediately when born. Breast-fed until day 21, then – fed with adapted formulas. Early physical and psychomotor development was age-coherent. Had 3 episodes of acute respiratory infection in the first year of life. Vaccinated according to an individual scheme. Non-complicated rheumatic heredity.

The child acquired the disease in April 2007 (at the age of 1 year 8 months), when pain, limp at walk and motion restriction in the left lower limb after sleep appeared 2 weeks after vaccination with a live poliomyelitis vaccine. The boy was examined by an orthopedist due to suspected dysplasia of the left hip joint, who revealed slight tone reduction in the left leg and absence of knee reflex; however, radiogram of hip joints did not reveal any pathology. The boy was forwarded for examination to an infectious diseases hospital, where the possibility of acute flaccid paralysis was ruled out. Stimulation electromyography did not reveal any pathologies, blood and urine analyses did not reveal any inflammatory shifts; virologic examination of the child and exposed persons did not reveal polio- and enteroviruses.

Limp and morning stiffness in the left hip joint intensified in June 2007; the child was hospitalized to the Mordovia republican children's clinical hospital (RCCH). Reduction in the

range of motions in the left hip joint and a lump on the left gluteus were revealed. The performed examination yielded normal values of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF). No pathologies of internal organs. Ultrasonic examination (US) of hip joints did not reveal any pathology. An orbicular lump of average echogenicity with clear even contours (8x5x9 mm) was visualized in the left gluteal area in the junction of subcutaneous fat and the muscle. Computed tomography (CT) of hip joints revealed widening of joint space in the left hip joint, no changes in the bone structure, reduced lateral dimension of the left gluteus maximus muscle and a subcutaneous capsule-free lump (fat tissue). Lipoma of the left gluteus was diagnosed. According to the complex examination, the following diagnosis was established: "Juvenile chronic arthritis of the left hip joint, active phase, activity – I, radiographic stage – 0-I, valvular dysfunction – I". The boy took non-steroidal anti-inflammatory drugs (NSAIDs). It was suggested to hospitalize the boy to the federal clinic in order to specify management tactics.

According to the complex examination at the pediatric diseases clinic of the First Sechenov MSMU, the directional diagnosis was confirmed. It was recommended to take 250 mg of sulfasalazine and 25 mg of diclofenac sodium per day. The boy was being observed locally for 1 year; he occasionally experienced hip joint pains after sleep and limp. The leg shortened by 2 cm within a year. The condition aggravated in June 2008 (pain syndrome intensified), and the child was examined by the out-of-staff head pediatric rheumatologist of the Ministry of Health of the Republic of Mordovia PhD in Medicine T.I. Kornilova. The general blood analysis revealed increase in ESR to 18 mm/h, in CRP – to 75 mg/l (the norm being up to 6). The US of hip joints revealed asymmetry of interarticular spaces. The US of internal organs revealed symptoms of reactive pancreatitis. Doses of sulfasalazine and diclofenac sodium were increased up to 375 mg and 50 mg per day, respectively. The patient was forwarded to the federal clinic in order to find adequate correction of the baseline therapy.

In October 2008, the boy was hospitalized to the pediatric diseases clinic of the First Sechenov MSMU with complaints of limp, pain at walk, motion restriction in the left hip joint, shortening of the left lower limb and morning stiffness. Scoliosis, slight muscular hypotension in the left lower limb, shortening of the left leg by 2 cm, partial atrophy of the gluteus, muscles of thighs and calf were observed at admission. Rotation and external abduction in the left hip joint were considerably restricted, whereas motility of lumbar spine was restricted insignificantly. No enthesopathies were observed. Other joints featured complete range of motion and tendency towards hypermobility.

Clinical and immunoassay of blood revealed no pathologies. Radiography of hip joints revealed osteoporosis of femoral bone on the left, with singular cystoid light areas, deformation of roof of acetabulum and unevenness of the joint space. CT of hip joints revealed symptoms of dysplasia or inflammatory alterations in the left hip joint. No data about aseptic necrosis of the left whirlbone is available. The boy was examined by an ophthalmologist, who revealed bilateral uveitis and keratitis on the right. The boy was examined at the Priorov Central institute of traumatology and orthopedics (CITO), where hospitalization was recommended in order to puncture the hip joint. That is why it was decided not to alter anti-rheumatic therapy before obtaining study results; after that, it was to determine the baseline drug replacement – cyclosporine or methotrexate (in view of the revealed uveitis). The child and his parents present himself to the CITO when expected. The child was not being observed locally either.

In April 2009, the parents consulted the Nasonova Scientific Research Institute of Rheumatology (SRIR) by themselves, where the child was diagnosed with aseptic necrosis of the left whirlbone. He was examined by an orthopedist at Zatsepin children's clinical hospital #19, and stayed there for inpatient treatment numerous times in 2009-2012 with diagnosis "Aseptic necrosis of the left whirlbone". No changes in laboratory parameters were observed during that period. The boy was not examined by a rheumatologist or an ophthalmologist. Drug therapy involved only NSAIDs at request. The child was not being observed locally either.

Due to exacerbation of the disease (development of a swelling and pain in the left ankle and the right elbow joints), in January 2012 the boy was examined by a local pediatric rheumatologist, who revealed a slight motion restriction and pain on movement in the right elbow joint; pronounced opening and rotation malfunction, flexion contracture, pain on movement, the left ankle joint and the left tarsus were moderately edematous and tender on palpation – in the left hip joint. Blood analysis: CRP – 10.1 mg/l (the norm being up to 6), RF – 9.5 IE/ml (the norm being up to 14).

At request of the parents, the child was forwarded for an examination to the FSBI “SRIR”, whereto he was hospitalized in June 2012 (after having received a course of treatment at Zatsepin children’s clinical hospital #19). The examination revealed the major histocompatibility complex antigen B27. Magnetic resonance imaging (MRI) of hip joint revealed deformation of the left whirlbone; radiography of ankle joints revealed pronounced spread increase in bone tissue radiolucency, singular cystoid light areas to the left, mild subchondral osteosclerosis in tarsal bones and narrowing of joint spaces in the left ankle joint. The boy was examined by an ophthalmologist, who revealed OD-uveitis in the stage of remission. The child was diagnosed with oligoarticular HLA B27-associated juvenile chronic arthritis in active phase, activity I-II on the basis of the anamnestic data and the complex examination. NSAID and methotrexate therapy was prescribed. Another hospitalization 3 months later was scheduled in order to evaluate therapy efficacy and decide whether it needed corrections. The patient did not present himself when expected. According to the parents, the child’s condition remained stable throughout a year and the boy was undergoing the recommended therapy.

The child’s condition aggravated in April-May 2013: pain and swelling in the left ankle joint spread towards the foot, pain and motion restriction in the right elbow joint. The child was hospitalized to the RCCH. Pronounced amyotrophy of the left hip and the left shin attracted much attention at the examination. The doctors observed weakness, emotional depression and arthralgiae. The boy could move around only crutching, attend to himself very little and required permanent aid of the mother. Moderate defiguration, pain on movement and palpation in the left ankle joint and the left tarsus, pronounced malfunction, flexion contracture and pain on movement in the left hip joint, swelling and flexion-extension restriction in elbow joints were observed.

Blood analysis revealed ESR acceleration to 16 mm/h, leukocytosis – up to $11.9 \times 10^9/l$. Immunological blood analysis: CRP – 6.4 mg/l (the norm being up to 6), RF – 6.7 (the norm being up to 14); it also revealed antibodies to double-helical DNA and positive antinuclear factor. Radiography of hip joints revealed aseptic necrosis of whirlbone. Ophthalmological examination revealed sluggish OU-uveitis. In view of inefficacy of the baseline therapy and factors of unfavorable prognosis (sluggish uveitis, lesion of hip joint), a council of physicians – Professor E.S. Zholobova, Professor L.A. Balykova, PhD in Medicine T.I. Kornilova – suggested supplementing therapy with GEBDs. Taking into consideration the course of uveitis, the preference was given to adalimumab. The parents were informed about the course of treatment and prognosis of uveitis. The parents expressed their preliminary consent to the therapy. Mantoux test revealed a 17-mm hyperemia, Diaskintest – 5 mm; CT of pectoral organs did not reveal any pathologies. In order to initiate biological therapy, the child was forwarded to the SRIR as agreed.

Being hospitalized at the SRIR, the child was examined by an ophthalmologist (Helmholtz Moscow Research Institute of Eye Diseases) in the course of complex examination in June 2013: rheumatoid OU uveitis (sluggish OD, subactive OS), partial complicated cataract. Tuberculous examination revealed tuberculosis. In view of inefficacy of the baseline methotrexate therapy, sluggish uveitis and possibility to take GEBDs locally, the council of the Institute’s physicians decided to prescribe additional adalimumab (40 mg every 2 weeks subcutaneously) in the setting of preventive anti-tuberculous therapy with isoniazid and pyrazinamide for 3 weeks. The parents expressed their informed consent.

Positive dynamics was registered after 2 injections of the drug: pain and edema in elbow joints reduced, ESR normalized (b. 1). After the 4th injection physicians observed reduction in pain in the hip joint, considerable reduction in edema and pain on palpation in the left tarsal joints; the functional status of tarsal joints improved. After the 6th injection physicians observed absence of pain in the left ankle joint and complete recovery of range of motions in elbow joints and registered a 50% improvement with regard to ACR_{pedi}. Mild increase in range of motions in the left hip joint was observed after the 8th injection. 70% improvement with regard to ACR_{pedi} was observed after the 12th injection. The child has been administered 16 adalimumab injections; no undesirable symptoms have been registered yet.

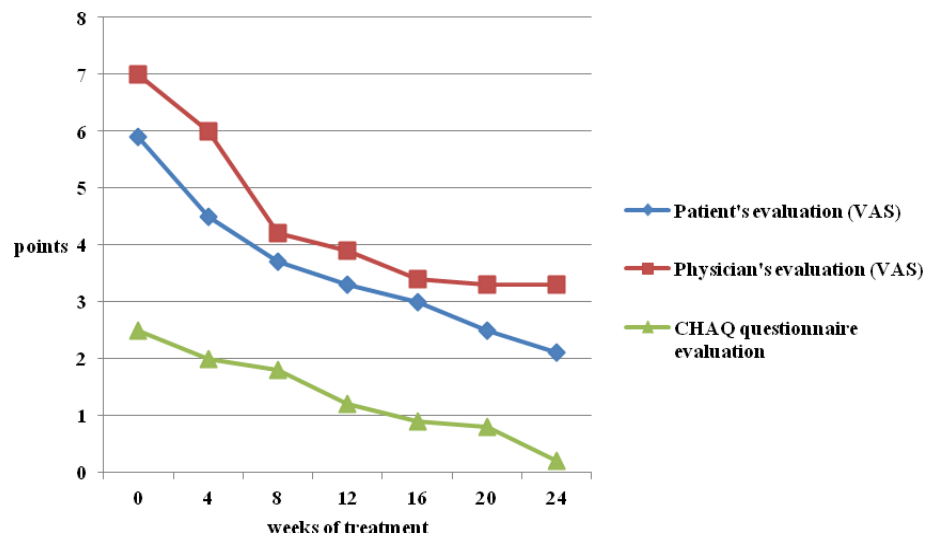
Table 1. Dynamics of clinical and laboratory parameters of patient S.

Parameter	10.2007	08.2008	12.2008	06.2012	05.2013	06.2013	10.2013
Number of joints with active arthritis	1	1	0	2	4	3	1
Number of joints with limited function	1	1	1	3	5	4	1
Laboratory parameters of activity:							
CRP (mg/l)	++++	75	3	10.1	6.1	20.2	3.0
ESR (mm/h)	18-20	14	8	14		33	5
Uveitis	-	-	Exacerbation	Exacerbation	Exacerbation	Exacerbation	Remission
Treatment	25 mg/day of diclofenac sodium	375 mg/day of sulfasalazine; 50 mg/day of diclofenac sodium	375 mg/day of sulfasalazine; 50 mg/day of diclofenac sodium	15 mg/week of methotrexate; 75 mg/day of Voltaren	20 mg/week of methotrexate; 75 mg/day of diclofenac sodium	40 mg per 2 weeks of adalimumab; 15 mg/week of methotrexate	40 mg per 2 weeks of adalimumab; 15 mg/week of methotrexate

Note. CRP – C-reactive protein, ESR – erythrocyte sedimentation rate.

NSAIDs have been completely withdrawn. Physicians observed considerable improvement in the quality of life and emotional tone of the child; the boy attends school and associates with peers (pic. 1). Uveitis remission has been registered. The child has started to feel better, his ability to attend to himself improved; range of motions in elbow joints, the left ankle joint and the left tarsal joints normalized completely, whereas pain syndrome and exudative changes disappeared. A strong tendency towards increase in range of motions in the left hip joint is observed; however, gait disorder (due to 1 cm shortening of the left limb and flexion contracture in the hip joint), body deformity and mild amyotrophy of the left hip and shin muscles (due to the prolonged malfunction of the left hip joint) persist (pic. 2 A-B).

Pic. 1. Physician's evaluation of disease activity dynamics, patient's evaluation of well-being dynamics according to the visual analog scale (VAS) and functional activity dynamics according to the CHAQ questionnaire (in the course of adalimumab treatment).



Pic. 2. The patient's condition after 3 months of adalimumab therapy.



CONCLUSION

The disease of this patient was characterized by oligosymptomatic course in the initial stages with subsequent progressive joint syndrome in the setting of low patient's adherence to treatment and

development of polyarthritis refractory to the baseline anti-rheumatic therapy, complicated by the left hip joint's destruction (aseptic necrosis of the left whirlbone) and pronounced functional incompetence of the patient. Aggressive, unfavorable course of the disease was characterized by development of uveitis complicated with a cataract. Prescription of adalimumab aided to improve joint syndrome (according to the ACR_{pedi} criteria) and achieve remission of uveitis after only 3 months of therapy. This clinical case proves high efficacy of adalimumab in patients with juvenile arthritis complicated with uveitis refractory to the baseline anti-rheumatic therapy.

REFERENCES

1. Alekseeva E. I. *Kachestvo zhizni. Meditsina – Life quality. Medicine*. 2008; 1: 14–17.
2. Choy E. H., Panayi G. S. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med*. 2001; 344: 907–916.
3. Schett G. Review: Immune cells and mediators of inflammatory arthritis. *Autoimmunity*. 2008; 41: 224–229.
4. Barrera P., Th. Boerbooms A. M., Janssen E. M. et al. Circulating soluble tumor necrosis factor receptors, interleukin-2 receptor, tumor necrosis factor α , and interleukin 6 levels in rheumatoid arthritis. *Arthritis Rheum*. 1993; 36: 1070–1079.
5. Kutukculer N., Caglayan S., Aydogdu F. Study of pro-inflammatory (TNF- α , IL-1 α , IL-6) and T-cell-derived (IL-2, IL-4) cytokines in plasma and synovial fluid of patients with juvenile chronic arthritis: correlations with clinical and laboratory parameters. *Clin Rheumatol*. 1998; 17: 288–292.
6. Feldmann M., Maini R. Role of cytokines in rheumatoid arthritis: an education in pathophysiology and therapeutics. *Immunol Rev*. 2008; 223: 7–19.
7. Tak P. P., Taylor P. C., Breedveld F. C. et al. Decrease in cellularity and expression of adhesion molecules by anti-tumor necrosis factor α monoclonal antibody treatment in patients with rheumatoid arthritis. *Arthritis Rheum*. 1996; 39: 1077–1081.
8. Black R. A., Rauch C. T., Kozlosky C. J. et al. A metalloproteinase disintegrin that releases tumor-necrosis factor- α from cells. *Nature*. 1997; 385: 729–33.
9. Barksby H. E., Milner J. M., Patterson A. M., Peake N. J. et al. Matrix metalloproteinase 10 promotion of collagenolysis via procollagenase activation: implications for cartilage degradation in arthritis. *Arthritis Rheum*. 2006; 54: 3244–3253.
10. Bradley J.R. TNF-mediated inflammatory disease. *J Pathol*. 2008; 214: 149–160.
11. Askermann C., Kavanaugh A. Tumor necrosis factor as a therapeutic target of rheumatologic disease. *Expert Opin Ther Targets*. 2007; 11: 1369–1384.
12. Scott D. L., Kingsley G. H. Tumor necrosis factor inhibitors for rheumatoid arthritis. *N Engl J Med*. 2006; 355 (7): 704–12.
13. Furst D. E., Keystone E. C., Braun J. et al. Update consensus statement on biological agents for the treatment of rheumatic disease, 2011. *Ann Rheum Dis*. 2012; 71 (Suppl. II): i2–i45.
14. Kahn P. Juvenile idiopathic arthritis: an update for the clinician. *Bulletin of the NYU Hospital for Joint Diseases*. 2012; 70 (3): 152–66.
15. Baranov A. A., Alekseeva E. I., Bzarova T. M., Valieva S. I., Denisova R. V., Isaeva K. B., Karagulyan N. A., Litvitskii P. F., Mitenko E. V., Sleptsova T. V., Fetisova A. N., Chistyakova E. G., Taibulatov N. I., Morev S. Yu. *Voprosy sovremennoi pediatrii – Current pediatrics*. 2013; 12 (1): 37–56.
16. Sigidin Ya. A., Lukina G. V. *Biologicheskaya terapiya v revmatologii. Izd. 2-e, dop.* [Biological Therapy in Rheumatology. 2nd edit., enl.]. Moscow, Practical medicine, 2009. 302 p.
17. Aikawa N. E., DeCarvalho J. F., Silva C A. et al. Immunogenicity of anti-TNF α agents in autoimmune diseases. *Clinic Rev Allerg Immunol*. 2010; 38 (2–3): 82–89.
18. Lovell D. J., Ruperto N., Goodman S., Reiff A., Jung L. Pediatric rheumatology collaborative study group, pediatric rheumatology international trials organisation: Adalimumab

- with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med.* 2008; 359: 810–820.
19. Alekseeva E. I., Lisitsyn A. O., Karagulyan N. A. *Voprosy sovremennoi pediatrii – Current pediatrics.* 2009; 8 (3): 88–94.
20. Imagawa T., Takei S., Umebayashi H., Yamaguchi K., Itoh Y., Kawai T. et al Efficacy, pharmacokinetics, and safety of adalimumab in pediatric patients with juvenile idiopathic arthritis in Japan. *Clin Rheumatol.* 2012 December; 31 (12): 1713–1721.
21. Dixon W. G., Symmons D. P. M., Lunt M. et al. Serious Infection Following Anti-Tumor Necrosis Factor- α Therapy in Patients With Rheumatoid Arthritis. *Arthritis Rheum.* 2007; 56: 2896–904.
22. Lovell D., Ruperto N., Reiff A., Jung Lawrence K., Higgins G., Kone-Paut I., Jones Olcay Y., McIlraith Melissa J., Andhivarothai N., Kupper H., Giannini Edward H., Peterson T., Martini A. Long-Term Efficacy and Safety of Adalimumab for up to 6 Years in Patients with Juvenile Idiopathic Arthritis. Abstract presented at: 75th Annual scientific meeting of the American College of Rheumatology (ACR); 11/5/2011. *Chicago, IL; USA.* 2011. Abstract MIS (7190791).
23. Furst D. E., Schiff M. H., Fleischmann R. M., Strand V., Birbara C. A., Compagnone D. et al. Adalimumab, a fully human anti tumor necrosis factor α monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol.* 2003; 30: 2563–2571.
24. Breedveld F. C., Weisman M. H., Kavanaugh A. F. et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate. *Arthrit Rheum.* 2006; 54: 26–37.
25. Van dePutte L. B., Atkins C., Malaise M., Sany J., Russell A. S., van Riel P. L. et al. Efficacy and safety of Adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis.* 2004; 63: 508–516.
26. Weinblatt M. E., Keystone E. C., Furst D. E. et al. Long term safety, efficacy and remission with adalimumab (Humira) and methotrexate combination therapy in rheumatoid arthritis (RA) 7-year analysis. Abstr. 9th Annual EULAR. 2008 meeting, Paris, AB0343.
27. Simonini G., Taddio A., Cattani M. et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. *Arthr Care Res.* 2011; 63 (4): 612–618.
28. Alekseeva E.I., Mitenko E.V., Valieva S.I., Bzarova T.M., Denisova R.V., Isaeva K.B., Sleptsova T.V., Chomakhidze A.M. *Voprosy sovremennoi pediatrii – Current pediatrics.* 2012; 11: 82–90.
29. Galstyan L. A., Zholobova E. S., Rozvadovskaya O. S., Bunin A. V., Starikova A. V. *Voprosy sovremennoi pediatrii – Current pediatrics.* 2012; 11 (6): 142–146.
30. Malievskii V. A., Nizhevich A. A., Pervushina E. P., Sapronova L. Yu. *Voprosy sovremennoi pediatrii – Current pediatrics.* 2013; 12 (4): 181–184.