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Experience of application of monoclonal antibodies to TNF α – adalimumab – in a child with juvenile idiopathic arthritis

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The article offers successful application of a preparation of human monoclonal antibodies to tumor necrosis factor (TNF) α – adalimumab – in the setting of a severe course of juvenile idiopathic arthritis characterized by inefficiency of the standard antirheumatic therapy and secondary resistance to chimeric antibodies to TNF α. Adalimumab treatment secured overcoming of the secondary infliximab inefficiency, rapid disease activity decrease, peripheral joints' function recovery and the patient's functional activity increase in a short space of time. The drug averted the patient's steadily progressing incapacitation and induced the clinical-laboratory disease remission development.

Keywords: *children, juvenile idiopathic arthritis, adalimumab, treatment.*

Juvenile idiopathic arthritis is a severe incapacitating disease characterized by destructive joint affection.

Use of methotrexate (15mg/m^2 of body surface) secures control over the disease in many patients with juvenile idiopathic arthritis [1]. However, the standard antirheumatic therapy does not attain stable remission in some patients [2-5]. In case of refractoriness to methotrexate, genetically engineered biologic drugs are used in rheumatologic practice [6], though in some cases they are ineffective. Development of the secondary resistance to the drug is possible after it has attained the good first effect. This happens especially often when chimeric monoclonal antibodies to tumor necrosis factor (TNF) α – infliximab – are used. According to A.E. van der Bijl et al., the secondary inefficiency of chimeric monoclonal antibodies develops in 50% of adult patients with rheumatoid arthritis [7]. Insufficient methotrexate efficiency and primary and secondary resistance to biologic drugs result in the disease progression. That is why the decision

to shift to a different genetically engineered biologic drug (GEBP), including the second TNF α inhibitor, in particular, adalimumab, is urgent [8, 9].

Adalimumab consists of recombinant human monoclonal antibodies IgG1 consisting of 1,330 amino acids. The drug is obtained on the basis of the recombinant DNA technology. It gets bound with p55 and p75 receptors of the soluble and membrane-associated TNF α. Adalimumab can activate the complement system; this results in lysis of cells with surface TNF α. The drug cannot get bound with or inhibit lymphotoxin (TNF β); it affects the level of adhesion molecules, which may take part in the migration of leukocytes (ELAM-1, VSAM-1 and ICAM-1). Adalimumab is administered subcutaneously once per 2 weeks; the drug's half-life is 2 weeks [10-13].

Results of controlled clinical trials and non-blind trials show that subcutaneous adalimumab administration is efficient and safe both at rheumatoid or psoriatic arthritis in adult patients and at juvenile idiopathic arthritis in children [14-25], which is why the shift to adalimumab may be prospective in case of primary or secondary inefficiency of the other GEBPs. This situation is clearly presented in the following clinical case.

Patient P., 6 years of age, has been observed at the rheumatology department of the Scientific Center of Children's Health since August 2009. The girl is of the first pregnancy (physiological course). Term, spontaneous delivery. Birth weight – 2,700g, body length – 49cm. Non-peculiar neonatality. Age-adequate early physical and psychomotor development. The vaccination had been conducted according to the National vaccination calendar until the age of 1.5 years. Medical history: acute respiratory infections 1-2 times a year; no infantile infections. Non-complicated inheritance in terms of rheumatic diseases.

The girl contracted the disease in April 2009 (at the age of 1 year 8 months). Left knee joint arthritis developed after an acute respiratory infection. Edema, hyperemia, joint area hyperthermia and intense tenderness were noted – the child did not lean on the leg. Right ankle joint affection developed within several days. Clinical blood analysis revealed the erythrocyte sedimentation rate (ESR) increase up to 35mm/h. The girl was hospitalized to the children's unit of the district hospital with diagnosis "Juvenile oligoarthritis", where she ineffectively received anti-inflammatory and antibacterial drugs. That is why in June 2009 the child was hospitalized to the Moscow children's municipal clinical hospital #9. Complaints of pain in the knee and right ankle joints, morning stiffness for up to 3 hours, exudative alterations in the knee and right ankle joints, intense tenderness and motion restriction of the aforementioned joints were observed at admission to the inpatient hospital. The clinical blood analysis revealed ESR increase up to 62mm/h; immunological blood analysis – strong positive C-reactive protein (++++). Infectious and oncohematological process course were ruled out by the conducted examination of the

patient. Diagnosis established: “Oligoarticular juvenile rheumatoid arthritis”. Prescribed treatment: nonsteroid anti-inflammatory drugs (NSAIDs) and hydroxychloroquine; glucocorticoids were locally administered to knee joints. Morning stiffness, low-grade fever and acute inflammatory alterations in knee and ankle joints persisted in the setting of the therapy, edema developed in the interphalangeal joint of the right foot’s second finger; the girl could not stand up on her feet; high level of laboratory parameters of disease activity remained. Hydroxychloroquine was replaced with methotrexate (5mg/m^2 of body surface); the girl received the second administration of glucocorticoids into the knee joints with brief positive effect. The girl was transferred to the rheumatology department of the RAMS SCCH in order to determine the following management tactics in August 2009 (4 months after the disease onset). The child’s condition at admission to the rheumatology department was estimated as severe. Exudative alterations in the knee and right ankle joints and in the interphalangeal joint of the right foot’s second finger were observed; motion of these joints was restricted and acutely painful; the girl could not stand up on her feet due to intense pain; the morning stiffness duration was 4 hours, intoxication symptoms were observed (skin pallor, dark shadows beneath the eyes); the patient was emotionally depressed. The clinical blood analysis recorded ESR increase up to 35mm/h. X-ray imaging of the affected joints revealed singular bone stick erosions. The diagnosis “Juvenile idiopathic arthritis” did not give rise to doubt due to the clinical presentation and data of the laboratory instrumental trials. It was decided to increase the methotrexate dose to 15mg/m^2 of body surface per week in order to reduce the disease activity and prevent the progression of destructive joint alterations. The girl had been receiving methotrexate in the aforementioned dosage for 3 months; however, no positive dynamics was recorded in the setting of therapy. Given aggressive and steadily progressing disease course and inefficiency of standard dosage methotrexate in the period of 3 months, the patient started receiving therapy with chimeric monoclonal antibodies to TNF α – infliximab in October 2009. The drug’s prescription was approved by the Academic Senate, local Ethic and Formulary Committees of the Scientific Center of Children’s Health. The child’s parents completed the informed consent to the use of infliximab. The patient had received Mantoux test and computed tomography of chest organs before the infliximab therapy in order to prevent tuberculosis. Computed tomography did not reveal nidal and infiltrative pulmonary alterations; Mantoux test was negative. Infliximab therapy began after the specific process was ruled out; methotrexate therapy remained in place in the same dosage (15mg/m^2 of body surface per week).

The girl’s condition improved in the setting of infliximab treatment: swelling of the affected joints decreased considerably after the very first drug’s infusion, motion volume in them increased, pain syndrome and morning stiffness duration reduced. Laboratory parameters of the

disease activity reduced by the 6th therapy week and normalized by the 10th week. Inflammatory alterations of the knee joints disappeared completely by the 6th week; however, flexion restriction and pain at extreme movements persisted. The motion volume in the affected joints recovered completely by the 10th infliximab therapy week (tb. 1).

Table 1. Dynamics of clinical and laboratory parameters of the disease activity in the setting of infliximab therapy in patient P.

Parameter	**October 2009**	**December 2009**	**January 2010**	**May 2011**
	Prior to infliximab prescription	**6 weeks into infliximab therapy**	**10 weeks into infliximab therapy**	**78 weeks into infliximab therapy**
Morning stiffness duration, minutes	240	20	0	60
Number of joints with active arthritis	4	2	0	3
Number of joints with restricted function	4	2	0	3
Overall doctoral assessment of the disease activity (VAS), points	8	5	0	5
Functional capacity value (CHAQ questionnaire), points	2.2	1.25	0	1.75
Erythrocytes, $x10^{12}$/l	4.79	4.94	4.96	4.23
Hemoglobin, g/l	115	121	132	110
Leukocytes, $x10^{9}$/l	9.08	9.94	8.23	8.56
Platelets, $x10^{9}$/l	439	355	349	390
ESR, mm/h	50	18	2	31
CRP, mg/l (norm - <5mg/l)	66	0.78	1	19

Note. VAS – visual analog scale; CHAQ – Childhood Health Assessment Questionnaire, children's life quality assessment questionnaire, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein.

Patient P. received 11 infliximab administrations without unfavorable phenomena. In June 2011, acute inflammatory alterations appeared in the knee joints after the injury. The girl's condition improved after the 12th infliximab administration; however, edema, pain, motion restriction in the knee joints, low-grade fever and 3-hour-long morning stiffness returned 3 weeks after the drug's infusion; laboratory parameters of the disease activity increased (see tb. 1). Everything indicated the development of secondary resistance to chimeric monoclonal antibodies to TNF α and served as a basis for infliximab withdrawal.

In August 2011 the girl was again hospitalized to the rheumatology department of the RAMS SCCH. The girl's condition was evaluated as severe. The child was emaciated, with pronounced body weight deficiency and femoral and tibial amyotrophy. Protracted morning stiffness (5 hours), daily body temperature rises to low-grade fever, weakness and arthralgiae were observed. The patient suffered from intense joint pains, the girl could not get out of bed, walk and serve herself and required constant mother's help. Joint syndrome was of the oligoarticular character with the affection of the knee and right ankle joints and the interphalangeal joint of the right foot's second finger, where exudative-proliferative alterations with sharp restriction of their functions were observed. Flexion contractures formed in the knee joints. Examination blood analysis: ESR increased up to 62mm/h, CRP – up to 166mg/l (tb. 2). Radiography of joints revealed destructive alterations corresponding to the second radiologic disease stage.

Table 2. Dynamics of clinical and laboratory parameters of the disease activity in the setting of adalimumab therapy in patient P.

Parameter	**August 2011**	**September 2011**	**November 2011**	**July 2013**
	Prior to adalimumab prescription	**2 weeks into adalimumab therapy**	**10 weeks into adalimumab therapy**	**2 years into adalimumab therapy**
Morning stiffness duration, minutes	300	60	5	0
Number of joints with active arthritis	4	4	0	0
Number of joints with restricted function	4	3	2	0

Overall doctoral assessment of the disease activity (VAS), points	9	5	2	0
Functional capacity value (CHAQ questionnaire), points	2.5	1.75	0.75	0
Erythrocytes, $x10^{12}$/l	4.06	4.43	4.55	4.67
Hemoglobin, g/l	103	110	114	130
Leukocytes, $x10^{9}$/l	8.16	8.48	8.64	7.87
Platelets, $x10^{9}$/l	529	394	366	285
ESR, mm/h	62	51	15	2
CRP, mg/l (norm - <5mg/l)	166	105	9	0.1

Note. VAS – visual analog scale; CHAQ – Childhood Health Assessment Questionnaire, children's life quality assessment questionnaire, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein.

Analysis of the anamnesis morbi of patient P. indicated the inefficiency of antirheumatic therapy, which included glucocorticoids for intra-articular introduction, NSAIDs and methotrexate and the development of secondary resistance to TNF α blocker – infliximab. At the same time, the child's severe condition required active therapeutic tactics. Secondary inefficiency to chimeric monoclonal antibodies to TNF α develops in connection with the appearance of neutralizing antibodies to the molecule's mouse fragment [8]. Given the patient's initial response to TNF α inhibitor and previous experience of shifting from one TNF α blocker to a different one [9], it was decided to prescribe the second TNF α inhibitor – adalimumab (drug name "Humira"), neutralizing antibodies to which are synthesized to a far lesser extent, as it is a completely human antibody [25].

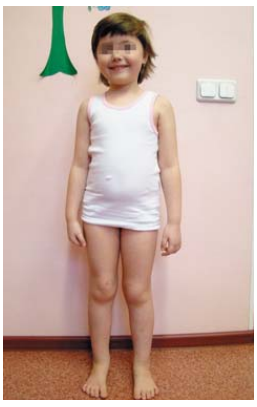
Adalimumab is a genetically engineered monoclonal antibody to the key anti-inflammatory cytokine of rheumatic diseases – TNF α; it consists entirely of a human protein. The drug blocks not only a circulating, but also an already connected with cellular receptors TNF α. By 2011, adalimumab had been registered in the USA and European countries as a drug for treating juvenile rheumatoid arthritis (in patients over 4 years of age), in the Russian Federation – in children over 13 years of age; since March 2012 it has been recommended for children over 4 years of age.

Patient P. was prescribed adalimumab in standard dosage – 40mg once in 2 weeks subcutaneously. The drug's prescription was approved by the Academic Senate, local Ethic and Formulary Committees of the Scientific Center of Children's Health. The SCCH Academic Senate authorized the use of adalimumab in children with juvenile arthritis in the SCCH rheumatology department. The child's parents signed the informed consent to the drug's use. The child received another computed tomography of chest organs and Mantoux test before the adalimumab prescription in order to prevent tuberculosis. No specific process data were obtained.

Analysis of the adalimumab therapeutic effect development rate showed that the girl became more active after the very first drug's injection, the fever terminated; morning stiffness and arthralgiae disappeared after 10 weeks of treatment (see tb. 2); exudative alterations considerably improved in the affected joints, the motion volume in them increased by the 10th week (pic. 1-3); laboratory parameters of the disease activity normalized and the inactive disease condition was registered after 10 weeks. Adalimumab treatment also had a positive effect on the patient's functional activity, improved her physical and emotional condition. The girl's functional status evaluation in the setting of adalimumab treatment came near the status of the almost healthy peers (see tb. 2).

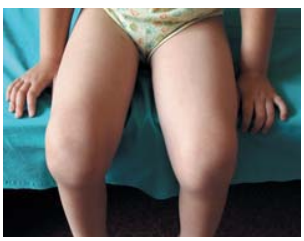
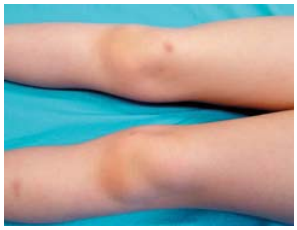
Pic. 1.

A – patient's general appearance prior to the adalimumab therapy; B – patient's general appearance in the setting of adalimumab therapy

A  B 

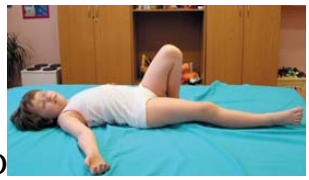
Pic. 2.

A – inflammatory alterations in the knee joints prior to the adalimumab therapy; B – inflammatory alterations in the knee joints in the setting of adalimumab therapy

A  B 

Pic. 3.

A – functional capacity of the knee joints prior to the adalimumab therapy; B-D – functional capacity of the knee joints in the setting of adalimumab therapy

A  B  C  D 

The girl proceeds with adalimumab treatment in the dosage of 40mg once in 2 weeks in combination with methotrexate in the dosage of 15mg/m^2 of body surface per week at the local polyclinic. The therapy has now been being in place for 2 years. No unfavorable phenomena of adalimumab therapy have been registered. NSAIDs have been completely withdrawn from the child's therapy. Clinical laboratory disease remission developed in the girl in the setting of adalimumab treatment; according to the radiography of the knee joints, destructive alterations are not progressing.

Conclusion

Analysis of the presented clinical case demonstrates severe and quickly progressing course of juvenile idiopathic arthritis characterized by the affection of joints, quick incapacitation of a child and development of secondary resistance to chimeric monoclonal antibodies to TNF α. Adalimumab therapy allowed overcoming resistance to chimeric antibodies and secured complete functional recovery of all the affected joints, normalization of laboratory parameters of the disease activity, disease remission and functional activity remission. It must be mentioned that there have been no unfavorable phenomena in response to the drug's administration. The obtained results indicate that the drug's choice was correct and prove high adalimumab efficacy for treating juvenile idiopathic arthritis that is torpid to the traditional antirheumatic therapy and resistant to chimeric antibodies to TNF α yet again.

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