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Results of an open label clinical phase IV study of efficacy and safety of abatacept in children and adolescents with polyarticular juvenile idiopathic arthritis without systemic manifestations in Russia

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The study was aimed at *appraising efficacy and safety of abatacept in children and adolescents with polyarticular juvenile idiopathic arthritis without systemic manifestations.* ***Patients and methods:*** *the study involved 15 patients of 13 (11-14.5) years of age; the average duration of the disease was 4 (3-5) years. Diagnosis was established on the basis of ILAR criteria. All the patients underwent standard clinical laboratory examination. Therapeutic efficacy was evaluated on the basis of pediatric criteria of the American College of Rheumatology (ACR_{pedi}). Target therapeutic efficacy parameters were as follows: determination of the number of patients with 30/50/70/90% ACR_{pedi} improvement in the first 4 months of the therapy and every 2 months after that; rate of attainment of inactive disease stage or remission of the disease.* ***Results:*** *after 4 months, 30/50% ACR_{pedi} improvement was attained in 60/30%; after 6 months, 30/50/70% ACR_{pedi} improvement was attained in 80/40/40%, respectively; after 12 months, 70% ACR_{pedi} improvement was attained in 80% of the patients. Inactive disease stage was registered in 6/15 (30%) and 10/15 (60%) of the patients after 6 and 12 months, respectively; remission – in 10/15 (60%) of the children after 12 months of treatment. Adverse events (only mild) were observed in 6/15 (40%) of the patients. Exacerbation of Herpes labialis infection was registered in 3 patients; acute respiratory infection – in 3 children.* ***Conclusions:*** *abatacept is efficient in patients with the polyarticular juvenile idiopathic arthritis refractory to treatment with glucocorticoids, methotrexate and combined immunosuppressive therapy.*
Keywords: *children, polyarticular juvenile idiopathic arthritis, abatacept, treatment.*

Introduction

Term "juvenile idiopathic arthritis" (JIA) describes a clinically heterogenic group of arthrites with onset before 16 years of age duration of more than 6 weeks [1]. This is the most widespread chronic rheumatic condition in children, which results in considerable decrease in the quality of life thereof [1-3]. JIA is an immunoaggressive disease, an important role in the development whereof is played by both genetic and external factors [1, 2, 4].
JIA treatment involves anti-inflammatory agents and immunosuppressants [5]. However, remission of the disease is not achieved in 50% of cases [6]. Resistance to therapy results in destructive alterations of joints, growth inhibition and incapacitation of the patients [5]. Prognosis of this severe incapacitating disease has considerably improved after genetically engineered biopharmaceuticals were introduced into rheumatologic practice [6-9]. Biological therapy is a set of therapeutic measures aimed at realizing the pathogenetic principle of treating

diseases with the help of the drugs blocking, replacing or imitating effects of endogenous biologically active substances. Genetically engineered biological agents render a maximally selective effect on the immune system, help to dispose of the indispensable link of the pathogenetic disease chain and only minimally affect physiological mechanisms [5, 6]. Biological agents are targeted at cytokines and receptors thereof, damage mediators, CD-molecules, co-stimulatory and co-inhibitory molecules. Protocols concerning differentiated prescription of genetically engineered biopharmaceuticals according to the JIA subtype have been developed [9, 10].

It is widely known that T lymphocytes play the crucial role in pathogenesis of rheumatoid arthritis [11, 12]. Activated T lymphocytes and other cells of the immune system generate anti-inflammatory cytokines and other biologically active substances. The balance of pro- and anti-inflammatory cytokines becomes unstable; synovial membrane becomes inflamed and joints degenerate [11]. That is why suppression of pathological activation of T lymphocytes is one of the important spheres of treatment of rheumatoid and JIA. 2 signals of an antigen-presenting cell are required in order to fully activate T lymphocytes. One of them is realized in the process of interaction of T-cellular receptors with molecules of the primary histocompatibility complex expressed on the membrane of antigen-presenting cells, whereas the second signal is realized in the process of interaction of co-stimulatory receptors on T lymphocytes with the corresponding ligands on antigen-presenting cells [11-13]. There are several mechanisms of co-stimulation. The best studied signal is provided by the interaction of molecule CD28 of T lymphocytes with molecule CD80/CD86 on antigen-presenting cells. Activated T lymphocytes express cytotoxic T lymphocyte-associated antigen 4 (CTLA4). CTLA4 binds with molecule CD80/CD86 with higher avidity; it is an endogenous inhibitor of co-stimulation of T lymphocytes [14].

Study of the mechanism restricting uncontrollable activation of T cells in the process of immune response capacitated development of such a drug as abatacept (Orencia by Bristol Myers Squibb). Abatacept is a fully human recombinant soluble protein consisting of extracellular human CTLA4 domain and the modified IgG_1 Fc-fragment. It is important to mention that the modified Fc-fragment binds with molecule CD64 very weakly and does not bind with molecules CD16 and CD32; this impedes development of antibody-dependent and complement-dependent cellular cytotoxicity resulting in cytolysis [15]. Like native CTLA4, this protein binds with molecule CD80/CD86 with higher avidity than with CD28 and blocks activation of T lymphocytes [15]. By suppressing activation and proliferation of T lymphocytes, abatacept reduces secretion of anti-inflammatory cytokines and autoantibodies without degenerating T and other types of lymphocytes. Preclinical studies demonstrated that abatacept is effective for treating collagen arthritis in rats [14].

Efficacy and safety of abatacept were studied in randomized double blind placebo-controlled studies of patients over 18 years of age with the active rheumatoid arthritis refractory to one of the immunosuppressants and/or tumor necrosis factor (TNF) α inhibitor [15-33]. Randomized double blind placebo-controlled study of efficacy and safety of abatacept involving 190 6-17-year-old children with different JIA forms (oligo-, polyarthritis [RF- and RF+], systemic form without systemic manifestations) is of particular interest [34]. Results of this and other studies demonstrated sufficient level of efficacy and high safety profile of abatacept for JIA; this allowed registering the drug for treating juvenile idiopathic arthritis in children over 6 years of age [34, 35].

The aforementioned served as the basis for this open label clinical phase IV study.

The study was aimed at appraising efficacy and safety of abatacept in children and adolescents with polyarticular juvenile idiopathic arthritis without systemic manifestations.

Patients and methods

STUDY SUBJECTS

The open prospective observational study involved patients with polyarticular JIA treated with abatacept from August 2010 to March 2012. Use of abatacept was approved by the Local Ethics Committee of the RAMS Scientific Center of Children's Health in all cases. Before the treatment parents of the children and children over 14 years of age would have to give written informed consent to participation in the "open label clinical phase IV study of efficacy and safety of abatacept in children and adolescents with polyarticular juvenile idiopathic arthritis (JIA) without systemic manifestations in Russia".

Clinical demographic description

15 patients (14 girls and 1 boy of 13 (11-14.5) years of age were observed (tb. 1). The average disease duration before prescription of abatacept was 4 (3-5) years.

Inclusion criteria

Established diagnosis "Juvenile idiopathic arthritis" (on the basis of ILAR criteria) [1], which is positive or negative in terms of the rheumatoid factor (RF+ or RF-); 6-17-year-old boys and girls (inclusively); anamnesis – at least 5 joints with active arthritis or at least 2 joints with active arthritis and 2 joints with motion restriction at the moment of inclusion in the study; previous inadequate response or intolerance to at least one baseline anti-inflammatory drug, except for biopharmaceuticals; informed consents of parents and patients over 14 years of age.

Exclusion criteria

Systemic JIA or occurrence of such systemic manifestations of the disease within 6 months prior to inclusion in the study as intermittent fever, rash, hepato- and/or splenomegaly, pleurisy, pericarditis, macrophage activation syndrome; active uveitis; infectious disease at the moment of inclusion in the study or frequent acute or chronic infections within 3 months prior to inclusion in the study; active tuberculosis requiring therapy within 3 previous years; increase in serum concentration of urea, creatinine, bilirubin, hepatic transaminases; leuko-, neutro-, thrombocytopenia; patients taking genetically engineered biopharmaceuticals (infliximab, adalimumab, rituximab, etanercept or tocilizumab).

STUDY METHODS

All the patients underwent the standard clinical laboratory examination. Hemoglobin concentration, count of erythrocytes, platelets and leukocytes, leukocyte differential, erythrocyte sedimentation rate (ESR), concentration of urea, creatinine, uric acid, bilirubin, transaminase activity in blood serum and clinical blood analysis were controlled once per 2 weeks. All the patients underwent diagnosis for tuberculosis, including Mantoux test with 2 TE, Diaskintest and computed tomography of lungs. Patients with positive tuberculin test were not included in the study, unless they started latent tuberculosis therapy 4 or more weeks prior to the study and had no radiographic signs of tuberculous infection.

The number of tumescent and painful joints, dysfunctioning joints, serum concentration of C-reactive protein (CRP) and ESR were determined monthly.

Therapeutic efficacy was determined on the basis of the pediatric criteria of the American College of Rheumatology (ACR_{pedi} 30, 50 and 70) including the following parameters: number

of joints with signs of active inflammation (with exudation and/or pain and dysfunction), number of dysfunctioning joints, ESR, serum CRP concentration, doctor global assessment of disease activity (with the help of a 100 mm visual analog scale; VAS), assessment of general well-being by the patient or his/her parent (with the help of the VAS); global health assessment with the help of the parental version of the special Childhood Health Assessment Questionnaire (CHAQ). Minimal value of the health condition index (CHAQ) is 0, maximal – 3. CHAQ index < 1.5 corresponded to minimal and moderate disorders, CHAQ > 1.5 – to marked disorders.
50% improvement is an at least 50% improvement of at least 3 out of the 6 aforementioned parameters in comparison with the initial values at a 30% deterioration of not more than 1 parameter out of 6. We also determined 70 and 90% improvement on the basis of the mentioned criteria. The effect was considered excellent in the event of 70 or 90% improvement, good – in the event of 50% improvement, satisfactory – in the event of 30% improvement.
The primary outcome measure of the study was determination of the number of patients with 30% improvement (according to the ACR_{pedi}) within 6 months of the therapy. Secondary outcome measures of the study consisted in determination of the amount of patients with 30, 50, 70 and 90% improvement (according to the ACR_{pedi}) within 4 months of the therapy and every 2 months after that (6, 8, 10 and 12 months after the beginning of the therapy). We also determined the number of patients with the registered 50 and 70% improvement (according to the ACR_{pedi}). Appraisal of the amount of children attaining the inactive disease stage and medically induced remission of the disease after 6 and 12 months of the therapy served as an additional outcome measure of the study.
We registered the inactive disease stage on the basis of the following criteria: no joints with active arthritis; normal ESR and CRP values; no disease activity according to the doctor (VAS); morning stiffness duration shorter than 15 minutes. Medically induced remission (according to the criteria by C. Wallace) was registered if the inactive disease stage remained for 6 consecutive months of observation [36].
The study was aimed at appraisal of safety and tolerance of the drug throughout 12 months of the therapy, detection of adverse events and acute infusion reactions, development of tumor diseases and considerable deviations of vital activity and laboratory parameters of the body.
By the therapy beginning, 12 (80%) children had polyarticular articular syndrome, 3 (20%) – oligoarticular (tb. 2). The number of joints with active arthritis was 10 (8-12), the number of dysfunctioning joints – 10 (8-11). Clinical activity of the disease was accompanied by the generalized inflammatory reaction. Median of the ESR exceeded the normal values 2 times, of the serum CRP concentration – 3 times (see tb. 2).
Thus, at the moment of abatacept treatment beginning, all patients with JIA featured active articular syndrome and high laboratory parameters of disease activity.

Previous therapy

Before the abatacept treatment, all the patients underwent anti-rheumatic therapy (in different modes) (tb. 3).
All the children took non-steroidal anti-inflammatory drugs (NSAIDs). Due to high disease activity, 2 patients underwent methylprednisolone (12.5 mg/kg of body weight per administration) pulse therapy at a local territorial medical establishment, 11 – intraarticular administration of glucocorticoids (1-10 times per year).
Before the abatacept prescription, all the patients were treated with methotrexate in the dose of 18 (15-22) mg/m^2 of body surface; 1 child took a combination of methotrexate and cyclosporine, 2 – of methotrexate and leflunomide; 2 – of methotrexate and sulfasalazine.

Abatacept administration pattern

Abatacept was administered intravenously in weeks 0, 2, 4 and every 4 weeks after week 4 for 12 months in the dose of 10 mg/kg of body weight per infusion. Infusions were conducted for 1 hour at a rate of 10 ml/h in the first 15 minutes and 130 ml/h after that.

Background therapy

Abatacept infusions were conducted in the setting of methotrexate intake in the dose of 18 (15-22) mg/m2 of body surface per week (tb. 3).

STATISTICAL DATA MANIPULATION

Statistical analysis of the data was performed with the help of program STATISTICA 6.0 (StatSoft Inc., USA). Quantitative parameters are represented as a median (25^{th} and 75^{th} percentiles). Alterations of quantitative parameters throughout the treatment were appraised with the Wilcoxon signed-rank test. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

Articular syndrome dynamics.

Analysis of articular syndrome activity dynamics parameters demonstrated that the number of joints with active arthritis was gradually decreasing throughout the abatacept therapy period. The number of joints with active arthritis statistically significantly decreased by the 4^{th} month of treatment: 10 (8-12) and 7 (5-8) before and after 4 months of treatment, respectively ($p < 0.01$). The number of joints with active arthritis had been 3 (2-4) ($p < 0.001$; pic. 1) by the 12^{th} month of treatment.

The same tendency was observed in terms of dysfunctioning joints, the number of which statistically significantly decreased after 6 months of treatment (pic. 2). Median of the number of dysfunctioning joints had decreased 5 times ($p < 0.001$; pic. 4 (3)) by the 12^{th} month of observation.

Along with reduction in the number of joints with active arthritis and dysfunctioning joints, we observed a considerable improvement of functional capacity of the affected joints of our patients (pic. 3 (4)).

Before the study, the functional insufficiency index (according to the parental CHAQ version) was 1.1 (1.0-1.1) points – moderate restriction of everyday activity of the patients.

The CHAQ index significantly decreased after 4 months of the abatacept treatment – 1.1 (1.0-1.1) and 0.7 (0.5-0.9) before and after 4 weeks of treatment, respectively ($p < 0.001$). 6 months later, the functional insufficiency index was 0.5 (0.5-0.7) points – no restrictions of everyday life. The CHAQ index had decreased down to 0.4 (0.3-0.5) points by the 12^{th} month of therapy (see pic. 3).

Dynamics of laboratory activity parameters.

Abatacept therapy also affected laboratory disease activity parameters. A statistically significant decrease in the ESR and the serum CRP concentration was observed in the setting of treatment (pic. 4(3), 5).

The ESR median was 28 (20-35) mm/h before treatment. The ESR steadily decreased throughout the period of observation and normalized by the 6^{th} month of therapy – 12 (7-15) mm/h (see pic. 4).

We also observed decrease and further normalization of the serum CRP concentration. This parameter exceeded the norm 3 times before treatment. 4 months later, the serum CRP

concentration statistically significantly decreased (16 and 8 g/l before and after treatment, respectively; $p < 0.001$). By the 10th month of therapy the CRP remained within the normal range in 11 (73%) patients (see pic. 5).
RF and antibodies to cyclic citrullinated peptide were observed in blood serum of 7 children before the therapy. 6 months later this parameter decreased twice (down to 40 IU/ml), 12 months later – 20 IU/ml (pic. 6). 6 out of the 7 patients became blood serum RF-negative.
Blood serum concentration of cyclic citrullinated peptide antibodies was 24 (12-64) IU/ml before treatment (exceeded the norm 3 times). It decreased to near-normal values (down to 7.5 [4-24] IU/ml) after 6 months of treatment (pic. 7). 5 out of the 7 patients became negative in terms of the blood serum concentration of cyclic citrullinated peptide antibodies by the 12th month of observation.

ACR_{pedi} improvement.

After 2 months of treatment, 30/50% improvement (according to the ACR_{pedi} criteria) was attained in 50 and 20% of the patients, respectively; after 4 months – in 60 and 30%, respectively. After 6 months of treatment, 30/50/70% improvement (according to the ACR_{pedi} criteria) was attained in 80, 40 and 40%, respectively; the inactive disease stage – in 4/15 (30%) of the children. 1 year later, 70% improvement (according to the ACR_{pedi} criteria) was observed in 70% of the patients; inactive disease stage and remission were registered in 10/15 (60%) of the patients (pic. 8).

Adverse events.

Abatacept treatment safety was appraised on the basis of the registered adverse events, laboratory parameters and physical examination results (arterial pressure, heart rate).
Adverse events were appraised in all the patients involved in the study.
Abatacept treatment was tolerated well; all the adverse events were mild, reversible and did not restrict the course of treatment. Infusion reactions (occurring during drug administration and within 24 hours thereafter) were not observed. We did not register any adverse events associated with alterations of laboratory parameters in the process of observation as well.
Infectious adverse events were observed in 6/15 (40%) of the patients. *Herpes labialis* infection and acute respiratory infection were registered in 3 and 3 children, respectively (tb. 4).
We did not reveal any cases of malignant transformation or register any fatal outcomes in the setting of the abatacept therapy.

Discussion.

Persistence of active arthritis at polyarticular JIA is a complicated therapeutic problem. Traditional immunosuppressants and TNF α inhibitors are not always efficient at this form of the disease [2-8]. Long-term use of glucocorticoids results in the development of severe adverse events and does not prevent development of destructive alterations of joints [37].
Results of several international randomized placebo-controlled studies in the setting of rheumatoid arthritis in adults and of one randomized placebo-controlled study in children demonstrated high efficacy of abatacept for treating this disease both in adults and children. Moreover, high safety profile of the drug was registered [20, 23, 25, 28, 31, 34].
Our study involved 15 patients with polyarticular JIA taking abatacept. We observed patients for 12 months. Most patients featured late arthritis lasting for more than 2 years; all the children were treated with methotrexate (in the standard dosage) and other immunosuppressants. It was a prospective observational study without a control group. It demonstrated high efficacy of abatacept (according to the ACR_{pedi} criteria). After 4 months of treatment, 30% improvement was registered in as many as 60% of the patients, 50% improvement – in 30% of the patients. After 6 months of treatment, 30% improvement was registered in as many as 80% of the patients, 50 and 70% improvement – in 40% of the patients; 30% of the patients attained the inactive disease stage. 80% of the patients attained 70% improvement by the 12th month of the therapy.

Abatacept efficacy analysis demonstrated that after 6 months of the therapy the inactive disease stage was registered in 5/15 (30%) of the patients, after 12 months – in 10/15 (60%) of the patients; disease remission – in 10/15 (60%) of the children.

A randomized double blind placebo-controlled study AWAKEN aimed at analysis of abatacept efficacy and safety involving 190 6-17-year-old children with different forms of JIA (oligoarthritis, polyarthritis [RF- and RF+], systemic arthritis without systemic manifestations) demonstrated similar abatacept efficacy. Thus, by the end of the open label phase of the study (after 4 months), 30/50/70% improvement (according to the ACR_{pedi} criteria) was registered in 65/50/28% of the patients [36]. After 6 months of the therapy, 82% of the children treated with abatacept featured 30% improvement (according to the ACR_{pedi} criteria) in comparison with 69% of the patients taking placebo. 50/70/90% improvement (according to the ACR_{pedi} criteria) was registered in 77/53/40% of the children treated with abatacept. By the end of the study, 43% of the patients treated with abatacept attained the inactive disease stage [34].

By the end of our study, 60% of the patients attained the inactive disease stage, apparently, due to a more homogenous and numerically insignificant group of patients. The AWAKEN study involved patients both with oligoarthritis and systemic JIA without systemic manifestations.

It ought to be mentioned that abatacept is well tolerated. In our study, adverse events were mild and observed only in 6 (40%) patients. The development rates of adverse events in the placebo group and the abatacept group of the AWAKEN study were similar: 55 and 62%, respectively. Postinfusion reactions were observed in 4% of the patients in the open label phase and in 3% of the patients both in the abatacept and the placebo groups in the double blind period. Severe side effects not associated with the drug and 1 case of leukemia were registered in 6 patients in the course of the open label phase.

Thus, the abatacept safety profile was slightly higher in our study yet altogether similar to the previously observed in patients with JIA (according to randomized studies); it is regular for the patients taking immunosuppressants [34, 35]. Adverse events consisted in mild infections, which did not alter laboratory parameters. We did not register any fatal outcomes in the setting of the abatacept treatment.

Conclusion

Results of a 1-year-long prospective observational study demonstrated that abatacept is efficient in patients with the RF+ and RF- forms of polyarticular arthritis refractory to treatment with glucocorticoids, methotrexate, cyclosporine and combined immunosuppressive therapy. The drug induced remission of the articular syndrome and ensured normalization of the laboratory disease activity parameters in 60% of the patients after 1 year of treatment.

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Table 1. Demographic parameters of the patients with polyarticular juvenile idiopathic arthritis involved in the study

Parameter	Group of JIA patients (*n* = 15)
Gender: boys/girls	1/14
Age (in years) (Me [25-75])	13 (11-14.5)
Age at disease onset (in years) (Me [25-75])	9 (8-11.5)
Disease duration (in years) (Me [25-75])	4 (3-5)

Table 2. Clinical parameters of the patients with polyarticular juvenile idiopathic arthritis involved in the study

Parameter	Group of JIA patients (*n* = 15)
Number of joints with active arthritis	10 (12-8)
Number of dysfunctioning joints	10 (11-8)
Doctor global assessment of health (100 mm VAS)	53 (43-62)
Global assessment of well-being by parents (100 mm VAS)	65 (55-75)
Total CHAQ index: 0 (the best possible) – 3 (the worst possible)	1.1 (1-1.2)
ESR (in mm/h)	28 (20-35)
Serum CRP concentration (in mg/ml)	16 (10-20)

Note. VAS – visual analog scale, CHAQ – Children Health Assessment Questionnaire (0-3 points), ESR – erythrocyte sedimentation rate, CRP – C-reactive protein.

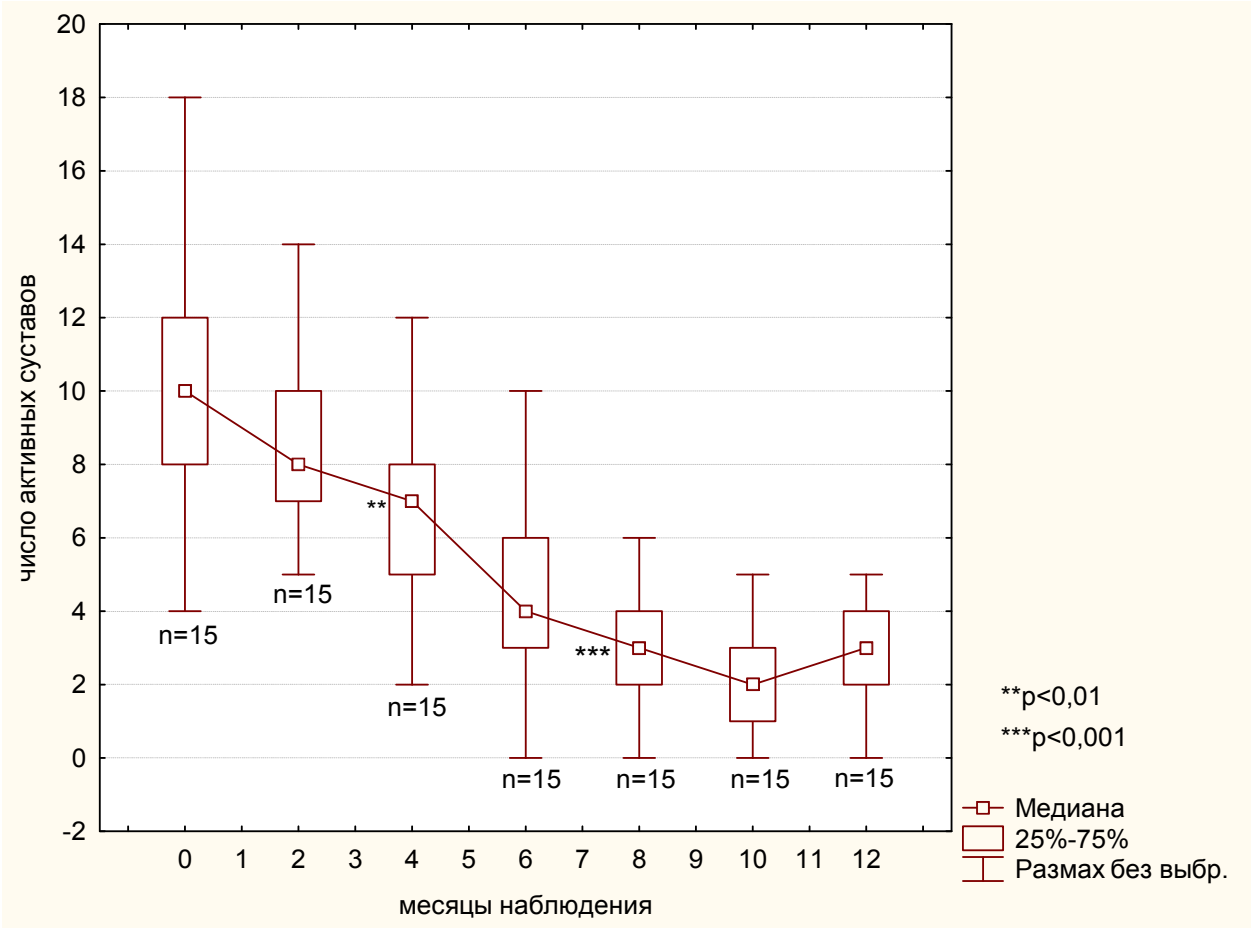
Table 3. Parameters of the background therapy of the patients with polyarticular juvenile idiopathic arthritis involved in the study

Parameter	Group of JIA patients (*n* = 15)
NSAIDs	15
Methylprednisolone pulse therapy	2
Topical therapy with glucocorticoids	11
Per os prednisolone	-
Methotrexate	15
Cyclosporine	1
Leflunomide	2
Sulfasalazine	2

Note. NSAIDs – non-steroidal anti-inflammatory drugs.

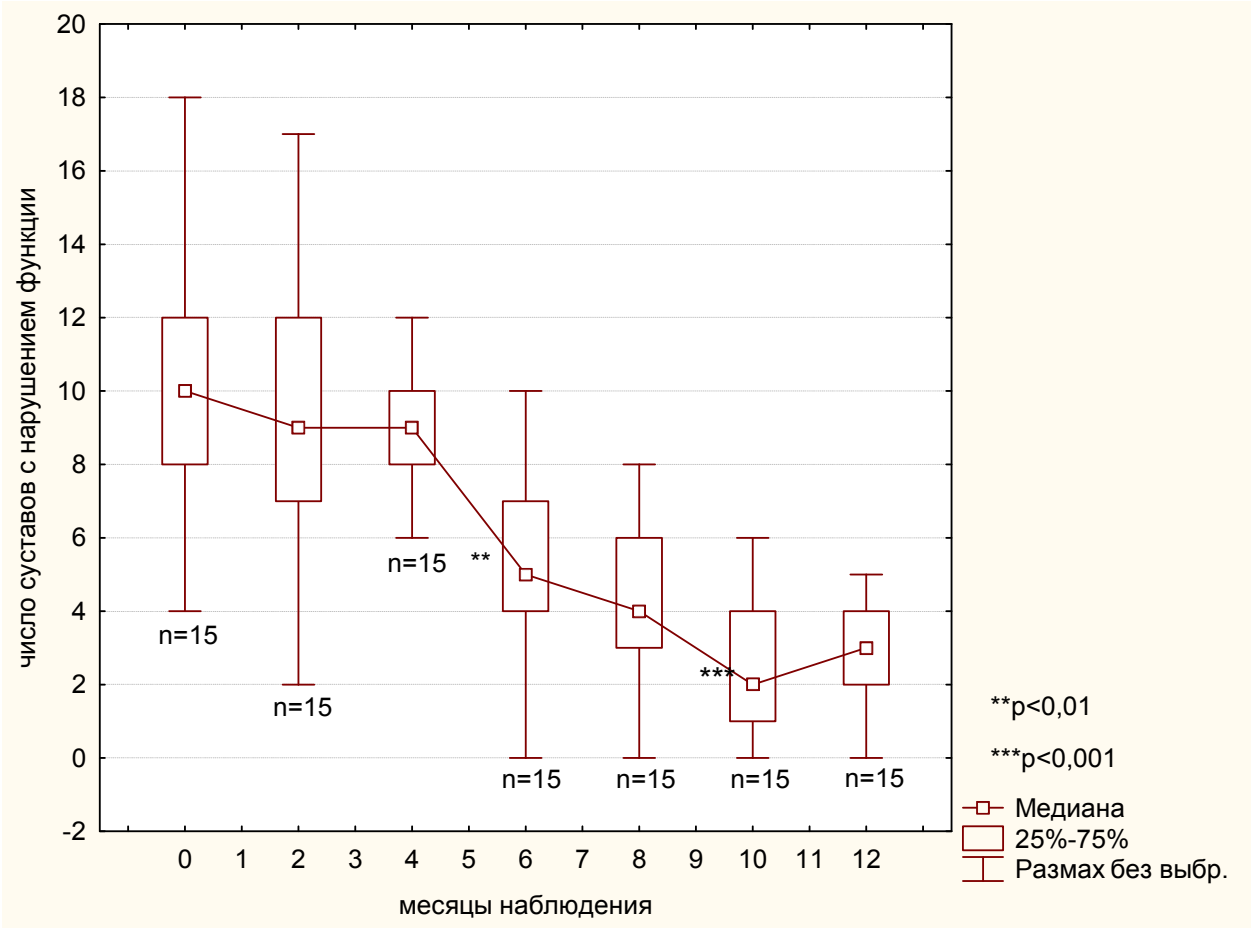
Table 4. Adverse events in the patients with polyarticular juvenile idiopathic arthritis in the setting of the abatacept therapy

Adverse events	Patients, n (%)
Infectious diseases:	
◊ Herpetic infection exacerbation	3 (20)
◊ Acute respiratory infection	3 (20)



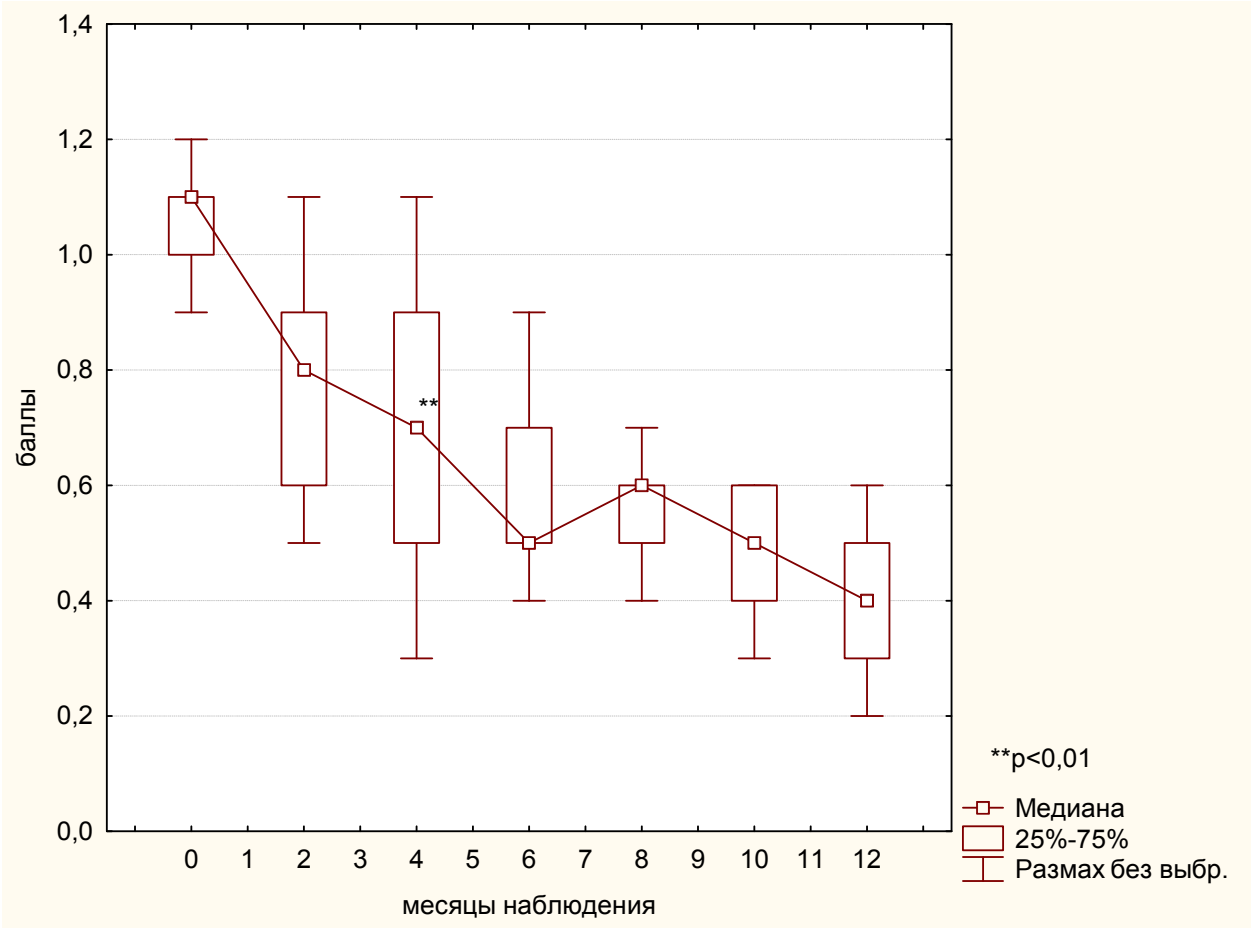
Pic. 1. Dynamics of the number of joints with active arthritis in patients with polyarticular juvenile idiopathic arthritis in the setting of the abatacept therapy

Hereinafter:	
число активных суставов	*number of active joints*
месяцы наблюдения	*months of observation*
Медиана	*Median*
Размах без выбр.	*Range (without outliers)*



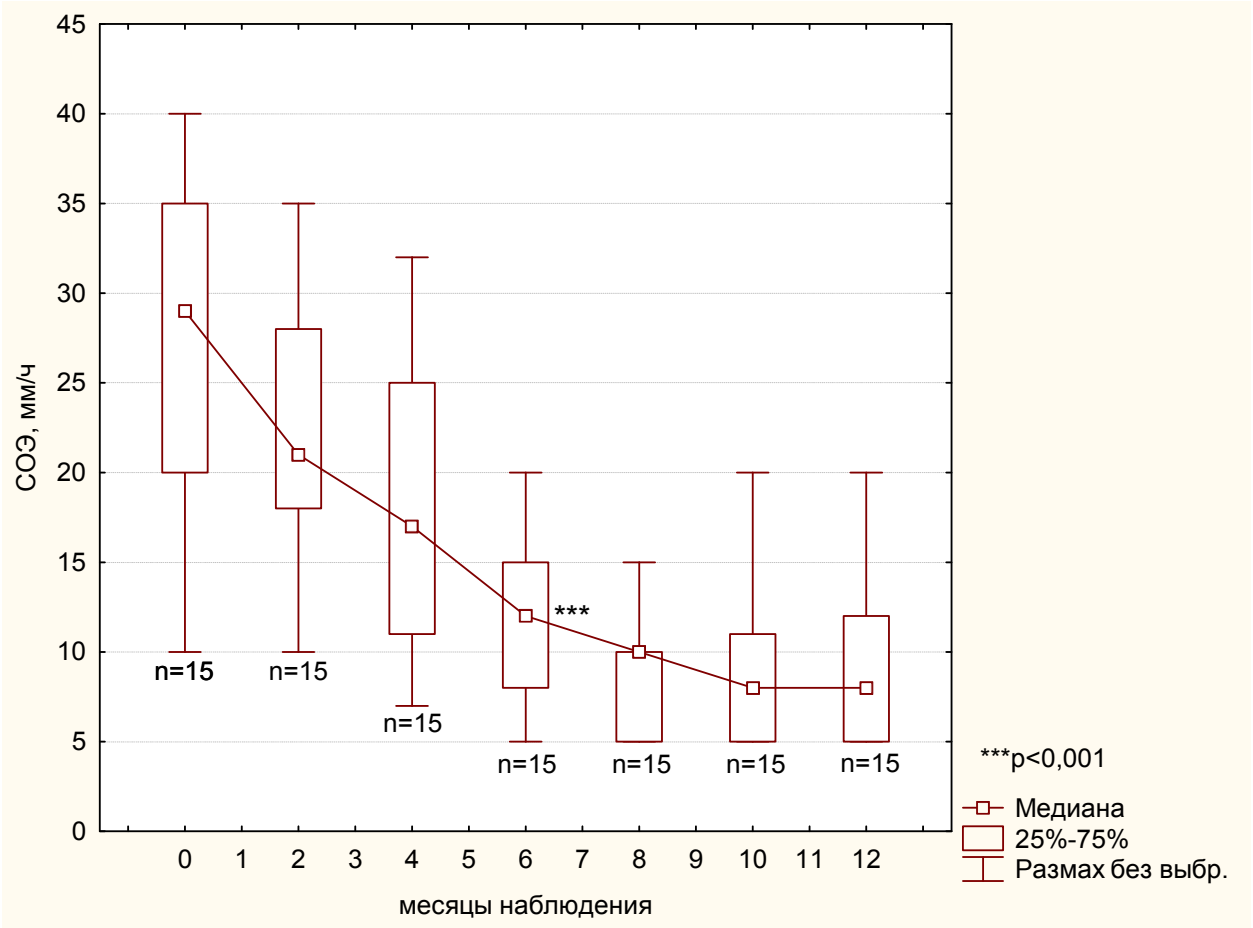
Pic. 2. Dynamics of the number of dysfunctioning joints in patients with polyarticular juvenile idiopathic arthritis in the setting of the abatacept therapy

число суставов с нарушением функции	*number of dysfunctioning joints*



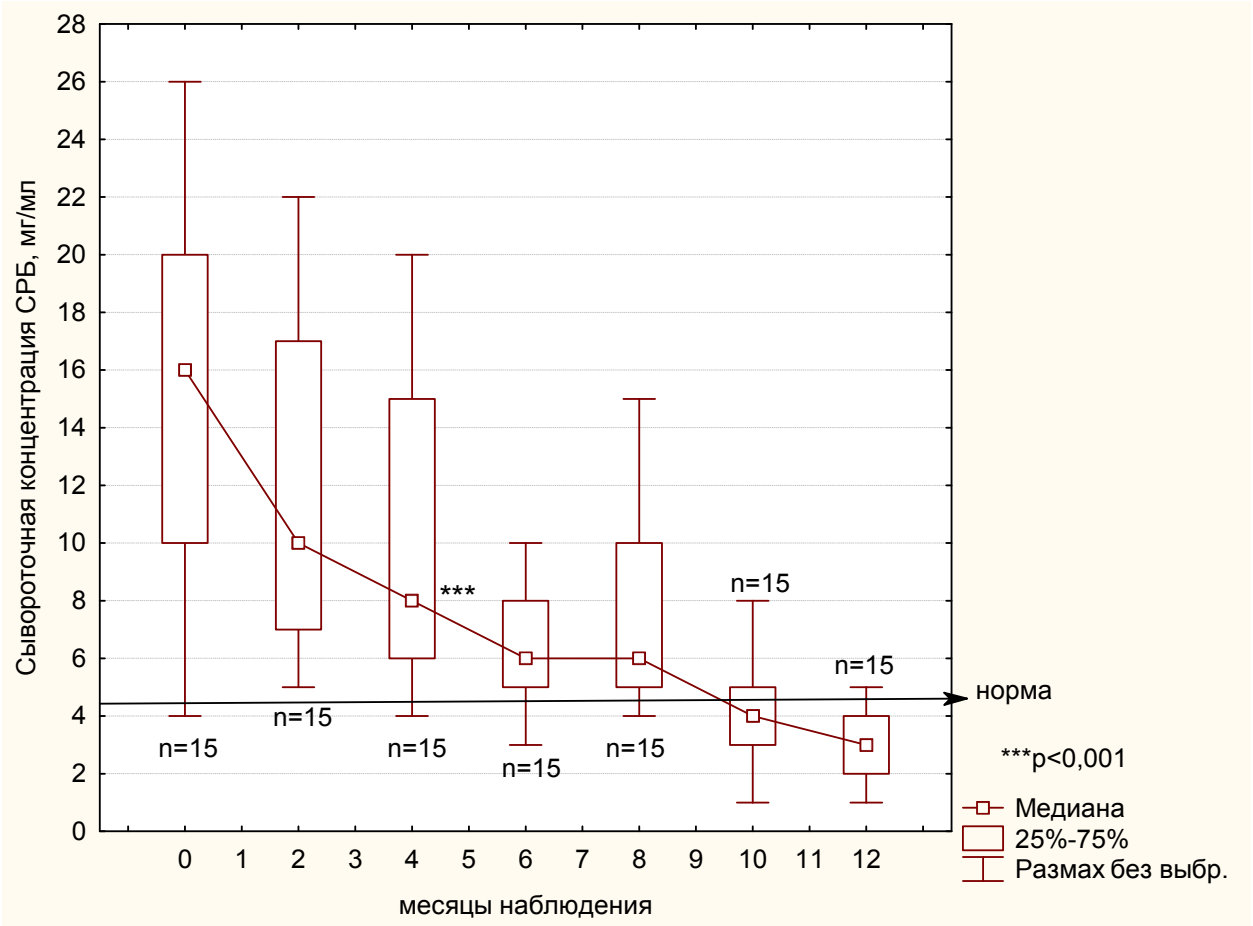
Pic. 3. Functional insufficiency dynamics in patients with polyarticular juvenile idiopathic arthritis treated with abatacept (CHAQ index)

баллы	*points*



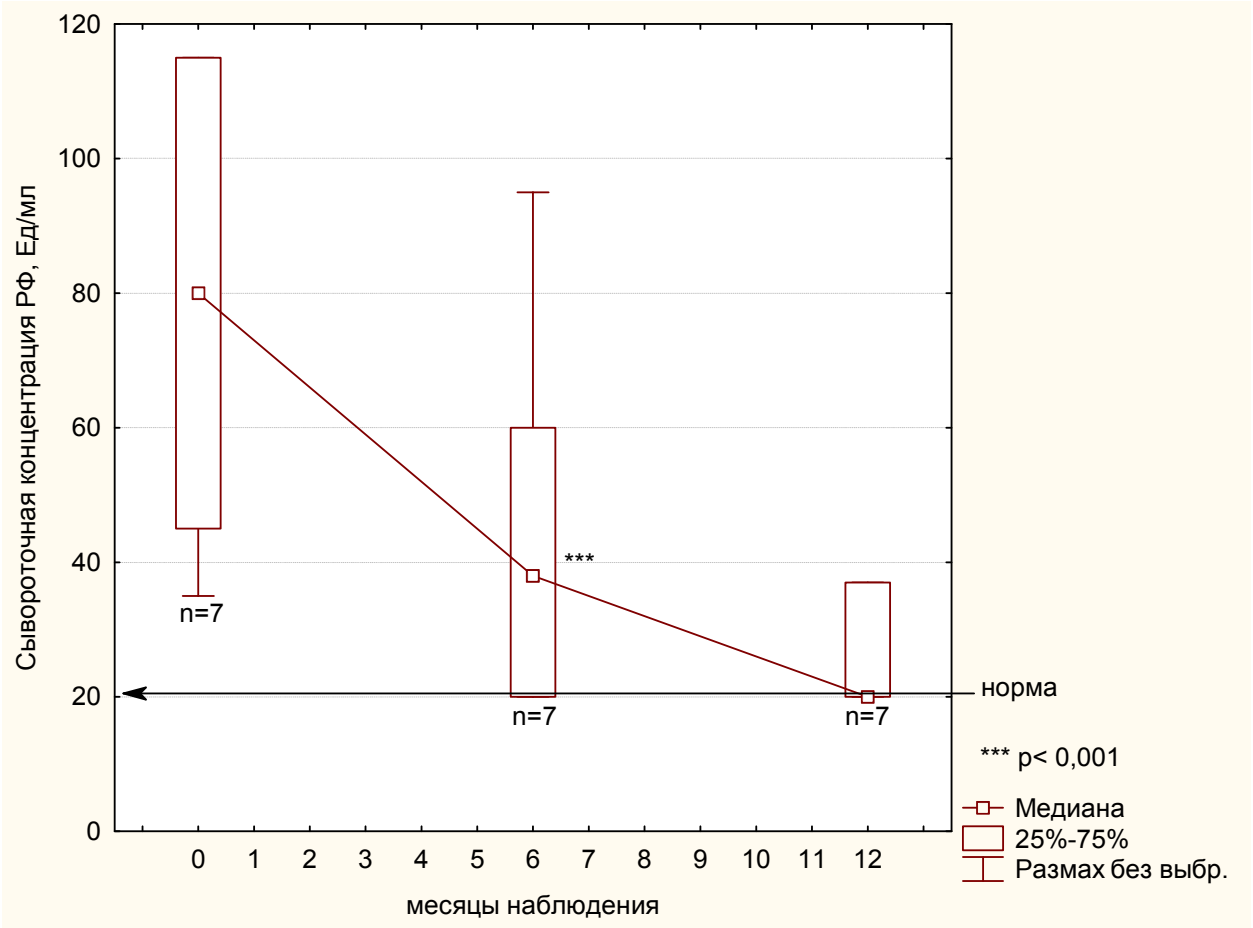
Pic. 4. Erythrocyte sedimentation rate dynamics in patients with polyarticular juvenile idiopathic arthritis in the setting of the abatacept therapy

СОЭ, мм/ч	*ESR (in mm/h)*



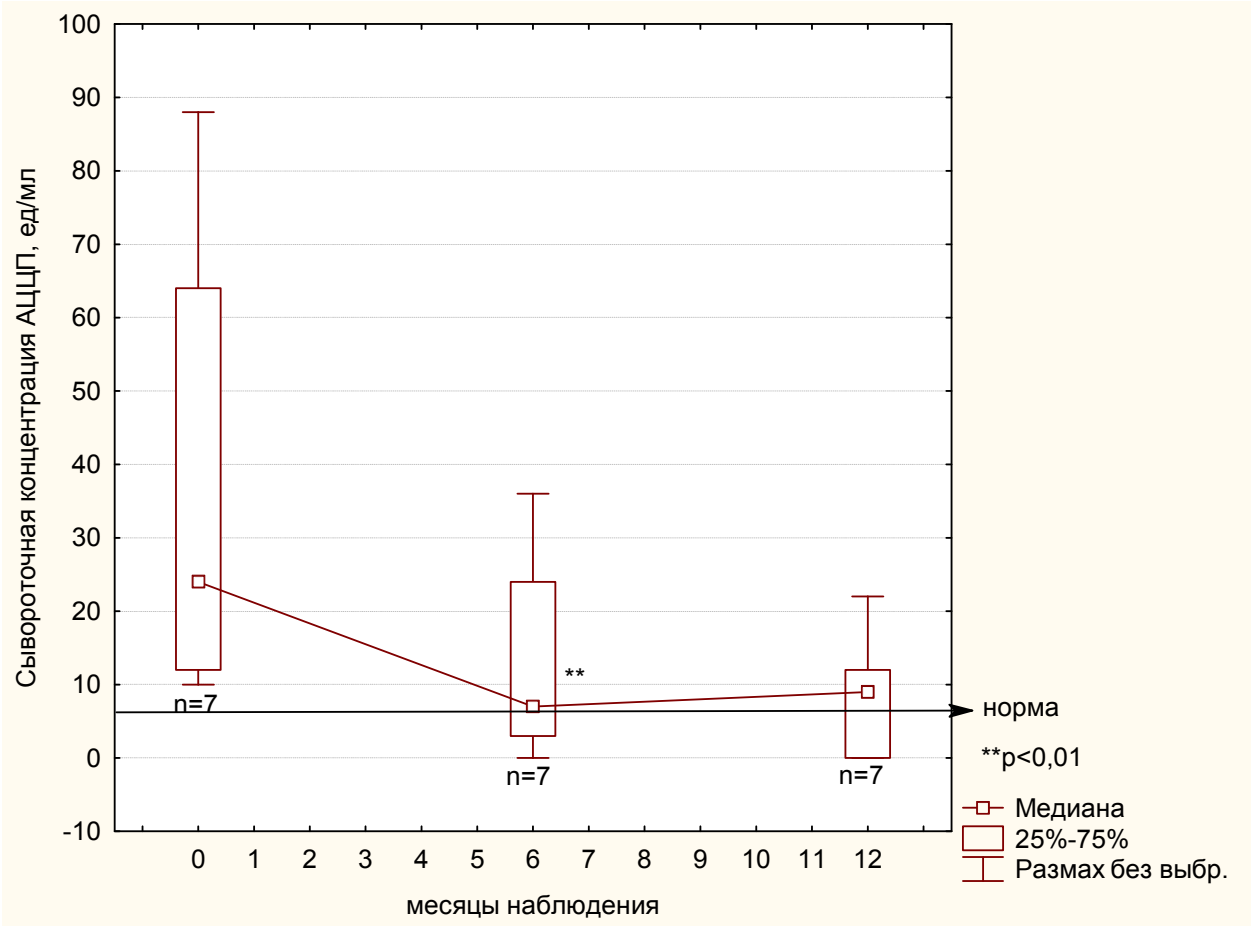
Pic. 5. Serum C-reactive protein concentration dynamics in patients with polyarticular juvenile idiopathic arthritis in the setting of the abatacept therapy

Hereinafter:	
Сывороточная концентрация СРБ, мг/мл	*Serum CRP concentration (in mg/ml)*
норма	*norm*



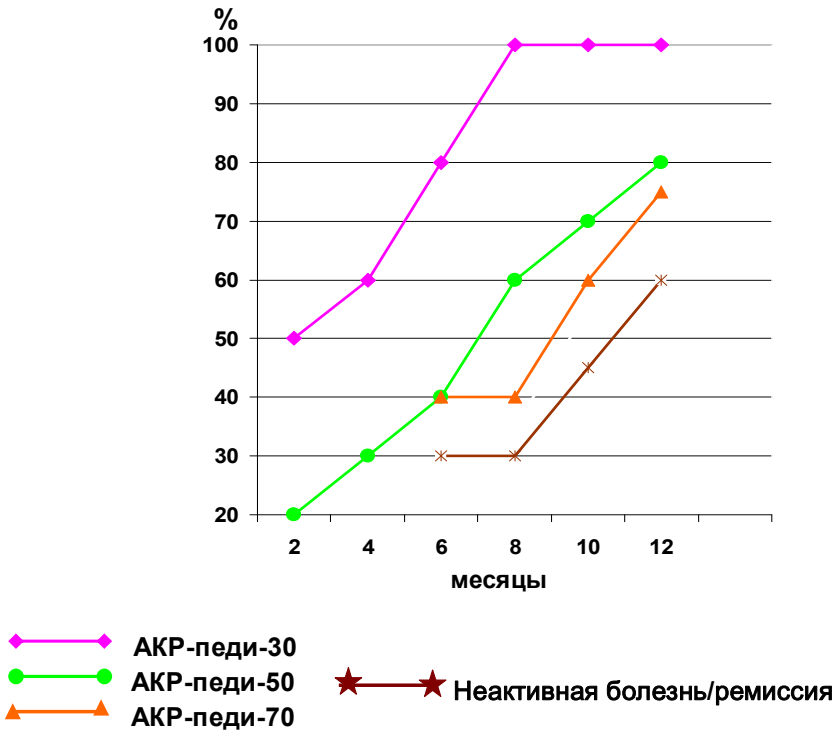
Pic. 6. Serum rheumatoid factor concentration dynamics in patients with polyarticular juvenile idiopathic arthritis in the setting of the abatacept therapy

Сывороточная концентрация РФ, Ед/мл	*Serum RF concentration (in IU/ml)*



Pic. 7. Serum cyclic citrullinated peptide antibodies concentration dynamics in patients with polyarticular juvenile idiopathic arthritis in the setting of the abatacept therapy

Сывороточная концентрация АЦЦП, ед/мл	*Serum CCPA concentration (in IU/ml)*



Pic. 8. Abatacept therapy efficacy (according to the pediatric criteria of the American College of Rheumatology) in patients with polyarticular juvenile idiopathic arthritis in the setting of the abatacept therapy

месяцы	*months*
АКР-педи	*ACR_{pedi}*
Неактивная болезнь/ремиссия	*Inactive disease/remission*