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Efficacy and Safety of Adalimumab Long-Term Administration with Immunosuppressants at Juvenile Idiopathic Arthritis without Systemic Manifestations

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Background. *Treatment of patients with juvenile idiopathic arthritis (JIA) is one of the most complex and urgent problems of rheumatology.* ***Objective.*** *Our aim was to evaluate the efficacy and safety of adalimumab therapy combined with immunosuppressants in patients with JIA without systemic manifestations.* ***Methods and Patients.*** *A monocentre observational comparative study was held. We studied the results of treatment of patients with JIA being treated with adalimumab combined with immunosuppressants (n = 215) and methotrexate (n = 200). The efficacy of the therapy was evaluated using the paediatric criteria of the American College of Rheumatology (ACRpedi) and remission criteria by C. Wallace during 5 years.* ***Results.*** *After 6 and 12 months the remission of articular syndrome was registered in 72 and 81% of patients treated with adalimumab combined with immunosuppressants, and in 53 and 65% treated with methotrexate. Laboratory indicators of the disease activity corresponded to the reference values after 6 months in 73 and 48%, after 12 months — in 94 and 68% of patients in the comparison groups, respectively. After 6 and 12 months of supervision the activity according to the CHAQ questionnaire was fully recovered in 63 and 79%; 47 and 62% of children. After 1 month the improvement according to the ACRpedi30/50/70 criteria was registered in 87/54/25% of the observed treated with adalimumab. After 6 months the ACRpedi30/50/70 index was 93/89/76% and 63/57/47% for adalimumab therapy with immunosuppressants and methotrexate, respectively. Adalimumab combined with immunosuppressants more quickly than methotrexate induced the stage of inactive disease/remission — after 5 (3; 8) and 12 (6; 18) months, respectively (p < 0.001). After 6 and 12 months of supervision the stage of inactive disease/remission was reported in 43 and 47% of patients treated with adalimumab combined with immunosuppressants, and in 9 and 38% of patients receiving the methotrexate therapy. Adalimumab and methotrexate were well tolerated by 58 and 73% of patients with JIA without systemic manifestations. The*

adverse events were reported in 42 and 27% of patients, but became the reason for drug dechallenge only in 6 and 10% of patients. ***Conclusion:*** *Adalimumab combination therapy combined with immunosuppressants has faster and more evident anti-inflammatory effect than the treatment with classical immunosuppressant methotrexate.*
Key words*: children, juvenile idiopathic arthritis, adalimumab, methotrexate, efficacy, safety.*

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RATIONALE

Juvenile idiopathic arthritis (JIA) is a systemic chronic disease that develops in children under the age of 16 years old; it is characterized by a primary joint lesions as well as pathology of other organs and tissues with the formation of multiple organ failure of various severity [1].

Treatment of juvenile arthritis remains one of the most complex and urgent issues of rheumatology [2]. A wide range of anti-rheumatic drugs is used in the treatment of this disease: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (oral, intravenous and intraarticular injections), quinoline derivatives, D-penicillamine, gold-containing drugs, sulfasalazine, leflunomide; immunosuppressants from the group of cytotoxic drugs (cyclophosphamide, azathioprine, chlorambucil), antimetabolites (methotrexate); selective immunosuppressants (cyclosporin) [3, 4]. Nevertheless, in many patients stable remission and control of the disease still cannot be achieved by means of basic antirheumatic drugs [5, 6]. The threat of disability in such patients predetermines the urge to develop and implement new approaches to pathogenetic therapy, based on modern medical technologies, as well as deciphering the fundamental mechanisms of the disease [7].

Significant progress in the treatment of rheumatic diseases is associated with the introduction into clinical practice of a fundamentally new class of drugs, under the general name of "genetically engineered biological drugs" (GIBD) [8-10]. GIBD are anti-inflammatory drugs, which are produced by means of biotech. Cytokines and their receptors, CD and co-stimulating molecules, etc. serve as the targets for GIBD. [11]. The main advantages of the biological therapy is the maximum selective effects on the immune system, which can eliminate an essential link in the pathogenesis chain without affecting cells of other organs and systems [12].

The key element in the pathogenesis of JIA without systemic manifestations is a tumor necrosis factor alpha (TNFα). It possesses cytotoxic, immunomodulating and pro-inflammatory properties, causing chronic inflammation, cartilage and bone destruction, and loss of the bone mass [13]. The central role of TNFα in the development of the JIA events became the basis for the creation of TNFα-inhibitor drugs [14].

The purpose of this study was to compare the efficacy and safety of long-term treatment of patients with JIA without systemic manifestations with GIBD adalimumab and immunosuppressant methotrexate.

METHODS

Study design

A monocenter observational comparative study was conducted.

Eligibility criteria

Inclusion criteria:

• the age under 18 years old;

• confirmed diagnosis of JIA according to ILAR criteria (International League of Associations for Rheumatology), including active chronic poly- or oligoarticular disease;

• the presence of more than one swollen joint and/or more than one painful joints with limited mobility within at least 6 months, and/or active uveitis;

• administration of NSAIDs and glucocorticoids at stable doses for at least 1 month prior to treatment with adalimumab;

• no evidence of tuberculosis (latent tuberculosis was excluded by means of Mantoux reaction and computed tomography of the chest);

• negative pregnancy test (for all girls over the age of 14 years old).

Non-inclusion criteria:

• any concomitant disease or deviation from normal laboratory values, which could affect the patient's participation in the study, according to the clinical evaluation of the researcher;

• any of the contraindications listed in the instructions for medical use of the drug, including:

- congestive heart failure, conditions with immunodeficiency;

- current infectious disease or the need for vaccination with live attenuated vaccine;

- severe uncontrolled systemic manifestations and/or the presence of biological evidence of macrophage activation syndrome; - abnormal liver function with liver aminotransferases activity more than two-fold exceeding the normal reference range;

• social or other reasons that may prevent the performance of regular medical check-ups.

Terms of study conduction

The study was conducted in the period from August 2008 to August 2014 on the basis of a specialized rheumatology department of the Scientific Center of Children's Health (Moscow).

Patients were sequentially enrolled.

Methods of reporting outcomes

All patients underwent a complete clinical laboratory and instrumental examination by the standards care in JA adopted in the Russian Federation. The following parameters were evaluated:

• activity of articular syndrome (number of swollen joints, joints with pain at palpation and movement, joints with impaired function, duration of the morning stiffness);

• functional activity of patients (according to the data of a special questionnaire Childhood Health Assessment Questionnaire, CHAQ); functional activity was considered expressed at CHAQ> 1,6, moderate - at the values from 0.64 to 1.6, the minimal - from 0.14 to 0.63;

• a global assessment of disease activity by physician and subjective assessment of well-being by patient or his parent (by 100 mm visual analog scale, VAS); the value of less than 5 points was considered as normal.

Evaluation of clinical activity of the disease was carried out prior to treatment, after 1, 3, 6 months and then once per year.

Laboratory indicators of disease activity, erythrocyte sedimentation rate (ESR) and serum concentration of C-reactive protein (CRP), were measured before treatment and, consequently, at each visit.

Treatment efficacy was evaluated by pediatric criteria of the American College of Rheumatology (ACRpedi) and C. Wallace remission criteria.

The effectiveness by ACRpedi was determined based on the overall patient's (parents') assessment of the state of health, the global assessment of the disease activity by a doctor by 100 mm VAS (points), functional capacity according to the CHAQ questionnaire, number of joints with active arthritis, number of joints with impaired function, the value of the ESR or CRP. The effectiveness by ACRpedi30/50/70 means improving at least by 30/50/70% for at least 3 of the 6 criteria with possible deterioration by 30% for not more than one indicator compared to the baseline value [2].

C. Wallace remission criteria of the disease include the absence of joints with active arthritis, absence of fever, rash, serositis, organomegaly, generalized lymphadenopathy, normal values of ESR and CRP, the absence of the disease activity according to the physician's judgement (by VAS), duration of morning stiffness is less than 15 min [2].

Medical intervention

The study does not imply an experimental medical treatment and all treatments were carried out in accordance with the standards/ guidelines for treatment of juvenile arthritis, adopted in Russian Federation [1].

Treatment outcomes

The target treatment efficacy indicator was the achievement of the inactive stage of the disease/remission with the use of the study drugs for at least three consecutive months in 1, 3, 6, 9 and 12 months, then once per year.

Evaluation of the safety of therapy was performed by means of recording the number of adverse events (AEs), which was considered as any adverse change in the medical condition of the patient who received the drug, regardless of the causal relationship with the treatment. The number of adverse events was calculated by the formula:

The number of adverse events/patient-year x 100 = the number of adverse events per 100 patient-years.

The total period of patients follow-up in years was intended under the patient-years.

Ethical review

The study was approved by the local ethics committees of the Scientific Center of Children's Health in August, 2008. Before treatment, the parents of all children and children over 14 years old gave written informed consent for its conduction.

Statistical analysis

Data processing was performed using STATISTICA software v. 6.0 (StatSoft Inc., USA). Quantitative attributes are presented as medians and 95% confidence intervals (CI). Differences were considered statistically significant at $p < 0.05$.

RESULTS

Study participants

The study involved 415 patients with JIA without systemic manifestations. Patients were divided into 2 groups: main (n = 215) and control group (n = 200). Patients of the main group received adalimumab in combination with immunosuppressive agents, patients of the group of comparison received methotrexate.

The effectiveness of adalimumab therapy with immunosuppressive agents was evaluated in 214 patients, as allergic reaction was reported in one child after the first injection, for that reason the drug was withdrawn. This patient was considered only when assessing the tolerability of adalimumab.

Characteristics of the patients is provided in Table. 1. Girls dominated in both groups. The age of patients at the time of inclusion into the study ranged from 0.6 to 17.2 years, duration of the disease ranged from 3 months to 15 years.

At the initiation of treatment, 196 (91.6%) patients of the main group and all patients in the group of comparison demonstrated active articular syndrome, in 18 (8.4%) patients of the main group - uveitis without active arthritis.

By the majority of clinical indicators, patients of both groups were comparable with each other. Statistically significant difference between the groups was observed for the 3 parameters. In the main group the duration of morning stiffness, the number of joints with active arthritis and well-being evaluation score by the patient and his parents were significantly higher than in the comparison group (Table 2).

High clinical disease activity was accompanied by an increase in laboratory parameters: ESR - in 143/214 (66.8%) and 121/200 (60.5%), serum CRP - in 115/214 (53.7%) and 134/200 (67%) of patients of the main group and the comparison group, respectively. ESR values and CRP serum levels were comparable in both groups (see Table 2).

Table 1. Characteristics of patients with juvenile idiopathic arthritis without systemic manifestations included into the study

Parameter	**Main group (n = 214)**	**Control group (n = 200)**	*P*
Girls, abs. (%)	128 (59)	120 (60)	0.982
Age, years	10.5 (7.0; 13.8)	6.1 (3.5; 11.2)	0.001
Age of the onset of the	4.0 (2; 7.15)	3.0 (2.0; 7.1)	0.390
Disease duration, years	4.0 (2.0; 7.2)	1.7 (0.7; 4.4)	0.001

Table 2. Clinical characteristics of patients with juvenile idiopathic arthritis (JIA) without systemic manifestations at the study entry

Parameter	**Main group (n = 214)**	**Control group (n =**	*P*
Diagnosis, abs. (%) Oligoarticular JIA Polyarticular JIA Enthesitis JIA	 62 (29.0) 89 (41.6) 63 (29.4)	 87 (43.5) 87 (43.5) 26 (13.0)	-
Uveitis, abs. (%)	109 (51)	0	-
Number of painful joints	4 (2; 10)	4.5 (2; 8,25)	0.199
Number of swollen joints	4 (2; 8)	4 (2; 6,25)	0.249
Number of joints with active arthritis	4 (2; 10)	4 (2; 6)	0.005
Number of joints with impaired function	4 (2; 10,75)	5 (2; 9)	0.296
Duration of morning stiffness, min	60 (20; 120)	45 (20; 60)	0.001
Patient's (parents') evaluation of well-being by visual analogue scale, points	73 (63; 87,75)	68 (50; 80)	0.005
Physician's overall assessment of the disease activity by visual analogue scale,	60.5 (50; 73,75)	60 (46; 80)	0.925
Functional ability by CHAQ, points	1 (0.5; 1.75)	1 (0.3; 1,5)	0.644
Erythrocyte sedimentation rate (ESR), mm/h (normal up to 15 mm/h)	23 (11; 40)	26 (10; 45)	0.676
C-reactive protein (CRP), mg/L (normal up to 5 mg/L)	5.89 (1; 18)	7.89 (1.38; 15,25)	0.850

According to a special questionnaire CHAQ data, expressed functional insufficiency (CHAQ index> 1.6) was observed in 66/214 (30.8%) and 46/200 (23%), moderate (CHAQ index 0.64-1.6) - in 87/214 (40.6%) and 102/200 (51%) patients of the main group and the group of comparison, respectively (see Table 2).

The general well-being according to the patient or his parents was significantly worse in the main group. According to the physician's assessment of the disease activity in patients of both groups, it did not differ significantly and corresponded to the moderate and a high degree. It should be noted that in both groups patients or parents assessed well-being worse than a doctor (see Table 2).

Thus, prior to treatment with adalimumab and methotrexate all children with JIA had active articular syndrome, functional insufficiency of varying degrees of severity, increased laboratory markers of activity (erythrocyte sedimentation rate, serum CRP), poor well-being and high activity of the disease according to patients (or their parents) and the doctor.

Dosage and administration of the drugs and follow-up duration

Adalimumab was administered at a dose of 40 mg (one syringe regardless of the weight and age of the child), once in two weeks, subcutaneously, in the abdominal region or the outer surface of the hand, after treatment of the skin with an alcohol swab. Dose and mode of adalimumab administration remained unchanged throughout the period of observation.

All children of the main group (n = 214) had received at least six injections of adalimumab (3 months of therapy). Within 3 months 214 patients were observed, 6 months – 191 (89%), 9 months - 166 (76%), 1 year - 157 (73%), 1.5 years - 131 (61%), 2 years - 108 (51%), 2.5 years - 70 (33%), 3 years - 51 (24%), 4 years - 17 (8%), 5 years - 9 (4%) children. Mean duration of follow-up was 1.8 (0.9, 2.5) years. 54 (25%) patients were excluded from

the study; 5 children have not reached the intermediate point "6 months", 29 - "1 year" point, 65 - "2 years" point, 113 - "3 years" point, 147 - "4 years" point, 152 - "5 years" point.

Methotrexate was administered at a dose of 15 (15; 20) mg/m^2 per week by subcutaneous or intramuscular injections, for at least 3 months. Within 6 months 150 (75%) were observed, 1 year - 122 (61%), 2 years - 112 (56%), 3 years - 107 (53.5%), 4 years - 100 (50%) patients. Mean duration of follow-up was 2.9 (0.6; 5) years. 102 (51%) patients were excluded from the study (reasons for exclusion from the study are provided in Section "Survival").

Background therapy

Background therapy and doses of immunosuppressive drugs are provided in Table 3. Adalimumab was assigned against the background of immunosuppressive treatment to 204 (95.3%) patients.

Table 3. Characteristics of background therapy in patients with juvenile idiopathic arthritis without systemic manifestations at the study entry

Drug/dosage	**Main group (n = 214)**	**Control group (n =**
Prednisolone *per os*, abs. (%) Dosage of the drug, mg/kg per day	20 (9.3) 0.2 (0.05; 0.35)	18 (9.0) 0.2 (0.1; 0.4)
Nonsteroidal anti-inflammatory agents, abs. (%)	135 (63.1)	183 (91.5)
Methotrexate, abs. (%) Dosage of the drug, mg/m^2 per week	188 (87.8) 15 (15; 20)	-
Cyclosporin, abs. (%) Dosage of the drug, mg/kg per day	8 (3.7) 4 (4; 4.5)	-
Sulfasalazine, abs. (%) Dosage of the drug, mg/kg per day	8 (3.7) 34 (33; 38)	-

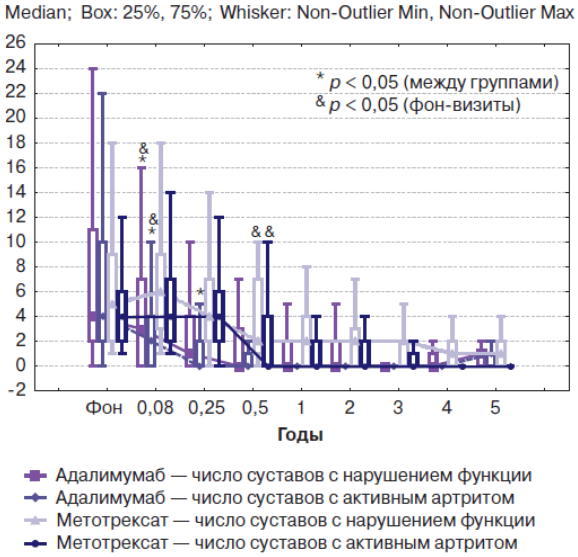
188 (87.8%) received methotrexate, 8 (3.7%) - combination of methotrexate with cyclosporin, and 8 (3.7%) patients - sulfasalazine. 20 (9.3%) children received prednisolone orally.

Characteristics of prior treatment

Prior to this study, all patients underwent anti-rheumatic therapy in various modes. 67 (31.3%) and 32 (16.0%) children of the main and control groups, respectively, were assigned oral prednisolone at a dose of 0.1 to 2 mg/kg per day at a place of residence in the territorial medical institutions; intra-articular injections of glucocorticoids were performed with a frequency of 1-12 injections per year in 102 (47.4%) and 88 (44%) patients, methylprednisolone pulse therapy at a dose of 5-30 mg/kg of body weight per administration was assigned to 14 (6.5%) and 6 (3%) patients in the two groups, respectively. All children received NSAIDs.

All patients of the main group before the study received immunosuppressive drugs: methotrexate - 197 (92%), cyclosporin - 94 (44%), leflunomide - 14 (6.5%), hydroxychloroquine - 27 (12.6%), sulfasalazine - 70 (32.7%), cyclophosphamide - 8 (3.7%) azathioprine - 5 (2.3%). In the group of comparison, methotrexate was the first immunosuppressant in 163 (81.5%) patients, the second or the third in 37 (18.5%); 6 (3%) children received cyclosporin, 30 (15%) - sulfasalazine, 1 (0.5%) - cyclophosphamide. Duration of anti-rheumatic therapy prior to the initiation of the study was 3.3 (2; 6.8) and 1.5 (0.6, 4) years in the main group and the group of comparison, respectively ($p < 0.001$).

Fig. 1. Dynamics of the number of joints in patients with juvenile idiopathic arthritis without systemic manifestations during therapy with adalimumab and methotrexate at the dose of 15 mg/m^2 per week



*p < 0.05 (between groups) &p < 0.05 (background-visits)
Background **years**
Adalimumab – number of joints with impaired function Adalimumab – number of joints with active arthritis Methotrexate – number of joints with impaired function Methotrexate - number of joints with active arthritis

Key findings

Articular syndrome

After 1 month (0.08 years) after the first injection of adalimumab the number of painful joints had decreased by 5 times, the number of swollen joints and joints with active arthritis – two-fold, the number of joints with impaired function - 1.3 times as compared with the baseline value (Fig. 1). The duration of morning stiffness decreased by 6 times and it became significantly lower than in children treated with methotrexate. In 157 (52.1%) patients joint pain was completely resolved, 71 (33%) had no joints with determined active arthritis. Children in the group of comparison within this follow-up period did not show the reliable dynamics of the values of clinical parameters of disease activity. In 6 (3%) patients who received methotrexate, the number of painful joints and joints with impaired function had decreased and in 14 (7%) patients articular syndrome had spread.

After 3 months, the value of markers of disease activity in the main group were still lower than in patients of the group of comparison. In patients treated with adalimumab, the median of the number of painful, swollen joints and joints with active arthritis has become equal to 0. The number of joints with impaired function decreased by 4 times. Morning stiffness was resolved in 188 (87.8%), articular syndrome - in 135 (63%) patients. In 54

(25.2%) patients articular syndrome transformed into oligoarthritis type of duration. In patients treated with methotrexate, significant dynamics of values of clinical parameters of disease activity at 3 months (0.25 years) have not been observed. The tendency towards the reduction of the number of painful joints, swollen joints and joints with dysfunction was observed (see Fig. 1).

After 6 months (0.5 years) in the main group, the median of the number of painful, swollen joints, and joints with active arthritis and dysfunction corresponded to 0. In the group of comparison for the first time during the observation period, significant decrease in all indicators of the articular syndrome activity was recorded. The median of the number of swollen and painful joints and joints with active arthritis as well as in the study group became equal to 0, the median number of joints with impaired function decreased by 2.5 times; duration of morning stiffness was reduced by 2 times. The difference between the two groups on these indicators at 6 months (0.5 years) of follow-up was leveled (see Fig. 1). Articular syndrome was resolved in 138/191 (72%) and 79/150 (53%), morning stiffness - in 175/191 (91.6%) and 55/150 (37%), the range of motion was fully recovered in 107/191 (56%) and 36/150 (24%) patients of the main group and control group, respectively.

After one year remission of articular syndrome was registered in 128/157 (81.5%) and 79/122 (65%); the full range of motions in the joints - in 99/157 (63%) and 40/122 (33%) patients of main group and control group, respectively. In 21/157 (13.4%) and 43/122 (35%) patients of both groups articular syndrome recurred as oligoarthritis in 8/157 (5.1%) and 6/122 (4.9%) in accordance with the type of arthritis.

After two years of remission of articular syndrome persisted in 90/108 (83%) and 79/112 (70.5%) patients treated with adalimumab and methotrexate, respectively. Active articular syndrome by the type of oligoarthritis remained in 15/108 (13.9%) and 27/112 (24%), on the type of polyarthritis - in 3/108 (2.8%) and 6/112 (5.3%) patients from both groups. However, articular syndrome was still significantly more active in patients treated with methotrexate. In 70/108 (64.8%) and 87/112 (78%) children in both groups there was no joints with motion restriction.

After three years remission of the articular syndrome was recorded in 47/51 (92%) and 79/107 (74%), complete restoration of the function in the joints - in 38/51 (74.5%) and 40/107 (38%) out of patients of both groups, remaining in the study. The joints with active arthritis were detected in 3/51 (5.9%) and 28/107 (26%) children of the main group and the group of comparison.

After four years remission of articular syndrome was observed in 14/17 (82%) and 79/100 (79%); the full range of motion in the joints - in 12/17 (70.6%) and 40/100 (40%) patients treated with adalimumab and methotrexate, respectively. In 3/17 (17.6%) and 21/100 (21%) children of the main and control group after four years articular syndrome continued to recur.

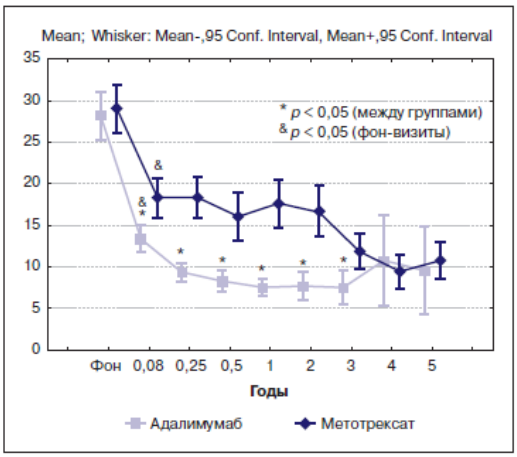
To the 5^{th} year, the median number of painful joints corresponded to 0 in both groups; the number of swollen joints, joints with active arthritis, with impaired function - 1 (0;1) in the main group and 0 (0;0) in the group of comparison (see Figure 1). Articular syndrome was resolved in the 4/9 and 79/98 (81%) patients, the range of motions in the joints was fully recovered in the 4/9 and 41/98 (42%) children who were treated with adalimumab and methotrexate, respectively.

Laboratory markers of disease activity

Dynamics of laboratory markers of activity (ESR, CRP) in the main group and the comparison group were as well controversial. One month after the first adalimumab injection ESR value declined compared to the baseline, as well as in relation to the values in the group of comparison and conformed to the reference values in 151/214 (71%) patients. Serum CRP value in patients treated with adalimumab also had declined compared to the baseline values as well as the values of the group of comparison and conformed to the reference values in 168/214 (78.5%) patients. In the group of children treated with methotrexate, the dynamics of laboratory parameters was unremarkable. ESR values and serum CRP concentration corresponded to the reference values in 150/214 (70%) and 90/200 (45%) patients of the main and control group, respectively (Fig. 2, 3).

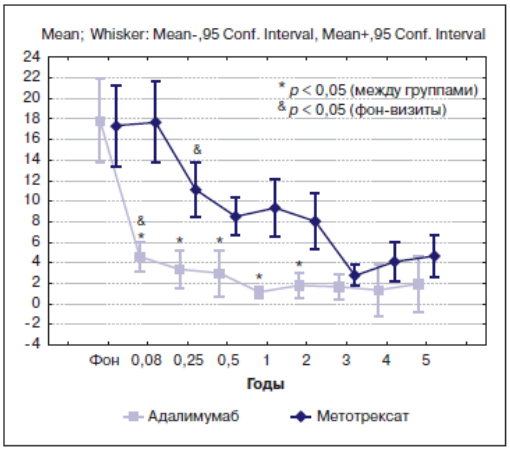
After 3 months in patients of the main group laboratory parameters continued to decline. ESR values and serum CRP concentration normalized in 198/214 (92.5%) and 141/214 (65.8%) patients, respectively. In the comparison group, ESR values returned to normal in 90/200 (45%) patients, however, the median of ESR values was still significantly higher than that of a study group (see Fig. 2). No significant dynamics of serum CRP levels in patients treated with methotrexate was observed, and they were as well significantly higher than in the main group (see Fig. 3). Serum CRP concentrations of normalized in 58/200 (29%) patients.

Fig. 2. Dynamics of the erythrocyte sedimentation rate in patients with juvenile idiopathic arthritis without systemic manifestations during therapy with adalimumab and methotrexate at the dose of 15 mg/m^2 per week



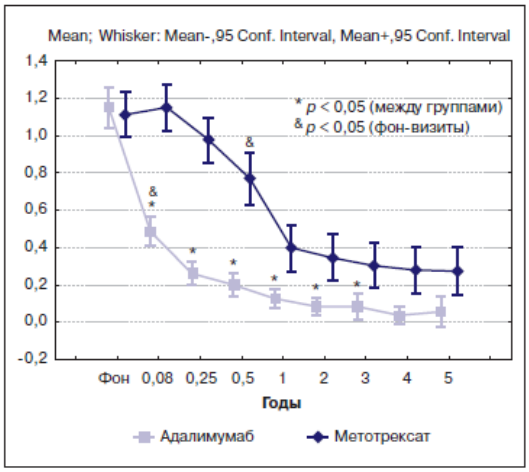
*p < 0.05 (between groups) &p < 0.05 (background-visits)
Background **years**
Adalimumab Methotrexate

Fig. 3. Dynamics of the C-reactive protein concentration in patients with juvenile idiopathic arthritis without systemic manifestations during therapy with adalimumab and methotrexate at the dose of 15 mg/m^2 per week



*p < 0.05 (between groups) &p < 0.05 (background-visits)
Background **years**
Adalimumab Methotrexate

Fig. 4. Dynamics of the joint function index in patients with juvenile idiopathic arthritis without systemic manifestations during therapy with adalimumab and methotrexate at the dose of 15 mg/m^2 per week



*p < 0.05 (between groups) &p < 0.05 (background-visits)
Background **years**
Adalimumab Methotrexate

After 6 months of laboratory markers of the disease activity went back to normal in 139/191 (72.8%) and 72/150 (48%) children treated with adalimumab and methotrexate,

respectively. Median CRP and ESR values matched normal values in both groups. However, ESR and CRP serum levels in patients treated with adalimumab were significantly lower than in patients treated with methotrexate (see Fig. 2 and 3).

After 1 year of laboratory markers of the disease activity ESR and CRP corresponded to normal values in 148/157 (94%) and 102/150 (68%) patients in both groups. A moderate increase in erythrocyte sedimentation rate persisted in 8/157 (5.1%) and 39/150 (26%), serum CRP level - in 9/157 (5.7%) and 48/150 (32%) children treated with adalimumab and methotrexate, respectively.

After 2 years, ESR and CRP serum levels decreased in both groups, but were lower in patients treated with adalimumab. Normal laboratory parameters were reported in 100/108 (92.6%) and 79/112 (70.5%) children of the main group and the group of comparison, respectively.

To the 3rd year follow-up, ESR and serum CRP levels corresponded to the normal reference range values in 46/51 (90%) and 89/107 (83%) patients treated with adalimumab and methotrexate. In the group of comparison ESR greater than 15 mm/h was recorded in 17/107 (16%) patients, increased serum concentrations of CRP - in 16/107 (15%) patients. Statistically significant differences between groups were not observed (see Fig. 2 and 3).

After 4 years, increased ESR and CRP serum concentration persisted in 2/17 patients of the main group. In the comparison group accelerated ESR was observed in 8/100 (8%), increased CRP serum concentrations - in 16/100 (16%) patients. Maximum ESR was 37 and 55 mm/h, serum CRP level – 20.11 and 53 mg/L in patients treated with adalimumab and methotrexate, respectively.

After 5 years, increased erythrocyte sedimentation rate was observed in 12/98 (12%) patients receiving methotrexate (max 48 mm/h), serum CRP - in 2/9 patients of the main group (max 9.75 mg/L), and 19/98 (19%) children of the group of comparison (max 53 mg/L).

The functional ability according to the CHAQ questionnaire

Impact of the study drugs on the functional ability of patients was also significantly different. Within 1 month after the first injection of adalimumab index of functional impairment by the CHAQ questionnaire decreased in comparison with the baseline value as well as in comparison with the control group (Fig. 4). There was no dynamics of this indicator observed in the group of patients treated with methotrexate.

Full functional activity was recorded in 88/214 (41%) and 16/200 (8%) patients of the main group and control group, respectively. The number of patients with severe functional impairment after 1 month of treatment in the main group decreased by 4.7 times and was 14/214 (6.5%), while prior to treatment it was 66/214 (30.8%).

By the 3rd month, the index of functional impairment in patients treated with adalimumab continued to decline and was lower than in the control group. In patients treated with methotrexate, the dynamics of this indicator was not observed (see Fig. 4).

In 111/214 (51.8%) patients treated with adalimumab, functional ability was fully restored; functional impairment remained at the same level in children who received methotrexate. Severe functional impairment was recorded in 7/214 (3.2%) and 55/200 (28%), moderate or minimal - in 96/214 (44.8%) and 159/200 (79.5%) patients of the main group and control group, respectively.

After 6 months in children of the main group functional activity by CHAQ index continued to improve significantly. The dynamics of this indicator was observed in patients treated with methotrexate. In patients treated with adalimumab functional index of impairment was still significantly lower than in the group of comparison.

Full functional activity according to the CHAQ questionnaire was recorded in 120/191 (62.8%) and 70/150 (46.7%), moderate or minimal functional impairment - in 65/191 (34%) and 62/150 (41.3%), severe functional impairment - in 6/191 (3.1%) and 18/150 (12%) patients of the main group and control group, respectively.

After 1 year, the index of functional impairment according to CHAQ questionnaire in the observed patients did not differ significantly. In 4/157 (2.6%) and 45/122 (37%) patients treated with adalimumab and methotrexate given value was above 1.

After 2 years functional activity according to CHAQ questionnaire was fully recovered in 85/108 (78.7%) and 70/112 (62.5%) patients of both groups. 4/108 (3.7%) and 13/112 (19%) patients had moderate functional impairment (CHAQ from 0.64 to 1.6), 19/108 (17.6%) and 19/112 (17%) had minimal impairment (CHAQ index from 0.14 to 0.63). Severely impaired functional ability remained in 4/108 (3.7%) and 10/112 (8.9%) patients of the main group and group of control.

After 3 years in 40/51 (78%) and 77/107 (72%) patients treated with adalimumab and methotrexate, respectively, the functional status according to CHAQ questionnaire was not impaired or minimally reduced; moderate functional impairment was registered in 2/51 (3.9%) and 20/107 (18.7%) children in both groups, and severe functional impairment in 10/107 (9.3%) patients of the group of comparison.

After 4 years functional ability according to CHAQ questionnaire in 14/17 patients in the main group was not impaired, in 2/17 – moderately impaired, and in 1 child minimal impairment was reported. In 70/100 (70%) patients in the group of comparison CHAQ index was equal to 0, in 13/100 (13%) it was above 1 point (suggesting a moderate and severe functional impairment); in 17/100 (17%) CHAQ index was within the range of 0.14-0.63, which corresponded to the minimum functional impairment.

After 5 years, the functional ability according to the CHAQ questionnaire was not impaired in 7/9 patients of the main group and 69/98 (70%) patients in the control group. In 2/9 and 7/98 (7%) children who received adalimumab and methotrexate, CHAQ index corresponded to the minimum functional impairment (0.14-0.63). Severe functional impairment (CHAQ index> 1.6) was registered in 8/98 (8%) patients from the comparison group.

Activity of the disease by the visual analog scale according to the doctor and subjective evaluation of the well-being according to the patient or his parents

The above-described pattern was also observed for the indicators of subjective health assessment according to the patient or his/her parents, and the disease activity according to the doctor.

Within 1 month after the first injection of adalimumab health assessment according to the child or his/her parents and disease activity according to the physician by VAS had decreased compared with the baseline values [Me (25%; 75%) - 73 (63; 87.75); 60.5 (50; 73,75) and 33 (12; 48); 30 (9; 40) points according to the patient's opinion/his or her parents and doctor before and after 1 month, respectively] and similar parameters in the control group [68 (50; 80) and 60 (46; 80); 68 (50; 80) and 61.5 (46; 80) points, respectively; $P < 0.0001$]. In the group of patients treated with methotrexate, change of the values of the above parameters did not occur.

After 3 months the disease activity according by VAS according to the doctor in the main group had decreased even more significantly [60.5 (50; 73,75) and 9.5 (0; 23,75) points before and after 3 months; p <0.0001] and did not exceed 5 points (corresponding to the normal reference range) in 87/214 (40.6%) patients; well-being by VAS according to the patient or his/her parents was significantly improved [73 (63; 87,75) and 12 (0; 27) points before and after 3 months; P <0.0001]. In the group of comparison indicators of the disease activity and health status according to the physician and parents did not change from the baseline and were significantly higher than in the main group [12 (0; 27) and 9.5 (0; 23,75) points - in the main group; 55.5 (41; 67) and 65 (50; 80) points - in the control group, p <0.0001].

After 6 months the disease activity by VAS according to the doctor continued to decline in the main group [60.5 (50; 73,75); 5 (0; 18) points before and after 6 months p <0.0001] and for the first time statistically significant decrease was observed in the control group [60 (46; 80) and 23 (12, 38) points before and after 6 months, respectively; P <0.0001]. This indicator in patients treated with adalimumab was significantly lower than in patients treated with methotrexate [5 (0; 18); 23 (12; 38) points, respectively; P <0.0001]. The general state of health of patients by VAS according to children and/or their parents was also improved in both groups [73 (63; 87.75); 6 (0 20.5) points - before and after 6 months in the study group; p <0.0001; 68 (50; 80); 32 (21, 46) points - before and after 6 months in the control group, p <0.0001]. However, patients treated with adalimumab, rated their health status and well-being significantly better than children receiving methotrexate.

After 1 year the disease activity by VAS according to the doctor continued to decline in the main group [60.5 (50; 73,75); 3.5 (0; 10.75) before and after 1 year; p <0.0001] and in the control group [60 (46; 80) and 1.5 (0; 23) before and after 1 year, respectively; P <0.0001]. Overall well-being of patients by VAS according to children's and/or their parents' opinion continued to improve in both groups [73 (63; 87.75); 4 (0; 13) - before and after 1 year in the main group, p <0.0001; 68 (50; 80); 23 (5; 34) - before and after 1 year in the control group, p <0.0001]. At that, patients treated with adalimumab, evaluated their condition and well-being significantly better than children, receiving methotrexate.

After 2 years, overall health status according to patient or parent's assessment had improved significantly in both groups of patients. At the same time the median of the above index in the main group was lower than in the comparison group [0 (0; 10.25) 5 (0; 24.75); p = 0.0010]. According to the doctor, the disease activity by VAS was low in both groups; the median corresponded to 0.

After 3 years the activity of the disease according to the physician and overall health status assessment according to the patient or his/her parents by VAS was evaluated as normal (<5 points) in 34/51 (66.7%) and 75/107 (70%) patients of the main and control groups, respectively. Median of the parameters for both groups was statistically equal to 0. Significant differences were observed between the groups.

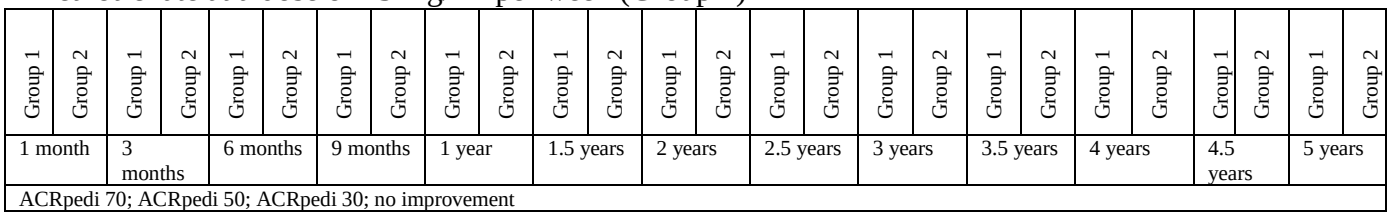
After 4 years good well-being according to the patient or his/her parents by VAS was recorded in 11/17 and 75/100 (75%) patients of the main group and the group of comparison [0 (0; 9) and 0 (0; 0), respectively]. According to the doctor, the disease remission (<5 points) took place in 12/17 and 77/100 (77%) patients treated with adalimumab and methotrexate, respectively. Activity of the disease persisted in 5/17 and 23/100 (23%) patients in the main and control group.

After 5 years of follow-up the median of the subjective general health assessment according to the patient (or his/her parent) by VAS remained equal to 0 in both groups. Remission of the disease was observed, according to the doctor, in 4/9 and 80/98 (82%) patients of the main group and the group of comparison.

Evaluation of treatment effectiveness according to ACRpedi criteria

After 1 month 87/54/25% of patients treated with adalimumab met the improvement criteria according to ACRpedi30/50/70, which was significantly higher ($p < 0.001$) than in patients treated with methotrexate (28/19/6%; Fig. 5). After 3 months ACRpedi30/50/70 response in the main group was 91/85/65% and it was still significantly higher ($p < 0.001$) than in the comparison group (37/23/7%). After 6 months, in patients treated with methotrexate effect of therapy was registered for the first time, accounting for 63/57/47% by ACRpedi30/50/70 criteria, but it was lower ($p < 0.001$) than in the main group (93/89/76%). After 9 and 12 months, the level of response according to ACRpedi criteria in patients receiving adalimumab, was still higher than during treatment with methotrexate: 95/92/82; 72/69/58% ($p < 0.001$) and 93/92/84; 78/73/67% ($p < 0.001$), respectively. After 2 years of treatment the difference between groups was reduced, 96/94/85 and 85/80/74% of patients ($p = 0.017$) met the improvement ACRpedi30/50/70 criteria. After 3 years, the difference in response was not detected: the response rate was 94/92/88 and 89/88/81% ($P = 0.650$) in patients treated with adalimumab and methotrexate, respectively. Over the next 2 years of follow-up efficiency of the study drugs according to ACRpedi criteria did not differ (see. Fig. 5).

Fig. 5. Improvement according to ACRpedi criteria in patients with juvenile idiopathic arthritis without systemic manifestations, treated with adalimumab (Group 1) and methotrexate at a dose of 15 mg/m^2 per week (Group 2)



Note (hereafter in Fig. 6, 7). "Group 1" — main group, "Group 2" — group of comparison.

Disease remission according to the C. Wallace criteria

Terms and frequency of achieving inactive disease/remission and its duration in the two groups were significantly different throughout the observation period. In 1 and 3 months from the initiation of treatment in the main group stage of inactive disease was reported in 32 (15%) and 71 (33%) patients, respectively. In the comparison group, no patients met the assessed criteria (Fig. 6). After 6 months the stage of the inactive disease/remission was registered in 82 (43%) patients treated with adalimumab, it was 4 times as high as this value in patients treated with methotrexate (9%). In 9 months a significant difference between the groups remained and it was 81 (49%) and 24 (19%), respectively. In 1 year the incidence of remission in the group of comparison showed two-fold increase and was 38%, it did not differ from the incidence in the main group (47%). After 2 years the difference between the two groups was completely leveled, stage of the inactive disease/ remission was reported in 56 (52%) and 60 (54%) patients ($p = 0.698$), respectively. In the next 3 years of observation, the study groups did not differ by the above index. Adalimumab induced stage of inactive disease/remission more quickly compared to methotrexate - 5 (3; 8) and 12 (6; 18) months, respectively ($P < 0.001$), and its duration was significantly longer than in the comparison group - 21 (14; 26) and 12 (8; 15) months, respectively ($p < 0.001$; see Figure 6).

Fig. 6. Incidence of inactive disease/remission development in patients with juvenile idiopathic arthritis without systemic manifestations, treated with adalimumab (Group 1) and methotrexate at a dose of 15 mg/m^2 per week (Group 2)

Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Baseline		1 month		3 months		6 months		9 months		1 year		1.5 years		2 years		2.5 years		3 years		3.5 years		4 years		4.5 years		5 years	
Active; not active																											

Additional findings

Effect of treatment with adalimumab and methotrexate at the dose of 15 mg/m^2 per week on the background therapy in patients with juvenile idiopathic arthritis without systemic manifestations

Adalimumab and methotrexate have NSAID-effect and hormone-sparing effect, but it is more pronounced for TNF-α inhibitor. High therapeutic effectiveness of adalimumab allowed to discontinue NSAIDs in 184 (86%) patients after 1 month, 212 (99%) – in 1 year of observation; to avoid prednisolone appointment *de novo* and increase of its daily dose in all patients; to reduce the dose of oral corticosteroids in 4 (20%) patients, and withhold their administration in one child; to discontinue intraarticular injections and intravenous infusion of glucocorticoids to all patients. Methotrexate exerts less pronounced anti-inflammatory and hormone-sparing effect properties, predetermined by its weaker therapeutic efficacy. After 1 month NSAIDs were discontinued in 60 (30%) after 1 year - 98 (49%) patients; prednisolone dose was reduced in 5 (28%), intraarticular and intravenous corticosteroids were discontinued in 176 (88%) and 100%, respectively.

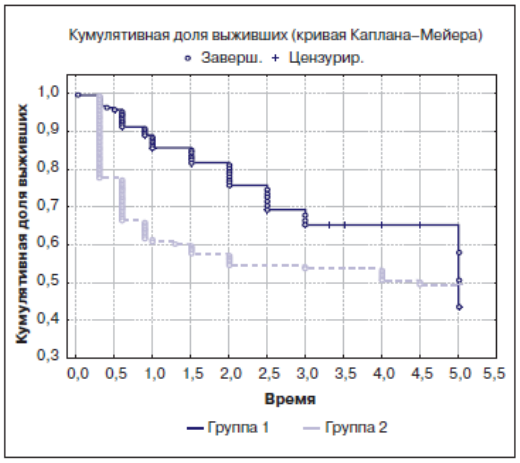
"Survival" of treatment with adalimumab and methotrexate at a dose of 15 mg/m^2 per week in patients with juvenile idiopathic arthritis without systemic manifestations

The cumulative effect of the "survival" of therapy with adalimumab was significantly higher than for the treatment with methotrexate throughout the observation period and in 6 months it accounted for 95 and 77%, in 1 year - 84 and 60%, after 2 years - 73 and 54%, in 3 years - 62 and 53%, in 4 years - 62 and 50%, after 5 years - 62 and 49% in the main group and the control group, respectively (Figure 7). Adalimumab and methotrexate were discontinued in 25.1% and 51% of patients (see Fig. 7).

During the first 6 months 19/215 (8.3%) and 50/200 (25%) patients discontinued their participation in the study, during the 1st year - 29/215 (13%) and 78/200 (39%), during the 2nd year of observations - 13/215 (6%) and 10/200 (5%) of patients receiving adalimumab and methotrexate (see Fig. 7).

The main reasons for the methotrexate discontinuation included primary (21%) and partial (11%) ineffectiveness; for adalimumab - organizational problems (7%), AEs (5.6%), primary lack of response to treatment (5.6%).

Fig. 7. "Survival" curve with adalimumab (Group 1) and methotrexate treatment at a dose of 15 mg/m^2 per week (Group 2) in patients with juvenile idiopathic arthritis without systemic manifestations



Cumulative fraction of survivors (Kaplan-Meier survival curve)		
Cumulative fraction of survivors	completed	censored
	Time	
	Group 1	Group 2

Adverse events

Adalimumab and methotrexate were well tolerated by 124 (58%) and 146 (73%) patients with JIA without systemic manifestations. AEs were reported in 90 (42%) and 54 (27%) patients, but they became the reason for the drug withdrawal only in 13 (6%) and 20 (10%) patients, respectively. The frequency of adverse events and serious adverse events during treatment with adalimumab was higher than with methotrexate (57.6 and 27.4; 8.5 and 1.9 per 100 patient-years; $p < 0.001$). Most often during treatment with adalimumab reactions at the injection site had occur (pain, 16.9 and 0.17 per 100 patient-years) and infectious AEs (35.3 and 20.7 per 100 patient-years; $p < 0.001$).

Infectious AEs included upper respiratory tract involvement - in 85 (39.5%) and 83 (41.5%), respiratory tract (bronchitis, pneumonia) – in 17 (7.9%) and 18 (9%) patients treated with adalimumab and methotrexate, respectively. Out of serious complications infections of the upper and lower respiratory tract (which were the reason for the admission to the hospital and appointment of antibacterial drugs), acute intestinal infections, urinary tract infections, generalized herpes infection, lymphadenitis, and hepatitis should be noted.

In patients treated with adalimumab, latent tuberculosis infection and pulmonary tuberculosis were more frequent, than with methotrexate therapy: 13 (6%) and 5 (2.5%) patients with a frequency of 3.2 and 0.9 per 100 patient-years, respectively ($p < 0.001$).

DISCUSSION

Evaluation of efficacy and safety of long-term treatment with TNFα inhibitors in patients with JIA is reasonably urgent. Marketing authorization of the drug of human monoclonal antibodies adalimumab in Russian Federation served as the basis for our study in 2008.

Evaluation of the effectiveness of adalimumab treatment

Prior to its registration for pediatric indications its efficacy and safety was studied in adults.

The PREMIER study [14] by the end of the 1st year of treatment showed 50% improvement according ACR criteria in 62% of patients receiving combination of methotrexate and adalimumab, and in 46% of patients treated with methotrexate. By the end of the 2nd year in 49% of patients who received combination therapy with genetically engineered biologic drugs and methotrexate, remission of the disease has been demonstrated.

In our study, we observed similar results. Global efficiency according to ACRpedi criteria of improvement and C. Wallace criteria for remission was significantly higher with adalimumab and methotrexate compared to the treatment with methotrexate alone for 3 years of observation. After 1 year, the level of response according to the ACRpedi50 criteria was 84 and 67% under the treatment with adalimumab and methotrexate, respectively. After 2 years, the stage of inactive disease/remission was reported in 52 and 54% of patients receiving adalimumab in combination with immunosuppressants and methotrexate, respectively.

Analysis of the Dutch registry for monitoring of patients with rheumatoid arthritis treated with adalimumab (DREAM) also showed a similar to our study efficiency. After 1 year satisfactory and a good response to treatment with adalimumab according to the criteria of the European League Against Rheumatism, EULAR was observed in 78% of patients [15].

The results of the largest open-labelled multicenter study of the effectiveness of adalimumab in combination with various immunosuppressants (ReAct) were published in 2007 [16]. The study included 6610 patients with rheumatoid arthritis, who were administered adalimumab at a dose of 40 mg/week subcutaneously for 12 weeks. By the 12th week of treatment in 69% of patients 20%, in 42% - 50%, in 18.4% - 70% improvement by ACR criteria was reported. According to EULAR criteria 33% of patients showed good response, while 83% - satisfactory response.

In our study the effectiveness of adalimumab after 3 months of treatment was also evaluated. The response rate according to the ACRpedi30/50/70 criteria was very high and was 91/85/65%.

In a double-blind randomized study ARMADA significantly more rapid decline of the disease activity during treatment with adalimumab compared to placebo was observed. Response to adalimumab therapy according to ACR50 criterion was observed in 55.2%, according to ACR70 - 26.9% of patients with rheumatoid arthritis [17].

In the Russian opened multicenter study of the adalimumab effectiveness in patients with rheumatoid arthritis already by the 2nd week of treatment (after the first injection of the drug), 20% improvement according to ACR criteria was reported in 34.3% of patients. Beginning from the 12th week, the effect of treatment (by ACR20) remained consistently high and was 86.3-87.9%. At the same time, the number of patients with more pronounced response to therapy with adalimumab (ACR50 and 70) progressively increased and by the 24th week it reached 66.7% and 26.3, respectively.

In our study, the first point was in determining the effectiveness was the 1st month. On this term, 87/54/25% of patients treated with adalimumab met the improvement criteria ACRpedi30/50/70. In 12 weeks, the level of response, according to ACRpedi30/50/70, had significantly increased and was 91/85/65%. The difference of our study is a higher percentage of patients meeting ACRpedi70 criteria, while there was no difference in the response level by ACRpedi30/50 criteria across trials.

In the Russian study by Karateeva D.E. et al., clinical improvement was accompanied by an increase of functional activity in patients with rheumatoid arthritis. HAQ index decreased from 1.9 ± 0.6 points at baseline to 1.1 ± 0.641 points to the 12th week and then

remained stable with a tendency towards further decrease (1.04 ± 0.8 points at the 24th week; p <0.001) [18].

In order to assess the functional activity of patients with JIA CHAQ questionnaire for the pediatric population was used. By the 12th week of treatment the mean value of the index of functional impairment in patients treated with adalimumab, significantly decreased from 1.15 ± 0.81 to 0.26 ± 0.45, in 24 weeks - to 0.20 ± 0.42 (p <0.0001).

Evaluation of the adalimumab treatment efficacy in children

There is a positive global experience with adalimumab for the treatment of JIA, including the results of numerous randomized clinical studies.

The study by D. J. Lovell, N. Ruperto et al. [19] had demonstrated 30% improvement in 67% of patients by ACRpedi criteria already after 2 weeks of treatment, in 77% - within 4 weeks. After 16 weeks of therapy 30% improvement according to ACRpedi criteria was achieved in 88% of children treated with adalimumab, and 95% of patients treated with adalimumab in combination with methotrexate; 70% improvement has been reported in 70% of patients [19].

In our study the majority of the patients of the main group received adalimumab in combination with immunosuppressive agents, and probably, in this regard, our findings are comparable with a group of patients treated with adalimumab with methotrexate in the study by D. J. Lovell, N. Ruperto et al. In 3 months, the level of ACRpedi30/70 response in our study was 91/65%, after 6 months - 93/76%.

In another study by the same authors after 48 weeks of treatment, response rate according to ACRpedi30/50/70 criteria was 73/61/24% [20].

In our study, the effectiveness of adalimumab was higher than in the study by D. J. Lovell, N. Ruperto et al. After 1 year of therapy, 93/92/84% of patients met the ACRpedi30/50/70 improvement criteria. Apparently, this is due to the fact that we had included along with patients with polyarticular JIA patients with resistant oligoarticular arthritis into the study.

The study by D. J. Lovell et al. of the effectiveness of prolonged use of adalimumab in children with polyarticular JIA had demonstrated that after 104 weeks 40% of children with JIA met the ACRpedi100 criteria [20]. We have shown that in 2 years (104 weeks) 52% of patients met the criteria of inactive stage of the disease.

D. J. Kingsbury et al. had evaluated the efficacy of adalimumab in the treatment of oligo- and polyarticular JIA in patients aged 2 to 5 years old. After 12 weeks, 91% of patients had positive clinical response (ACRpedi30), which by the end of the 24th week of observation was maintained in 84% of patients [21]. In our study, 33/214 (15%) patients under the age of 5 years old had participated. After 12 weeks of treatment with adalimumab, the response rate by ACRpedi30 criterion was 91%, in 24 weeks - 93%, which was comparable with the results by D. J. Kingsbury et al.

The results of the six-year study by D. J. Lovell, N. Ruperto et al. clearly demonstrated high efficiency of long-term therapy with adalimumab. With increasing duration of the use of the drug, especially in combination with methotrexate, efficiency of adalimumab was not reduced [22]. In our study, long-term use of adalimumab were not accompanied by the escape phenomena. After 3 years of treatment inactive stage of the disease/remission was reported in 69%, in 4 years - 59%, in 5 years - 44% of patients.

In the available literature, we did not find sufficient information on the "survival" of therapy with adalimumab. In a multicenter, randomized, double-blind, 48-week, placebo-controlled study D. J. Lovell, N. Ruperto et al. evaluated the "survival" of therapy in patients with JIA who continued into the double-blind phase of the study. As a result, 32-week treatment was completed by 96% of patients, 4% withdrew from the study for various reasons

(1 patient - due to violations of the study protocol, 1 patient withdrew his consent for the study, 3 - for other reasons) [20]. With long-term (6 years) observation D. J. Lovell, N. Ruperto et al. had revealed that the exacerbation of the disease was observed in 43 and 37% of patients treated with adalimumab or adalimumab in combination with methotrexate, and 71 and 65% of placebo-treated patients without/with methotrexate [20, 22].

In our study, the cumulative "survival" of adalimumab therapy was 95% in 6 months, 84% - after one year, 73% - after 2 years. Throughout the whole observation period, 25% of patients had discontinued treatment. During the first 6 months of the study 8.3% dropped out, the first year - 13%, the second year - 6% of patients. The main reasons for the adalimumab discontinuation include organizational problems (7%), adverse events (5.6%) and primary lack of efficacy (5.6%).

Evaluation of the safety of adalimumab treatment

In the safety analysis of adalimumab in a multicenter, randomized, double-blind, placebo-controlled 48-week study, presented by D. J. Lovell, N. Ruperto et al., was shown that adalimumab generally is well tolerated by patients with JIA. The most common adverse events were infections (mainly acute respiratory). 4 patients treated with adalimumab and 2 - with placebo had serious side effects during the blind phase of the study. Cases of tuberculosis and opportunistic infections have been reported [19].

According to other data by the same authors, cases of severe miliary and extrapulmonary tuberculosis were reported [22]. Cases of invasive opportunistic infections are also documented (disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis, listeriosis) [20].

The ReAct study in 6610 adult patients with rheumatoid arthritis serious infectious complications (including active TB) were reported in 3.1% of patients, demyelinating disease - in 0.06%, systemic lupus erythematosus - in 0.03% [16].

Analysis of the tolerability of TNFα inhibitor therapy in our study had shown that adalimumab and methotrexate are well tolerated by 58 and 73% of patients with JIA without systemic manifestations. AEs were reported in 42 and 27% of patients, but they became the reason for the drug withdrawal only in 6 and 10%, respectively. Most often on the background of anti-TNF-therapy reactions at the injection site had developed (pain, 16.9 and 0.17 per 100 patient-years) and infectious AEs (35.3 and 20.7 per 100 patient-years; $p < 0.001$). Pulmonary tuberculosis had occurred in 5/215 (2.3%) patients: focal - in 1, disseminated - in 1, disseminated pulmonary tuberculosis, tuberculosis of the intrathoracic lymph nodes and pleural effusion - in 1, infiltrative tuberculosis - in 2 children. The cases of death from tuberculosis, as well as severe opportunistic infections and autoimmune diseases in our study were not reported.

Thus, in this study, efficacy of adalimumab in combination with immunosuppressants was slightly higher than that of adalimumab monotherapy in studies by other authors [18]. The efficacy of adalimumab in combination with immunosuppressants (88% with methotrexate) turned out to be comparable with data of similar studies [19, 20, 22].

It should be noted that all children were administered adalimumab at a dose of 40 mg once per 2 weeks regardless of the child's age and weight. This is due to the fact, that the study was launched prior to the registration of the drug for pediatric indications, and we had used treatment regimen, registered for adult patients with rheumatoid arthritis. D. J. Lovell, N. Ruperto et al. had demonstrated that dose of the drug does not affect its efficacy or tolerability. In the first period of the extended opened phase, the authors evaluated the efficacy of adalimumab at a dose of 24 mg/m^2 administered once per week. In the next phase, children weighing less than 30 kg were administered TNFα inhibitor at a fixed dose of 20 mg once in two weeks in children weighing 30 kg and above – at the dose of 40 mg once in two

weeks [22]. Differences in the efficacy and tolerability were not observed at different dosages. Data, demonstrated by D. J. Lovell, N. Ruperto et al., allow us to compare our results with those of other researchers.

Study limitations

The main limitation of the study worth mentioning is the absence of randomization at the distribution into groups, which would allow to minimize bias and biased researchers.

CONCLUSION

TNFα inhibitor adalimumab exerts more rapid and pronounced anti-inflammatory effect compared to classical immunosuppressant methotrexate. Within 1 month after the first injection, adalimumab provided a significant reduction in the clinical and laboratory parameters of the disease activity, improvement of the joint function and overall health in 73% of patients. Methotrexate has slower and less pronounced anti-inflammatory effect. Against the background of methotrexate monotherapy reliable dynamics of clinical and laboratory parameters of the disease activity and improvement of the functional status of patients was registered only after 6 months from the initiation of treatment. Anti-TNF-therapy in a short time provides improvement and recovery of functional activity of the joints as well as daily activity of children with juvenile idiopathic arthritis without systemic manifestations. Functional activity of children treated with methotrexate, throughout all the observation period (5 years), was significantly lower than with adalimumab. The cumulative "survival" with adalimumab therapy in patients with juvenile idiopathic arthritis without systemic manifestations was significantly higher than that in methotrexate treatment and is associated with a significantly lower risk of treatment discontinuation with regard to its ineffectiveness.

CONFLICT OF INTERESTS

E.I. Alexeeva – received research grants from pharmaceutical companies Roche, Abbott, Pfizer, Bristol-Myers Squibb, Centocor, Novartis.
T.M. Bzarova – received research grants from pharmaceutical companies Roche, Pfizer.
S.I. Valieva - received research grants from pharmaceutical companies Roche, Bristol-Myers Squibb.
R.V. Denisova - received research grants from pharmaceutical companies Roche, Centocor, Novartis.
T.V. Sleptsova - received research grants from pharmaceutical company Centocor.
O.L. Lomakina, K.B. Isaeva, E.G. Chistyakova, Chomakhidze A.M., A.N. Fetisova have indicated they have no financial support/ conflict of interests to declare.

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