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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

CLINICAL-DIAGNOSTIC FEATURES AND EFFICACY OF ANTI-CYTOKINE THERAPY OF JUVENILE IDIOPATHIC ARTHRITIS

Speciality: 3220.01 – "Pediatrics"

Field of science: Medical Sciences

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GENERAL DESCRİPTİON OF THE WORK

Relevance of the topic. One of the pressing issues in pediatric rheumatology is chronic inflammatory joint diseases in children. Juvenile idiopathic arthritis (JIA) is a polygenic, multifactorial disease with a highly complex immune-aggressive pathogenesis. According to current concepts, JIA represents a heterogeneous group of disorders that include various nosological forms with complex etiopathogenesis and immunogenetic origins, differing patterns of disease course, and variable prognosis and outcomes of the pathological process[1,2].

The clinical manifestations and inflammatory mechanisms of JIA differ in certain respects from those observed in adult rheumatoid arthritis. A characteristic feature of juvenile arthritis is growth retardation, first described by George Frederic Still in 1897. Growth impairment in children with this disease is characterized by decreased growth velocity, dwarfism, as well as local developmental abnormalities of the joints involved in the pathological process. Growth delay observed in patients with JIA, particularly in those receiving hormonal therapy, has significant social implications and ultimately leads to psychosocial maladaptation.

The term JIA refers to a group of chronic arthritides that occur in children and share certain common characteristics. According to the current classification proposed by the International League of Associations for Rheumatology (ILAR, 2007), disease categories are defined based on clinical and laboratory data. Some of these categories are further subdivided into different forms[3]. Depending on the number of affected joints, the presence of extra-articular manifestations, systemic symptoms, as well as serological and genetic factors, JIA is classified into

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[2] Sur, L.M. Different chronic disorders that fall within the term juvenile idiopathic arthritis / L.M. Sur, R. Gaga, E. Duca [et al.] // Life (Basel). 2021; 11(5):398. doi: 10.3390/life11050398.

[3] Martini, A. Juvenile idiopathic arthritis / A. Martini, D.J. Lovell, S. Albani [et al.] // Nat Rev Dis Primers. 2022; 8(1): 5. doi: 10.1038/s41572-021-00332-8

oligoarticular, polyarticular, systemic, psoriatic, enthesitis-related, and undifferentiated arthritis[4]. These diseases are united by a tendency toward a chronic progressive course, which significantly affects the child's quality of life and carries a high risk of early disability[5]. In addition, the Pediatric Rheumatology International Trials Organization (PRINTO) has described the initial steps of a process aimed at developing a new classification of JIA[6].

The global incidence of juvenile idiopathic arthritis (JIA) ranges from 2 to 16 cases per 100,000 children. In different countries, the prevalence of JIA varies between 0.05% and 0.6%. The disease occurs in all age groups, is registered worldwide across all climatic and geographic zones, and affects all racial and ethnic groups. Girls are more frequently affected than boys. The mortality rate ranges from 0.5% to 1%[7]

Among the most significant endogenous factors is genetic predisposition, manifested by the expression of specific antigens of the major histocompatibility complex.

The pathogenetic picture of JIA is based on a complex combination of genetically determined and acquired disturbances of immunoregulatory mechanisms which, in response to various pathogenic stimuli, activate the immune system[8] A so-called malfunction of the immune system leads to the production of antibodies against joint tissues, primarily against the synovial membrane, which in turn triggers autoimmune inflammation.[4]

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[4] Zaripova, L.N. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches / L.N. Zaripova, A. Midgley, S.E. Christmas [et al.] // Pediatric Rheumatology (2021) 19:135. https://doi.org/10.1186/s12969-021-00629-8.

[5] Məmmədova, Z.U. Yuvenil artritlər və həyat keyfiyyəti anlayışı // Azərbaycan təbabətinin müasir nailiyyətləri, №4, 2019, 92-95.

[6] Martini, A. Toward new classification criteria for juvenile idiopathic arthritis: first steps, pediatric rheumatology international trials organization (PRINTO) international consensus / A. Martini, A. Ravelli, T. Avcin [et al.] // J Rheumatol. 2019; 46(2):190-197. DOI:https://doi.org/10.3899/jrheum.180168

[7] Саламзаде, Г.З. Влияние тоцилизумаба на клинико-лабораторные показатели при ювенильном ревматоидном артрите / Г.З.Саламзаде, С.Н.Мусаев // Azərbaycan Təbabətinin Müasir nailiyyətləri (Bakı), 2016, №2, səh.303-305.

[8] Rezus, E. From Pathogenesis to Treatment-New Perspectives in Rheumatology / E. Rezus, C. Codreanu // Int J Mol Sci. 2023 Oct 26;24(21):15590. doi: 10.3390/ijms242115590.

According to the ILAR classification proposed by the International League of Associations for Rheumatology, one of the subtypes of JIA is systemic-onset juvenile arthritis (sJIA). It is a chronic childhood disease characterized by the presence of quotidian fever persisting for at least two weeks, arthritis, rash, serositis, lymphadenopathy, and hepatosplenomegaly. sJIA is an autoimmune disease of unknown etiology with a polygenic mode of inheritance and an autoinflammatory component. The severity of the disease is обусловед by the development of serious complications, including serositis along with persistent polyarthritis leading to severe functional impairment. Currently, approximately 5–15% of all cases of JIA are attributed to sJIA[9].

The goal of therapy for sJIA is to achieve control of inflammatory activity and to prevent complications associated both with the disease itself and with aggressive treatment, such as growth retardation, destructive joint changes, and functional impairment.

Systemic manifestations of the disease and inflammatory changes in the joints persist despite ongoing therapy, leading to a high risk of joint destruction and dwarfism[10].

Unfortunately, the advances achieved in the treatment of JIA have not made it possible to slow disease progression in the majority of patients. At the same time, in recent years there has been a trend toward an increasing number of cases characterized by progressive joint damage, leading to disability and reduced quality of life[11]

Object and subject of research:

The object of the study were 80 patients diagnosed with juvenile idiopathic arthritis. The clinical diagnostic features, quality of life and

[9] Young, D. K. Differential diagnosis of juvenile idiopathic arthritis / D. K. Young, V. J. Alan, C. Woojin // J. Rheum. Dis. 2017; 24 (3): 131-137. DOI: 10.4078/jrd.2017.24.3.131. https://doi.org/10.4078/jrd.2017.24.3.131

[10] Vastert, S.J. Editorial: toward Personalized Treatment for Systemic Juvenile Idiopathic Arthritis / S.J. Vastert, P.A. Nigrovic //Arthritis Rheumatol. 2018; 70 (8): 1172–1174. doi: 10.1002/art.40501.

[11] Məmmədova, S.N. Yuvenil revmatoid artritli uşaqlarda mədə-bağırsaq simptomları və onların həyat keyfiyyəti ilə əlaqəsi / S.N. Məmmədova, L.Ə. Hidayətova, Z.U. Mamedova // Azərbaycan Pediatriya jurnalı, 1, №3, 2023

effectiveness of anti-cytokine therapy were studied as the subject of the study in these patients.

Purpose of the study:

Study of clinical-diagnostic features of juvenile idiopathic arthritis and assessment of the effectiveness of anti-cytokine therapy.

The tasks of the research:

1. To assess the disease activity in children with juvenile idiopathic arthritis using the DAS28 index.

2. To study the clinical and diagnostic significance of interleukin-6 in children with juvenile idiopathic arthritis.

3. To evaluate the effectiveness of the IL-6 inhibitor tocilizumab and its impact on clinical and laboratory parameters in the treatment of patients with juvenile idiopathic arthritis.

4. To study the effect of tocilizumab on the quality of life of patients with juvenile idiopathic arthritis therapy using the CHAQ, PedsQL Generic Core Scale and PedsQL Rheumatology Module questionnaires.

5. To study the relationships between clinical and laboratory parameters in children with juvenile idiopathic arthritis.

Research methods: Research methods include clinical, laboratory, instrumental, and statistical methods.

Main provisions of the dissertation submitted for defense:

1. High levels of IL-6, IgA, IgM and IgG in patients with JIA indicate the severity of the joint syndrome.

2. The use of the IL-6 inhibitor tocilizumab leads to a significant effective normalization of the joint condition in comparison with standard basic therapy in patients with JIA.

3. Tocilizumab significantly reduces laboratory markers of disease activity compared with standard basic therapy in patients with juvenile idiopathic arthritis

4. In patients with JIA, tocilizumab therapy has a significant positive effect on extra-articular complications of the disease.

5. The use of the tocilizumab improves the quality of life of patients with JIA.

Scientific novelty of the work:

A comprehensive evaluation of the efficacy of the IL-6 inhibitor tocilizumab was conducted in various forms of juvenile idiopathic arthritis, with particular focus on its effects on joint syndrome, laboratory markers of disease activity, extra-articular complications, and the quality of life of patients with JIA based on the CHAQ, PedsQL Generic Core Scale, and PedsQL Rheumatology Module questionnaires.

.The relationships between clinical and laboratory parameters were studied, and the sensitivity and specificity of laboratory indicators as diagnostic markers in juvenile idiopathic arthritis were determined.

Practical significance: The use of tocilizumab will expand therapeutic options and improve the quality of life of patients with juvenile idiopathic arthritis, particularly in those refractory to standard basic therapy.

Also, anti-cytokine therapy, due to the selectivity of action, will help to avoid undesirable side effects of hormonal and cytostatic drugs.

Assessment of the quality of life of patients with juvenile idiopathic arthritis based on specialized questionnaires is an important component of clinical monitoring and has high practical significance in determining the effectiveness of the therapy administered.

Approval of research work: The results of the scientific work were presented on November 22-23, 2018 at the XXII Republican Scientific Conference of Doctoral Students and Young Scientists, on May 6-8, 2024 at the Scientific and Practical Congress "Actual Problems of Medicine", on May 6-8, 2025 at the Medical Conference dedicated to the 102nd birthday of national leader Heydar Aliyev and the 95th anniversary of Azerbaijan University, on May 6-8, 2026 at the “Summit of Healthcare and Technology” dedicated to the Year of Urban Planning and Architecture.

Application of the research: The results of the study are used in the examination and treatment of children with juvenile idiopathic arthritis in the Educational and Therapeutic Clinic of the

Azerbaijan Medical University, and are also incorporated into the research and curriculum of the Department of Children's Diseases II of the Azerbaijan Medical University.

The organization in which the dissertation work was carried out: Dissertation work was performed at the Educational-Therapeutic Clinic of the Azerbaijan Medical University, the Immunological Laboratory of the Azerbaijan Medical University.

Published scientific works: On the topic of the scientific dissertation, 26 scientific works were published, including 10 articles 16 theses.

Structure and Scope of the Dissertation. The dissertation is presented in Russian and comprises 183 pages (201 910 characters). It consists of an Introduction (11 200 characters), a Literature Review (56 550 characters), Materials and Methods (13 200 characters), Chapter III (29 270 characters), Chapter IV (20 150 characters), Chapter V (37 360 characters), a Conclusion (32 020 characters), Conclusion (1 720 characters), Practical Recommendations (440 characters), a list of references, and a list of abbreviations. The dissertation is illustrated with 32 tables and 33 figures. The bibliography includes 220 sources.

MATERIALS AND METHODS OF THE RESEARCH

The study was conducted at the Department of II Children's Diseases of AMU, in the Educational and Therapeutic Clinic of the Azerbaijan Medical University, the Scientific Research Immunological Laboratory of the Azerbaijan Medical University in accordance with the set goals and objectives. To achieve the set goals and objectives, 100 children aged 2 to 18 years were involved in the examination. 80 of them were children with the determined diagnosis of JIA. 20 practically healthy children formed the control group.

All children included in the study were selected according to the inclusion criteria.

The inclusion criteria for the study were:

• Established diagnosis of JIA (according to the ILAR 2007 classification criteria);

• Age from 2 to 18 years;

• Patients with an active phase of JIA (DAS28> 2.6);

•Absence of pathologies in various organ systems accompanied by severe impairment of their functions.

The criteria for exclusion from the study were:

• Unconfirmed diagnosis of JIA;

• Other diseases accompanied by joint syndrome

•The presence of diseases that are a contraindication to the administration of immunosuppressive therapy

The condition of the joints was assessed using three parameters: tenderness, swelling, and stiffness. Joint tenderness was determined using the Ritchie index: 0 - no pain, 1 - the patient reports pain upon palpation, 2 - the patient winces, 3 - the patient pulls the limb away from the doctor's hands. The presence of joint swelling was determined as follows: 0 - no swelling, 1 - swelling present (visual or palpable).

To assess the condition of the body, all children underwent a complete blood count on the XT-4000 device by SYSMEX, manufactured in the Russian Federation, using the Stromatolyser - 4DS, FFS - 800A reagents. The erythrocyte sedimentation rate was determined by Westergren. All patients underwent a biochemical blood test. In order to detect bone metabolism disorders, the content of ionized calcium in the blood (Ca++) was determined on the Beckman Coulter device (USA). Serum iron (Fe) was determined using the Avsat kit (USA). To assess the functional status of the liver, the levels of liver transaminases ALT, AST were determined. The level of C-reactive protein (CRP) was also measured. For the clinical diagnosis of the disease, rheumatoid factor (RF) was determined.

Immunological studies were also performed. Antinuclear antibodies (ANA) were also determined by the indirect immunofluorescence method. Anti-cyclic citrullinated peptide (ACCP) were determined in the blood serum of the children under study. The analysis was performed by the ELISA method using the Cobas E 170 analyzer from Rosh (France). Antibodies reacting with double-stranded DNA (Anti-ds-DNA) and single-stranded DNA (Anti-ss-DNA) were also determined. Immunological studies also included the determination of interleukin-6 (IL-6), immunoglobulins

of class A, M, G. Serum antibodies - IgA, IgG, IgM were determined using reagents manufactured by the company "Hema-Medica" by the ELISA on the "Medispec 6000 (RT-6000, Microplate Reader)" device. The serum IL-6 level was also determined by the ELISA method on the Medispec-6000 device (R6T-6000, Microplate Reader) using reagents manufactured by INVITROGEN. The study used a solid-phase sandwich-type ELISA. The IL-6 level was determined by the antigen-antibody reaction, as well as by the enzymatic process. The color intensity recorded during the reaction was estimated in direct proportion to the amount of IL-6 in the serum.

The X-ray stage of arthritis was determined according to the Steinbrocker classification. The study was conducted using the Plexa Vision device from Hiladzu (Japan).

The children were assessed for activity of JIA using the DAS28 (Disease Activity Score 28) scale recommended by the American College of Rheumatology (ACR), which is the most commonly used scale in everyday clinical practice. By DAS28 scale was assessed the condition of 28 peripheral joints using 4 baseline parameters: the number of tender joints, the number of swollen joints, the overall health assessment by the patient using a visual analogue scale, and the erythrocyte sedimentation rate.

Patients with JIA were assessed for quality of life using the Childhood Health Assessment Questionnaire (CHAQ), Pediatric Quality of Life Inventory (PedsQL) Generic Core Scale, and a special questionnaire, Pediatric Quality of Life Inventory (PedsQL) Rheumatology Module.

The health status was assessed using a special CHAQ questionnaire, including 30 questions on the following 8 scales: "dressing & grooming", "arising", "eating", "walking", "hygiene", "reach", "grip", "activities". Each question contains 4 answer options: without any difficulty, with some difficulty, unable to do, inability to perform. The functional impairment index value varies from 0 to 3. The higher the value, the worse the functional ability. CHAQ index < 1.5 corresponds to minimal and moderate impairments, CHAQ index > 1.5 — severe.

PedsQL Generic Core Scale is a validated general questionnaire for assessing quality of life. It consists of 23 questions on the

following 4 scales: physical functioning scale, emotional functioning scale, social functioning scale, school functioning scale.

A specialized questionnaire for assessing the quality of life of a child with rheumatic diseases, the PedsQL Rheumatology Module, consists of 22 questions, which are combined into 5 scales: pain/morning stiffness scale, daily activities assessment scale, treatment tolerance scale, worry scale, and communication scale.

The point assessment of both questionnaires in the range from 0 to 4 (0 - never, 1 - almost never, 2 - sometimes, 3 - often, 4 - almost always) is made on the basis of the answer received. The process of recoding both questionnaires is the translation of the answers on the Likert scale into points, which constitute a quantitative assessment of the quality of life on a 100-point scale. The higher the final value, the higher the quality of life of the child.

The research is classified: by volume – selective; by method – observational; by material – prospective; by location – clinical; by design – analytical; by type – scientific; by time – cross-sectional and longitudinal research.

All obtained data were loaded into a special statistical map, brought into a single system of measurements of quantitative and digitally coded qualitative data. For statistical processing, the methods of variation, dispersion, discriminant, correlation and ROC analyses were used. To compare transverse quantitative data, the methods of variation statistics were used: parametric t-Student-Bonferroni criterion, nonparametric - Mann-Whitney rank U-test, Kruskal-Wallis median H-test, as well as Wilcoxon rank W-test in longitudinal studies. Qualitative features were compared by the Pearson Chi-Square $\chi 2$-test. The ANOVA test was used in the dispersion analysis, with statistical evaluation of the results by the F-Fisher criterion. ROC analysis was performed to assess the diagnostic value of statistically significant factors. The relationship between qualitative and quantitative indicators was determined using nonparametric correlation analysis ρ (Rho)-Spearman. In all cases, the "0" hypothesis was rejected at $p < 0{,}050$. Calculations were performed in the SPSS-26 statistical package.

RESEARCH RESULTS AND THEIR DISCUSSION

We examined 100 children, 80 of whom are patients with diagnosis of JIA (boys - 51.2%, girls - 48.8%), 20 - formed the control group (boys - 25%, girls - 75%). The average age of children in the control group was 9.1 ± 0.8 years, patients with JIA - 9.6 ± 0.5 years.

Then, depending on the course of the disease, we divided all patients with JIA into patients with articular syndrome without pronounced systemic manifestations (87.5%) and patients with a systemic course (12.5%).

Among the children with the articular form examined by us, boys (50%) and girls (50%) were in equal numbers. Among the children with the systemic form, girls predominated - 60%, and boys made up 40%. The average age of patients with the articular form was 9.7±0.5 years, patients with the systemic variant of the course - 9.2±1.3 years.

According to the treatment method, we divided the patients into two groups: Group I consisted of patients who received standard basic therapy, Group II - patients who received the drug tocilizumab. Among the patients in Group I, boys accounted for 53.0%, girls - 47.0%, Group II - boys - 28.6%, girls - 71.4%. The average age of patients in Group I was 9.4±0.5 years, in Group II 10.6±1.1 years.

We performed complete blood test, biochemical, and immunological blood tests on all children.

When comparing acute-phase parameters in the examined children, the following pattern was observed. The mean erythrocyte sedimentation rate (ESR) in the control group (8.9 ± 0.9 mm/hr) and in the JIA group (44.3 ± 3.5 mm/hr) showed a statistically significant difference ($p_u < 0.001$*). A significant difference was also found between children with the articular form and the systemic form of the disease ($p_u = 0.031$*). The mean C-reactive protein (CRP) levels in the control group (3.5 ± 0.2 mg/L) and in the JIA group (43.7 ± 5.4 mg/L) also differed markedly ($p_u < 0.001$*). When comparing average structural values in patients with the articular form and the systemic form higher CRP levels were observed in children with the systemic form of the disease; however, the difference did not reach statistical significance ($p_u = 0.363$).

Anemia is one of the common complications of rheumatic diseases. In this case, it refers to anemia of chronic disease (ACD). When comparing the red blood cell (RBC) count and hemoglobin (HGB) levels in the control group (RBC: $4.7 \pm 0.0 \times 10^{12}$/L; HGB: 12.6 ± 0.1 g/dL) and the JIA group (RBC: $4.4 \pm 0.1 \times 10^{12}$/L; HGB: 11,7±0,9g/dL), statistically significant differences were found for both parameters (RBC $p_u = 0.004$*; HGB $p_u < 0.001$*). In the articular form and the systemic form statistically, significant intergroup differences were observed for HGB ($p_u = 0.011$*), whereas RBC did not show a statistically significant difference ($p_u = 0.057$). The mean serum iron (Fe) level in the control group was 36.4 ± 7.0 µg/dL, while in the JIA group it averaged 32.7 ± 4.3 µg/dL ($p_u = 0.484$). In ACD, serum iron levels are typically reduced or within the normal range, reflecting functional iron deficiency. This explains the lack of response to iron supplementation.

In the biochemical blood analysis, the mean level of ionized calcium (Ca^{++}) in children of the control group was 1.2 ± 0.0 mmol/L, whereas in patients with JIA it was 1.0 ± 0.0 mmol/L, demonstrating a statistically significant difference ($p_u < 0.001$*). The concentration of Ca^{++} is considered an important marker of bone metabolism. Its decrease is observed in bone resorption, which may be induced by pharmacological treatment, particularly the use of glucocorticosteroids. When comparing the mean Ca^{++} levels between the articular and systemic forms of the disease, no statistically significant intergroup difference was found ($p_u = 0.749$).

In the immunological blood analysis, the mean level of ACCP in the control group was 9.6 ± 0.5 U/L, whereas in patients with JIA the mean value was 36.2 ± 17.2 U/L, demonstrating a statistically significant difference ($p_u = 0.001$*). In pediatric practice, the early appearance of these antibodies is of considerable importance, as in the absence of a full set of JIA classification criteria, they serve as an important diagnostic marker. The concentration of ACCP also allows assessment of disease severity and prognosis, since the presence of these antibodies is considered one of the factors associated with disease progression. In children with the articular (39.9 U/L) and systemic (6.0 U/L) forms, statistical analysis of average structural values did not reveal a statistically significant difference ($p_u = 0.366$).

We also determined the level of IL-6. When comparing its mean values in the control group (1.4 ± 0.2 pg/mL) and the JIA group (6.2 ± 1.4 pg/mL), a statistically significant difference was observed (p_u = 0.025*). However, comparison between the articular form and the systemic form did not reveal statistically significant differences (p_u = 0.647).

In assessing immune status parameters, we determined the levels of immunoglobulins A, M, and G. In the control and JIA groups, the mean values of IgA (p_u = 0.021*) and IgM (p_u < 0.001*) showed statistically significant intergroup differences, whereas IgG did not (p_u = 0.175). When comparing the mean immunoglobulin levels between patients with the articular and systemic variants of the disease course, no statistically significant differences were found (IgA p_u = 0.475; IgM p_u = 0.760; IgG p_u = 0.476).

As noted before, all patients with JIA had their joints assessed based on clinical indicators, and X-ray examination of the affected joints was also performed to identify arthritis and determine its stages.

Thus, during X-ray examination of the joints of the hand, stage I was diagnosed in 12.5% of patients, stage II in 3.8%, and stage III in 2.5% of patients. With regard to the wrist joints, the following results were obtained: stage I was diagnosed in 13.8% of patients, stage II – in 2.5%. Arthritis of the elbow joints at stage I was observed in 8.8%, at stage II – in 1.3% of patients. X-ray examination of the shoulder joints revealed stage I arthritis in only 6.3% of patients. Arthritis was most commonly diagnosed in the knee joints. Stage I was observed in 32.5% of patients, and stage II in 7.5%. The ankle joints also had a higher incidence of arthritis compared to other joints. Stage I arthritis was observed in 18.8% of patients, and stage II arthritis was observed in 6.3%. Arthritis was least common in the temporomandibular joints. Only 1.3% had stage I arthritis.

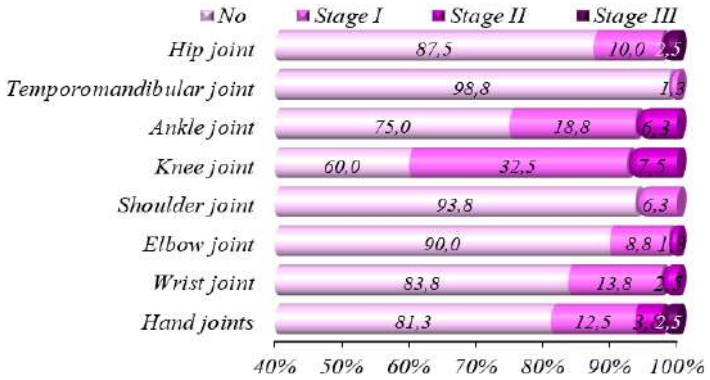
Arthritis of the hip joints at stage I was observed in 10%, and stage III arthritis was observed in 2.5%.

The stages of arthritis of the affected joints in patients with JIA are shown in the graph.2.

Further, assessing the degree of disease activity using the DAS28 index in patients with JIA, we obtained the following results:

the average value was 4.55±0.10, with a low degree being established in 7.5% of patients, a moderate degree in 68.8%, and a high degree in 23.8% of patients. The DAS28 index in the group of patients with the articular form averaged 4.55±0.11, while in the group of patients with the systemic form it was 4.53±0.29. There was no significant intergroup difference (p_u=0.988).

We then assessed patients' quality of life using three questionnaires. The CHAQ questionnaire's scores for all eight scales and the overall score (p<0.001*) showed significant intergroup differences before treatment (table1).



Graph 1. Radiographic stages of arthritis of the affected joints

Table1

Quality of life according to the CHAQ questionnaire

	Treatment								
	Basic				Tocilizumab				
	M	Me	Q1	Q3	M	Me	Q1	Q3	p_u
CHAQ (general score)	1.33	1.20	1.20	.50	1.81	1.80	1.50	2.10	<0,001*
1. Dressing&grooming	1.67	1.50	1.30	.80	2.43	2.40	2.00	2.80	<0,001*
2. Arising	1.13	1.00	1.00	.00	1.57	1.50	1.00	2.00	0,030*
3. Eating	1.56	1.30	1.30	2.00	2.04	1.85	1.70	2.30	0,003*
4. Walking	0.83	0.50	0.50	.50	1.57	1.50	1.50	2.00	0,001*
5. Hygiene	0.98	1.00	0.80	.00	1.38	1.50	1.00	1.50	0,014*
6. Reach	1.42	1.30	1.30	.50	1.83	1.80	1.50	2.00	0.011*
7. Grip	1.08	1.00	0.80	.20	1.49	1.40	1.20	1.60	0,002*
8. Activities	2.03	2.00	1.80	2.20	2.26	2.20	2.20	2.40	0,020*

Note: p_u – statistical significance of differences between group parameters was assessed using the Mann–Whitney U test. * – -«0»-hypothesis is rejected.

Thus, children prescribed tocilizumab had lower quality of life scores on the CHAQ questionnaire before treatment.

Patients' quality of life was assessed using the PedsQL Generic Core Scale and PedsQL Rheumatology Module questionnaires (table2).

Table2

Quality of life according to the PedsQL Generic Core Scale, PedsQL Rheumatology Module questionnaires

	Treatment								p_u
	Basic				Tocilizumab				
	M	Me	Q1	Q3	M	Me	Q1	Q3	
PedsQL Generic Core Scale	40.7	40.3	36.4	46.3	34.3	34.3	32.7	37.3	0.012*
1. Phisical functioning	16.7	15.6	9.4	25.0	10.9	11.0	9.4	15.6	0.114
2.Emotional functioning	66.3	70.0	60.0	75.0	60.4	62.5	50.0	70.0	0.111
3. Social functioning	54.3	65.0	50.0	65.0	41.8	40.0	40.0	50.0	0.016*
4. School functioning	25.3	20.0	15.0	30.0	23.9	25.0	20.0	30.0	0.894
PedsQL Rheumatology Module	66.2	65.9	64.7	70.9	60.8	61.0	59.3	66.8	0.060*
1. Pain/stiffness	28.8	31.3	25.0	31.3	24.6	25.0	18.8	25.0	0.026*
2. Daily activities	70.0	70.0	65.0	75.0	62.1	60.0	55.0	70.0	0.018*
3.Treatment	67.2	66.7	62.5	70.8	54.2	52.1	45.8	62.5	<0.001*
4. Worry	83.4	91.7	66.7	91.7	75.6	91.7	0.375	91.7	
5.Communication	81.7	75.0	75.0	100.0	87.5	100.0	75.0	100.0	0.185

Note: p_u – statistical significance of differences between group parameters was assessed using the Mann–Whitney U test. * -«0»-hypothesis is rejected.

The total score on the PedsQL Generic Core Scale questionnaire (p_u=0.012*) before treatment had a significant between-group difference and was lower in children who were prescribed anti-cytokine therapy. Regarding the total score on the PedsQL Rheumatology Module questionnaire, no significant difference was obtained (p_u=0.060). However, the scores on the pain/stiffness (p_u=0.026*), daily activities (p_u=0.018*), and treatment (p_u<0.001*) scales had a significant difference and were lower in children who were subsequently prescribed anti-cytokine therapy.

To compare the efficacy of tocilizumab with standard basic therapy, we then assessed clinical and laboratory parameters during treatment. As noted above, patients were divided into groups I (basic therapy) and II (tocilizumab), depending on the treatment method.

Initially, we compared the condition of the joints over time based on the presence of pain upon palpation, the presence of swelling, and the status of functional activity.

Thus, pain in the hand area in 27 patients of I group after treatment was absent in 6 of them (p_w=0.003*). In II group, pain disappeared in 11 of 12 patients with this symptom (p_w=0.001*) (p_u=0.061). Swelling of the hand joints in 27 patients of I group after treatment was absent in 7 of them (p_w=0.008*). In group 2, swelling disappeared in all 11 patients with this symptom (p_w=0.001*) (p_u=0.018*). Limitation of movement in the joints of the hands of patients of group 1 after treatment significantly decreased in 1 of 14 patients with functional disorders of this joint (p_w=0.083). In group II, the range of motion was almost completely restored in 5 of 8 patients with limited motion (p_w=0.011*) (p_u=0.906).

Then the condition of the wrist joints was assessed. Tenderness of the wrist joints of 24 patients in I group was absent in 7 of them after treatment (p_w=0.002*). In II group, tenderness has passed in 6 of 7 patients with this symptom (p_w=0.020*) (p_u=0.131). Swelling of the wrist joints of 24 patients in the I group passed in 3 of them after treatment (p_w=0.083). In the II group, swelling passed in 7 of 8 patients with this symptom (p_w=0.008*) (p_u=0.062). Limitation of motion in the wrist joints of 10 patients in the I group after treatment was restored in 1 (p_w=0.157). In the II group, the range of motion was almost completely restored in all 5 patients with limited motion (p_w=0.034*) (p_u=0.145).

The elbow joints condition after treatment was as follows. Tenderness of the elbow joints observed in 20 patients of the I group, after treatment was absent in 3 patients (p_w=0.046*). In the II group, tenderness passed in 6 of 7 patients with this symptom (p_w=0.002*) (p_u=0.033*). Swelling of the elbow joints, observed in 21 patients of I group, was absent in 5 patients after treatment (p_w=0.025*). In the II group, swelling passed in 6 of 7 patients with this symptom (p_w=0.014*)

(p_u=0.158). Limitation of motion of the elbow joints, observed in 7 patients of the I group, remained unchanged after treatment (p_w=1.000). In the II group, the range of motion was almost completely restored in 3 of 4 patients with limited motion (p_w=0.059) (p_u=0.679).

Next, we assessed the status of the shoulder joints after treatment. Tenderness of the shoulder joints of 12 patients in the I group was absent in 5 of them after treatment (p_w=0.025*). In the II group, pain disappeared in all 3 patients with this symptom (p_w=0.083) (p_u=0.205). Swelling in the shoulder joints of 21 patients in the I group was absent in 4 of them after treatment (p_w=0.046*). In the II group, swelling disappeared in 5 of 6 patients (p_w=0.025*) (p_u=0.132). Limitation of motion in the shoulder joints in 2 patients of the I group with this symptom remained unchanged after treatment (p_w=1.000). In the II group, the range of motion was almost completely restored in both patients with movement disorders (p_w=0.157) (p_u=0.512).

The status of the hip joints after treatment was presented as follows. Tenderness of the hip joints, which was observed before treatment in 15 patients of the I group, was absent after treatment in 2 patients, and remained unchanged in the rest (p_w=0.157). In the II group, tenderness, which was observed in 1 patient, completely disappeared after treatment (p_w=0.317) (p_u=0.183). The range of motion in the hip joints, impaired in 14 patients of the I group, was completely restored after treatment only in 2 patients (p_w=0.157). In the II group, the range of motion was almost completely restored in only one patient out of 14, who had severe limitation of motion before treatment (p_w=0.317) (p_u=0.264).

The status of the temporomandibular joints after treatment was presented below. Tenderness of the temporomandibular joints, which was observed only in 3 patients of the I group, did not decrease after treatment (p_w=1.000). In the II group, tenderness of this joint was not observed in any of the 14 patients (p_w=1.000) (p_u=0.419). Impaired range of motion of the temporomandibular joints in 1 patient of group 1 remained unchanged after treatment (p_w=1.000). In the II group, the range of motion before treatment was not impaired in any patient (p_w=1.000) (p_u=0.545).

The status of the knee joints after treatment was presented as follows. Tenderness of the knee joints, revealed in 55 patients of the 1st group, was absent in 12 of them after treatment (p_w=0.001*). In the 2nd group, tenderness observed in 12, disappeared after treatment in 9 (p_w=0.005*) (p_u<0.001*). Swelling of the knee joints, noted in 54 patients of the 1st group, was absent after treatment in 3 (pw=0.083). In the 2nd group, swelling disappeared in 8 of 11 patients with this symptom (p_w=0.005*) (p_u<0.001*). The range of motion in the knee joints, impaired in 34 patients of the 1st group after treatment, was almost completely restored in 3 (p_w=0.083). In the II group, the range of motion, impaired in 8 patients, was restored in 5 (p_w=0.020*) (p_u=0.040*).

The status of the ankle joints after treatment was presented as follows. Tenderness of the ankle joints, which was observed in 40 patients in the I group, was absent in 11 of them after treatment, and in the rest it decreased insignificantly or remained unchanged (p_w=0.001*). In the II group, tenderness, which was noted in 9 patients, was completely eliminated in 8 (p_w=0.004*) (p_u=0.001*). Swelling of the ankle joints, present before treatment in 38 patients of the I group, was absent in 3 of them after treatment (p_w=0.083). In the II group, swelling, which was noted in 10 patients, was absent in 9 of them after treatment (p_w=0.003*) (p_u=0.002*). The range of motion in the ankle joints, which was impaired in 22 patients of the I group before treatment, was restored after treatment in only 1 patient (p_w=0.317). In the II group, the range of motion, limited in 8 patients, was restored after treatment in 7 patients (p_w=0.008*) (p_u=0.169).

Thus, in the group of patients receiving tocilizumab, we observed a more noticed normalization of parameters in almost all joints. The most noticed normalizations were observed in the knee and ankle joints.

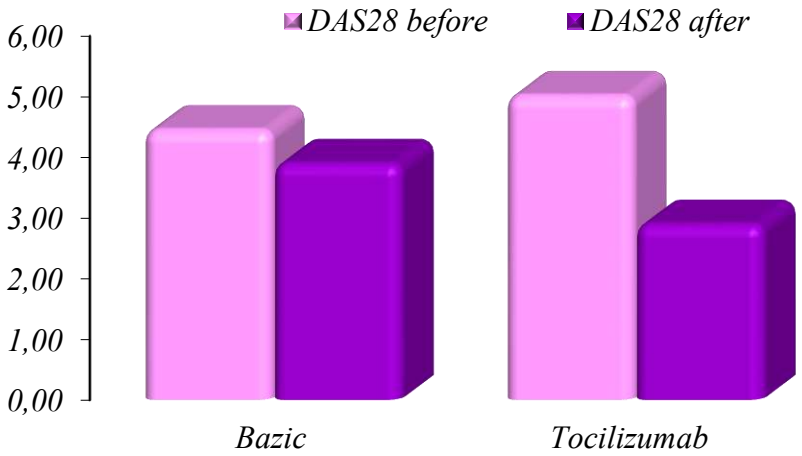
Next, we assessed laboratory parameters after treatment. The following results were obtained regarding acute phase indices. ESR after treatment in the I group was 29.0±3.1mm/hr, and in the II group, 12.5±2.3 mm/hr (p_u=0.005*).

The CRP level in the I group after treatment averaged 32.5±6.9 mg/l, while in the II group it averaged 11.0±4.6 mg/l (p_u=0.037*).

In order to evaluate anemic syndrome during treatment, the hemoglobin (HGB) level was studied. The hemoglobin level after treatment in the I group reached 11.2±0.2 g/dl. In the II group - 12.4±0.3 g/dl (p_u=0.007*).

The level of Ca^{++} after treatment in the I group was 0.98±0.02mm/l. In the II group - 1.01±0.04mm/l. Although a statistically significant difference was not obtained (p_u=0.532), we see a more significant increase in the level of Ca^{++} after treatment in the II group.

Next, we assessed the DAS28 index after treatment. Thus, the degree of activity after treatment in patients of the I group averaged 3.90±0.12 (95% CI 3.66; 4.13), and in patients of the II group - 2.89±0.17 (95% CI 2.53; 3.25). A significant difference was obtained (p_u<0.001*). This indicates a significant decrease in the DAS28 index after treatment in the group where anti-cytokine therapy was administered (graph 2**.**).



Graph 2. DAS28 index in both groups after treatment

In the course of our scientific work, the quality of life of JIA patients was assessed after treatment. Significant positive results was obtained for all scales of the CHAQ questionnaire. In the basic therapy group: 1) dressing/grooming (p_w=0.005*); 2) arising

(p_w=0.034*), 3) eating (p_w=0.002*); 4) walking (p_w=0.046*); 5) hygiene (p_w=0.026*); 6) reach (p_w=0.016*); 7) grip (p_w=0.023*); 8) activities (p_w=0.010*). In the anti-cytokine therapy group: 1) dressing/grooming (p_w=0.001*); 2) arising (p_w=0.001*), 3) eating (p_w=0.001*); 4) walking (p_w=0.001*); 5) hygiene (p_w=0.001*); 6) reach (p_w=0.001*); 7) grip (p_w=0.001*); 8) activities (p_w=0.001*). However, no intergroup difference in the overall CHAQ questionnaire score was obtained during treatment (p_u=0.249) and was noted only for individual scales of "hygiene" (p_u=0.045*) and "reach" (p_u=0.040*) and was more significant in the tocilizumab group.

In relation to all scales of the PedsQL Rheumatology Module questionnaire, the quality of life after treatment had significant differences. In the basic therapy group: 1) pain/stiffness of movements (p_w=0.001*); 2) daily activities (p_w=0.010*), 3) treatment (p_w=0.002*); 4) worry (p_w=0.011*); 5) communication (p_w=0.034*). In the anticytokine therapy group: 1) pain/stiffness of movements (p_w=0.001*); 2) daily activities (p_w=0.002*), 3) treatment (p_w=0.001*); 4) worry (p_w=0.003*); 5) communication (p_w=0.024*). The intergroup differences in the overall value (p_u<0.001*) and all indicators (except the worry scale) for this questionnaire were significant and were more significant in the tocilizumab group.

In relation to all scales of the PedsQL Rheumatology Module questionnaire, the quality of life after treatment had significant differences. In the basic therapy group: 1) pain/stiffness (p_w=0.001*); 2) daily activities (p_w=0.010*), 3) treatment (p_w=0.002*); 4) worry (p_w=0.011*); 5) communication (p_w=0.034*). In the anticytokine therapy group: 1) pain/stiffness (p_w=0.001*); 2) daily activities (p_w=0.002*), 3) treatment (p_w=0.001*); 4) worry (p_w=0.003*); 5) communication (p_w=0.024*). The differences between groups in the overall value (p_u<0.001*) and all indicators (except the worry scale) for this questionnaire were significant in the tocilizumab group.

Next, we examined the correlation relationships between clinical and laboratory parameters in children with JIA.

As a result, we obtained significant positive and negative correlations between various parameters, among which we would like to highlight the following. The HGB level was negatively correlated

with parameters reflecting the severity of the process: CRP (ρ=-0.387, p=0.001*), ESR (ρ=-0.505, p=0.000*), DAS28 (ρ=-0.471, p=0.000); as well as with arthritis of the shoulder joints (ρ=-0.238, p=0.034). The obtained relationships reflect the dependence of the severity of anemia of chronic diseases, characteristic of autoimmune diseases, on the severity and activity of the process.

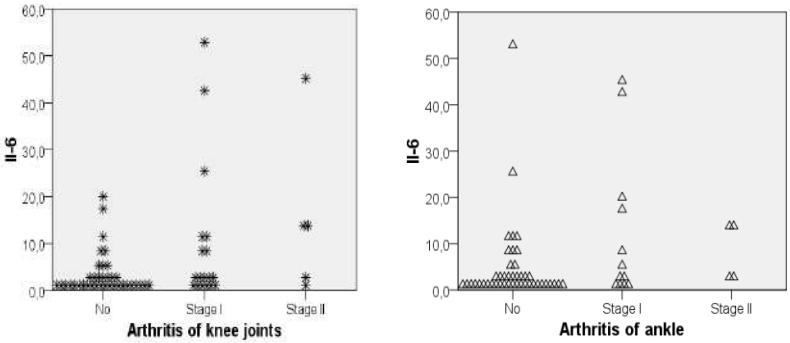
The Ca^{++} level had a significant negative correlation with: CRP (ρ=-0.301, p=0.040), IgG (ρ=-0.421, p=0.009), IL-6 (ρ=-0.334, p=0.043), arthritis of the ankle joints (ρ=-0.315, p=0.031) and hand joints (ρ=-0.360, p=0.013). A significant negative correlation of Ca^{++} with the parameters reflecting the severity and activity of the process allows us to assert that the cause of bone resorption processes in JIA, in addition to steroid intake, is also the high activity of the process associated with the activation of osteoclasts production and differentiation by IL-6.

Statistical analysis revealed a positive correlation between IgA and arthritis of the following joints: hand (ρ=+0.397, p=0.002), elbow (ρ=+0.299, p=0.020), shoulder (ρ=+0.331, p=0.010), and knee (ρ=+0.366, p=0.004). These results suggest that high IgA levels correlate with the severity of the joint syndrome.

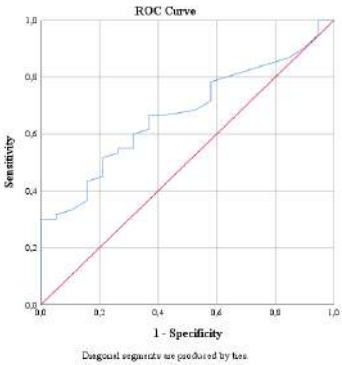
A positive correlation was also obtained between increased IgG concentrations and arthritis of the following joints: hand (ρ=+0.317, p=0.014) and shoulder (ρ=+0.291, p=0.024). Thus, it can be concluded that high IgG levels also correlate with the severity of joint syndrome.

Finally, a positive correlation was obtained between IL-6 and arthritis of the knee (ρ=+0.314, p=0.015) and ankle joints (ρ=+0.334, p=0.009), which were the most common joints affected in our patients. This explains the high efficacy of the IL-6 inhibitor tocilizumab in our patients (graph.3).

In the next stage of our work, we assessed the diagnostic value of several parameters by determining their sensitivity and specificity using receiver operating characteristic (ROC) analysis. The results for assessing the diagnostic value of IL-6 in JIA are presented on the graph.4



Graph 3. Graphical representation of the relationship between IL-6 and knee and ankle arthritis



			95% CI	
Area	Stand. error.	Asymp.sig.	Lower bound	Upper bound
0,671	0,063	0,025	0,547	0,795

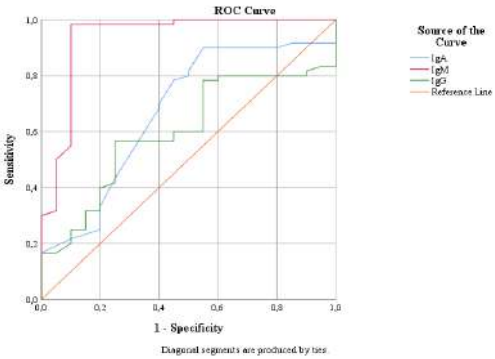
Graph.4. Specificity and sensitivity of IL-6 in JIA

Taking into account the obtained results, according to which the ROC curve area for IL-6 is 0.671±0.063; 95% CI - 0.547–0.795, p=0.025, IL-6 can be considered a statistically significant diagnostic criterion for disease severity.

Then we determined the sensitivity and specificity of immunoglobulins A, M, and G (graph.5).

Thus, for the IgA, the ROC curve area was 0.673±0.071; 95% CI - 0.533 - 0.813, p=0.021; for the IgM indicator S=0.602±0.067; 95% CI - 0.856 - 1.000, p=0.000; for the IgG indicator S=0.936±0.041; 95% CI - 0.470 - 0.733, p=0.175.

Thereby, based on the results of the ROC analysis, the following conclusions can be drawn: IgA and IgM are statistically significant diagnostic criteria for disease severity. Only IgG had no significant diagnostic value.



Parameter	Area	Stand. error	Asymp.sig.	95% CI Lower bound	95% CI Upper Bound
IgA	0,673	0,071	0,021	0,533	0,813
IgM	0,936	0,041	0,000	0,856	1,000
IgG	0,602	0,067	0,175	0,470	0,733

Graph 5. Specificity and sensitivity of IgA, IgM, IgG in JIA

Thus, our study demonstrated the diagnostic significance of IL-6, IgA, IgM, and IgG in assessing the severity of articular syndrome in JIA. Treatment with tocilizumab had a more pronounced effect compared with basic therapy on clinical manifestations, laboratory parameters, and quality of life in patients with JIA.

RESULTS

1. In children with JIA, assessment of disease activity using the DAS28 index showed that 7.5% of patients had low disease activity, 68.8% had moderate activity, and 23.8% had high disease activity [12].

2. As a result of ROC analysis (specificity (Sp) = 78.9 ± 9.4%), the diagnostic value of IL-6 (p_u = 0.025*) as a criterion for disease severity was established [24].

3. After treatment with tocilizumab, compared with basic therapy alone, more pronounced effects were observed: normalization of the joint status and a reduction in disease activity and inflammatory markers (according to the DAS28: 43% achieved inactive disease, 21% low activity, and 36% moderate activity). ESR normalized in 85% of patients and CRP in 64%. Hemoglobin levels increased, reaching normal values in 79% of patients, and Ca^{++} levels increased in all patients [10].

4. Treatment with tocilizumab resulted in a more pronounced improvement in the quality of life of JIA patients compared with the basic therapy, as measured by the PedsQL Generic Core Scale (p_u=0.007*) and PedsQL Rheumatology Module (p_u<0.001*) questionnaires, with a significant intergroup difference. The overall CHAQ score showed no intergroup significant difference (p_u=0.249) [25, 26].

5. As a result of analyzing the relationships between clinical and laboratory parameters, the following findings were established: IL-6 levels correlated with arthritis of the lower limb joints (knees: $\rho = +0.314$, $p = 0.015$; ankles: $\rho = +0.334$, $p = 0.009$) and with Ca^{++} levels ($\rho = -0.334$, $p = 0.043$); IgA correlated with arthritis of the joints (hands: $\rho = +0.397$, $p = 0.015$; elbows: $\rho = +0.299$, $p = 0.020$; shoulders: $\rho = +0.331$, $p = 0.010$; knees: $\rho = +0.366$, $p = 0.004$); IgG correlated with arthritis of the joints (hands: $\rho = +0.317$, $p = 0.014$; shoulders: $\rho = +0.291$, $p = 0.024$); Ca^{++} levels negatively correlated with arthritis of the joints (hands: $\rho = -0.315$, $p = 0.031$; ankles: $\rho = -0.362$, $p = 0.001$) and with markers of high disease activity (CRP: $\rho = -0.301$, $p = 0.040$; IgG: $\rho = -0.421$, $p = 0.009$; IL-6: $\rho = -0.334$, $p = 0.043$). Hemoglobin levels showed negative correlations with markers of high disease activity etc. [21].

PRACTICAL RECOMMENDATIONS

1. In children with JIA, it is advisable to determine the concentration of IL-6, IgA, IgM and IgG to assess the severity of the joint syndrome.

2. The use of the DAS28 index is recommended for monitoring the degree of disease activity in juvenile idiopathic arthritis allows for the assessment of the effectiveness of tocilizumab therapy.

3. The administration of tocilizumab as part of combination therapy for juvenile idiopathic arthritis is recommended in order to achieve high therapeutic efficacy in extra-articular complications and to improve the quality of life of these patients.

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LIST OF ABBREVIATIONS

JIA	– Juvenile idiopathic arthritis
sJA	– Juvenile arthritis of systemic onset
IL-6	– interleukin-6
DMARDs	– disease-modifying antirheumatic drugs
TNF-α	– tumor necrosis factor alpha
EULAR	– European League Against Rheumatism
ACR	– American College of Rheumatology
ILAR	– International League Against Rheumatism
NSAIDs	– nonsteroidal anti-inflammatory drugs
GCS	– glucocorticosteroids
DMARDs	– disease-modifying antirheumatic drugs
PRINTO	– Pediatric Rheumatology Research Organization
DAS28	– Disease Activity Index for 28 joints
ACD	– Anemia of Chronic Disease
WBC	– White blood cells
NEUT	– Neutrophils
RBC	– Red blood cells
HGB	– Hemoglobin
ACCP	– anti-cyclic citrullinated peptide

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