Seropositive juvenile rheumatoid arthritis: analysis of the spectrum of clinical manifestations and therapy according to a retrospective study

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Seropositive juvenile rheumatoid arthritis (JRA) is the rarest subtype of juvenile idiopathic arthritis (JIA) that is the equivalent of RA in adults and is manifested mainly by a symmetric polyarticular lesion, rapid structural disease progression with the formation of intraarticular erosions, the presence of positive rheumatoid factor (RF), and/or anti-cyclic citrullinated peptide (CCP) antibodies.

Objective: *to analyze demographic, clinical, and laboratory features of seropositive JRA and drug therapy according to a retrospective 10-year study.*

Patients and methods. *The retrospective study enrolled patients diagnosed with seropositive JRA confirmed according to the ILAR classification, who were treated at the Childhood Rheumatology Department, V.A. Nasonova Research Institute of Rheumatology, from 2010 to 2020. Demographic indicators, data from clinical, laboratory, and instrumental examinations, and performed therapy were assessed.*

Results and discussion. *The investigation enrolled 70 patients, amounting to 6.5% of the total number of patients with all clinical types of JIA. Among them, there was a great preponderance of girls (88.6%); the ratio of boys to girls was 1:7.8. The median age of onset of JRA was 12.2 [7.0; 14.0] years; the median duration of disease at diagnosis verification was 6 [4; 12] months; the median number of active joints at diagnosis of JRA was 16.5 [10.75; 23.25]; oligoarthritis was identified in 11.2% of patients at disease onset (within the first 6 months). During the first year of the disease, radiographic Stages II, III, and IV were defined in 42.9, 50, and 7.1%, respectively. Positive RF was found in 94.3% of patients; there was positivity for anti-CCP antibodies in 78.6%, a combination of positivity for RF and anti-CCP antibodies in 72.9%; only positive anti-CCR antibodies were seen in 5.7%. The median ESR at diagnosis verification was 29 [19.75; 44.5] mm/h; that of CRP was 15.0 [6.9; 34.4] mg/l. The extra-articular manifestations of the disease were found in 18 patients (25.7% of the total number of patients): fever in 5 (7.2%); lymphadenopathy in 17 (24.3%); lung damage in 3 (4.3%); rheumatoid nodules in 2 (2.9%); pericarditis in 1 (1.4%) patient, and uveitis in 1 (1.4%). Sjögren's syndrome was diagnosed in 25.7% of patients; autoimmune thyroiditis in 8.6%. A family history of autoimmune diseases was recorded in 22.8%.*

Nonsteroidal anti-inflammatory drugs and glucocorticoids were used in 97.1 and 48.6% of patients; respectively; the patients received synthetic disease-modifying antirheumatic drugs (sDMARDs): only methotrexate (MTX) [n=55 (78.6%)], sequentially 2 sDMARDs [n=10 (14.3%)], 3 sDMARDs [n=5 (7.1%)]; biological agents (BAs) [n=66 (94.2%)]. During the first year of the disease, Biological therapy was initiated because of the rapid progression of the erosive process in 78.6% of patients. 64.3% of children took one BA, 18.6 and 7.1% received two and three BAs, respectively. Abatacept (ABC) as the first BA was used most often (45.7%). The reasons for revision of therapy were its secondary inefficiency in most cases and serious adverse reactions in 4 patients (ABC- and infliximab-related infusion reactions in 2 cases and conversion of tubercular tests in 2). The differences in the anti-CCP antibody detection rate were statistically insignificant in the group that used only one BA effectively long and in the group that needed to switch to another BA. When choosing a BA, preference was given to tocilizumab or rituximab (RTM) in patients with seropositive JRA in the presence of systemic manifestations, and high clinical and laboratory activities and to RTM or ABC in those with detected Sjögren's syndrome.

Conclusion. *Seropositive JRA is a rare subtype of JIA that has an initially unfavorable course. Most patients require early aggressive therapy, including MTX and a BA due to the rapid progression of erosive arthritis. The presence of systemic manifestations and/or Sjögren's syndrome plays a defining role in choosing a specific BA. The presence of anti-CCP antibodies does not affect the selection or change of a BA.*

Keywords: *seropositive juvenile rheumatoid arthritis; rheumatoid factor; anti-cyclic citrullinated peptide antibodies; methotrexate; children*

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Juvenile idiopathic arthritis (JIA) is one of the most common diseases in the practice of a pediatric rheumatologist, which can have a significant negative impact on a child's physical activity, prospects for full socialization and quality of life in general [1–3]. Unlike rheumatoid arthritis (RA) in adults, in which rheumatoid factor (RF) is detected in the overwhelming majority of patients, seropositivity for RF, as well as pclassicc autoimmune rheumatic diseases, are extremely rare in childhood, which reflects the physiological characteristics of the child's body and immunopathology of JIA with the dominance of antigen-nonspecific patterns of innate rather than acquired immunity. Seropositivity for RF is one of the prognostically unfavorable factors in JIA, requiring the earliest possible prescription of effective therapy, primarily methotrexate (MT) and GEBD [4]. Seropositive juvenile rheumatoid arthritis (JRA) is the rarest subtype of JIA, which accounts for 3% to 10% in the structure of all clinical variants of JIA [1]. According to the ILAR (International League of Associations for Rheumatology) classification criteria, *seropositive JRA / JIA is arthritis with damage to ⩾5 joints within the first 6 months of the disease, associated with positive RF in two tests within 3 months, which develops in children not older than 16 years old [1]. Most often, JRA debuts at the age of 8n15 years* [1, 2]. The disease has pronounced gender differences – up to 80% are girls [1, 2]. As a rule, this subtype of JIA is characterized by a more aggressive course; the probability of achieving a stable remission is the lowest among all juvenile arthritides and does not exceed 5% [1, 3, 5, 6]. Structural changes in the joints can develop during the first 6 months of the disease with the possible formation of ankylosis in the wrist bones by the end of the first year of the disease in the case of inadequate therapy; destructive arthritis occurs in 50% of patients [1–3, 5].

According to F. Oliveira-Ramos et al. [5], seropositive JRA in more than 95% of cases evolves into classic seropositive RA in adults with an extremely poor prognosis. In a study of the total genetic risk, J. Jia et al. [7] found that seropositive JRA is genetically the most identical to adult RA compared to other JIA subtypes; therefore, we can speak about common mechanisms of pathogenesis and a similar clinical picture of these diseases. Today RA in adults is regarded as a very heterogeneous disease in terms of pathogenetic mechanisms, which is reflected in a wide variety of phenotypes and allows RA to be considered not as pone diseasec, but as a clinical and immunological syndrome [8], which requires individual selection of targeted therapy, depending on specific features of its clinical picture and the rate of progression of the inflammatory process. Taking into account the genetic and clinical identity of seropositive RA in adults and seropositive JRA, this statement can be fairly extrapolated to childhood.

It has been established that the presence of positivity for RF and antiпcyclic citrullinated peptide antibodies (ACCP) in pediatric patients positively correlates with the activity of the disease and the rate of X-ray progression [9, 10].

Thus, despite the small proportion of patients with seropositive JRA in the structure of JIA, the unfavorable course of this clinical variant requires special attention both to the peculiarities of its clinical picture and timely administration and correction of the therapy.

In the laboratory of rheumatic diseases of children of V.A. Nasonova Research Institute of Rheumatology on the basis of the available database, a group of patients with seropositive JRA who underwent treatment from 2010 to 2020 was identified, which served as the basis for this study.

The aim of the study was to analyze the demographic, clinical and laboratory characteristics of seropositive JRA and drug therapy based on the data of a retrospective 10-year observation.

Patients and methods. The retrospective study included all patients with seropositive JRA, confirmed in accordance with the ILAR (International League of Associations for Rheumatology) classification criteria [1], who were hospitalized in the pediatric rheumatology department of V.A. Nasonova Research Institute of Rheumatology from 2010 to 2020, demographic data, results of clinical, laboratory and instrumental examinations, and therapy were evaluated. All patients, in accordance with the clinical guidelines for the examination of patients with juvenile arthritis, underwent a standard laboratory and instrumental examination, including a clinical blood test, biochemical blood test, screening immunological examination, general urinalysis, renal function examination, electrocardiography, echocardiography, ultrasound examination of internal organs and joints, X-ray of the affected joints with an emphasis on the most clinically significant areas of the lesion, as well as of the chest organs, if indicated, magnetic resonance imaging of the joints, computed tomography (CT) of the chest organs. RF IgM was determined by nephelometric method, ACCP – by enzyme immunoassay.

The study was carried out within the framework of the fundamental research work of the Laboratory of Rheumatic Diseases

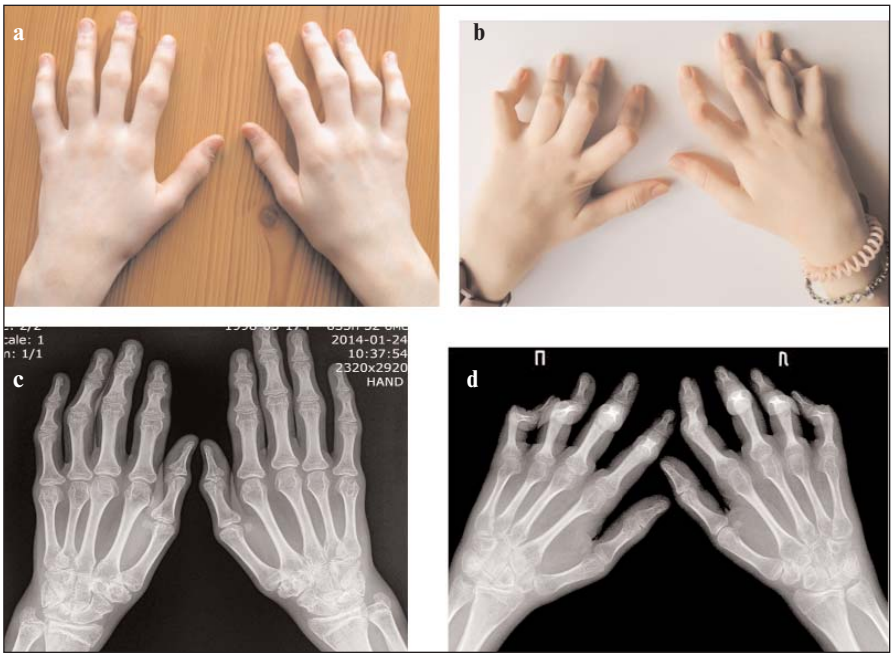

Fig. 1. *The appearance and radiographs of the hands in female Patient M. aged 16 years, with JRA seropositive for RF, radiographic X-ray Stage III (a, b) and in female Patient N., aged 14 years, with JRA seropositive for RF and anti-CCP antibodies; radiographic Stage IV (c, d). The authors' own observations*

Table. Clinical and laboratory characteristics of patients depending on positivity for RF and ACCP

Characteristics	Only RF+ patients (n=15)	Only ACCP+ patients (n=4)	Patients with RF+ and ACCP+ (n=51)
Boys, %	6.7	0	13.7
The median age of JIA at onset, Me [interquartile range (IQR) 25; 75], y.o.	9.0 [4.2; 12.8]	12.5 [12.0; 12.6]	12.5 [7.6; 14.45]
RF, IU/ml (normal 0–15.0), Me [(IQR) 25; 75]	29.8 [25.0; 447.8]	0	125.5 [41.7; 253.25]
ACCP, U/ml (normal 0–5.0), Me [(IQR) 25; 75]	0	16.6 [13.25; 35.2]	164.9 [50; 300]
ESR, mm/h (normal 0–15), Me [(IQR) 25; 75]	25 [20; 48]	24 [12.25; 34.5]	28 [19.5; 43.5]
CRP, mg/L (normal 0–5.0), Me [(IQR) 25; 75]	15.0 [12.25; 35.3]	33.0 [18.5; 36]	15.0 [6.55; 34.7]
The median of the number of active joints at the time of	17 [8; 26]	13 [11.5; 16]	17 [12; 23]
JIA verification, Me [(IQR) 25; 75]			
The number of patients with extra-articular manifestations, %	13.3	0	31.4

of Children of V.A. Nasonova Research Institute of Rheumatology.

Statistical processing of the obtained data was carried out using the Statistica 8.0 software (StatSoft Inc., USA). Descriptive statistics were used to assess quantitative variables: median (Me [25th; 75th percentile]), percentage.

Results. The diagnosis of seropositive JRA was confirmed in 70 patients, or 6.5% of all JIA patients during the indicated period. Among them there were 11.4% of boys, the ratio of boys and girls was 1: 7.8. The median age of JRA onset was 12.2 [7.0; 14.0] years; the median duration of the disease at the time of diagnosis verification was 6 months [4; 12]; the median number of active joints at the time of JRA verification – 16.5 [10.8; 23.3], oligoarthritis was revealed in 11.2% of patients at the onset of the disease (in the first 6 months).

During the first year of the disease, according to the instrumental examination, X-ray stage II was established in 42.9% of patients, stage III – in 50% and stage IV – in 7.1% of patients (Fig. 1).

94.3% and 78.6% of patients were positive for RF and ACCP, respectively, a combination of positivity for RF and ACCP was detected in 72.9% of patients, only 5.7% had positive ACCP (see the Table). The median ESR at the time of diagnosis verification was 29 [19.75; 44.5] mm / h, the median CRP is 15.0 [6.9; 34.4] mg / L. Extra-articular manifestations of the disease were found in 18 (25.7%) patients: fever – in 5 (7.2%), lymphadenopathy – in 17 (24.3%), lung involvement – in 3 (4.3%) (Fig. 2), rheumatoid nodules – in 2 (2.9%), pericarditis – in 1 (1.4%), uveitis – in 1 patient (1.4%).

Sjogren's syndrome was diagnosed in 25.7% of patients, autoimmune thyroiditis – in 8.6%. A burdened family history of autoimmune pathology was noted in 22.8% of patients.

The vast majority (97.1%) of patients received nonsteroidal anti-inflammatory drugs. Glucocorticoids (GCs) were used by 48.6% of patients; disease-modifying antirheumatic drugs (DMARDs) were prescribed to all patients: monotherapy with methotrexate (MT) п to 55 (78.6%) patients, sequentially 2 and 3 DMARDs п to 10 (14.3%) and 5 (7.1%) patients, respectively. Therapy with GEBD was started in 66 (94.2%) patients, and in 55 (78.6%) patients it was started during the first year of the disease due to rapid progression of the erosive process.

Most of the patients (64.3%) received only one GEBD, 18.6% and 7.1% of children received 2 and 3 GEBDs, respectively. Abatacept (ABA) was more often prescribed as the first GEBD – in 45.7% of cases, etanercept (ETA) was used in 17.1% of patients, adalimumab (ADA) – in 10.0%, rituximab (RTM) – in 7.1 %, infliximab (INF) – in 5.7%, tocilizumab (TCZ) – in 4.3%, golimumab (GLM) – in 2.8%, sarilumab (SAR) – in 1.4% of patients. The second GEBD was the following: RTM – in 28.6% of patients, ADA – in 23.8%, ABA – in 19%, ETA – in 14.3%, TCZ – in 9.5%, GLM – in 4.8%. The third GEBD was: ADA – in 37.5% of children, TCZ and RTM – in the same percentage of cases (25% each), ETA – in 12.5%. Sequentially 4 GEBDs (ABA п ETA п ADA п TCZ; ABA п ETA п ADA п RTM; TCZ п ABA п ADA п RTM) were received by 4.3% of patients (Fig. 3).

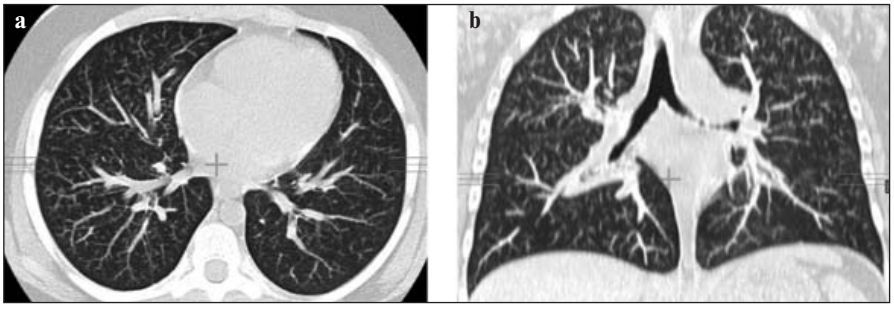

Fig. 2. *Multislice CT of the lung (a, b) in female Patient S., aged 9 years, with JRA, polyarthritis, positive for RF and anti-CCP antibodies, with systemic manifestations (lymphadenopathy, rheumatoid nodules, lung damage (bronchiolitis), rheumatoid nodules in the lung). The authors' own observation*

The reasons for the revision of the treatment regimen in most cases were secondary inefficacy of therapy, as well as serious adverse reactions in 4 patients (infusion reactions to ABA and INF – in 2, positive tuberculin skin tests – in 2). There were no statistically significant differences in the frequency of detection of positivity for ACCP and the survival rate of genetically engineered biologic therapy in the group with effective long-term use of only 1 GEBD and in the group in which a change of GEBD was required. In the presence of systemic manifestations, high clinical and laboratory activity

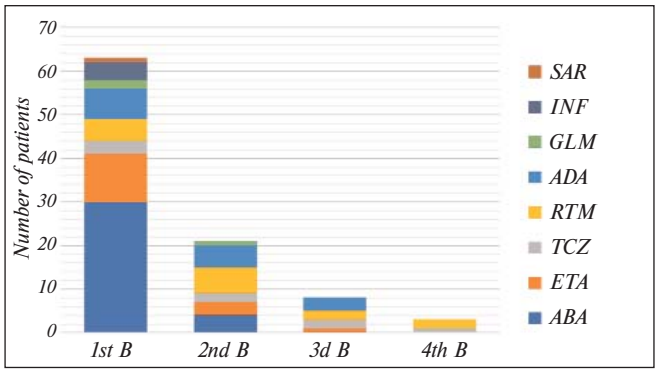

Fig. 3. *BAs used in patients with seropositive JRA*

within the framework of seropositive JRA, the preference was given to TCZ or RTM, and in patients with diagnosed Sjogren's syndrome п to RTM or ABA.

Discussion. Seropositive JRA is one of the rarest JIA subtypes. Its incidence in European countries and the United States is at the level of 0.3–0.7 per 100 thousand patient-years, and the total prevalence is 6.7 per 100 thousand of the child population [11]. The proportion of patients with seropositive JRA in the structure of JIA in our study was 6.5%, which corresponds to the results of a recently published Swedish study (6.8%) [10], as well as the data on the frequency of this subtype in general (3п10%) [2]. The results of this study concerning sex differences and the age of onset of the disease coincide with those of most previously published works [1, 2, 12].

Among our patients, 94.3% were RF positive, 4 more children were included in the study based on the new proposals published in 2019 on the classification criteria for JIA, which makes it possible to verify the diagnosis in the presence of at least one positive test for ACCP without mandatory positivity for RF [13]. At the time of diagnosis, the median duration of the disease was 6 months, which is consistent with the data from similar studies conducted in Sweden and the United States: 5.0 and 6.6 months, respectively [11, 12]. Almost a quarter of patients (22.8%) had a hereditary burden of autoimmune pathology, which corresponds to the literature data on the increased frequency of familial aggregation of autoimmune diseases [1, 11]. So, according to the results of the study by C.F. Kuo et al. [14], the risk of developing RA in children whose parents suffer from this disease is increased by 4.65 times, with a high probability of onset in childhood and adolescence.

In the first 6 months of the disease, 11.2% of patients in the study group had oligoarticular lesion, which confirms the need for mandatory determination of RF and, if possible, ACCP in all patients with a presumptive diagnosis of JIA. In the new recommendations for the diagnosis of JIA, the term ppolyarthritisc was replaced by parthritisc due to the fact that the number of affected joints is no longer a classification criterion [13]. In accordance with the international classification of JIA (ILAR), the definition of "rheumatoid" is not used in the name of the RF-positive subtype, which reflects the historical roots of the existing disagreements associated with the previously unreasonably widespread use of the term "rheumatoid arthritis" in relation to childhood.

The groups identified by us on the basis of the presence / absence of RF and ACCP were not comparable in terms of the number of patients, therefore, based on the presented material, we can only speak about the trends traced and compare the results obtained with the information available in the literature. In 72.9% of our patients, both positive RF and positive ACCP were detected, which corresponds to the data of E. Berthold et al. (70.6%) [12] and M. van Rossum et al. (73%) [15]. The analyzed groups practically did not differ in the laboratory activity, while a significantly larger number of patients (31.4%), positive for both indicators, had systemic manifestations compared to those who had only positive RF (13.3%). Among patients positive only for ACCP, no signs of consistency were found, which may be due to their small number and low titer of autoantibodies.

According to the literature, in RA an association is found between the level of ACCP and the severity of interstitial lung disease (ILD). In addition, it is assumed that ACCPs play an independent role in the development of ILD, since in patients with high levels of these autoantibodies, changes in the lungs can be detected even in the absence of RA [16]. Significantly lower values of ACCP with negative RF in our study correspond to the data of M. Sp?rchez et al. [17], who showed that ACCPs are detected in lower titers in RF-negative patients with JIA, but at the same time they are significantly associated with a higher frequency of polyarticular lesions ($p = 0.016$), as well as with the presence of earlier joint damage ($p < 0.001$), which indicates the need to determine ACCP levels even in the absence of RF-positivity.

Currently, there is no systematized information about the frequency of systemic manifestations in this subtype of JIA, with the exception of some descriptions. According to studies conducted in seropositive RA, extra-articular manifestations in adults are more often observed at the onset and in the first years of the disease: rheumatoid nodules – up to 30% of cases, pleuritis – up to 10%, ILD – up to 12% [18]. In children, such manifestations are less common. Studies from the late 20th century demonstrate, that lung involvement in seropositive JRA is observed in about 4% and is most often represented by lymphocytic interstitial pneumonia, lymphoid follicular bronchiolitis, pleuritis [19]. The researchers noted a dissociation between the X-ray picture and minimal impairment of external respiration. According to a large series of observations, the frequency of uveitis in children with seropositive JRA is 1.4п4.5% [1]. In our study, rheumatoid nodules were detected only in 2 (2.9%) patients, uveitis – in 1 (1.4%), lung involvement – in 3 (4.3%) patients.

Seropositive JRA is one of the most prognostically unfavorable JIA subtypes, which is confirmed by our data: the formation of an advanced X-ray stage was observed already in the first year of the disease, therefore, for practicing pediatric rheumatologists, along with the issues of timely diagnosis, the problem of choosing a therapeutic tactic is relevant. According to the literature, the frequency of achieving stable remission in seropositive JRA is the lowest – less than 5% [1, 3, 20]. Even with timely initiated adequate therapy with early prescription of DMARDs and GEBD, the remission rate is 42п65% [1].

Adverse factors requiring early aggressive therapy, in accordance with the ACR (American College of Rheumatology) recommendations of 2019, include positivity for RF and ACCP, signs of joint damage according to imaging methods [4]. The modern concept of JRA treatment provides for the immediate appointment of pathogenetic therapy after the diagnosis is established; MT is usually used as the first-line drug [1, 2, 6, 20]. According to the 2019 ACR guidelines, MT is preferred over leflunomide or sulfasalazine [4]. All our patients used DMARDs, MT п as the first drug. Similar data are given by E. Berthold et al.

[12]. At the initial stage of the therapy, almost half of our patients received GCs in medium or low doses, which is due to the activity and rapidly progressive course of the disease and is consistent with the latest ACR recommendations. In accordance with these recommendations, in the treatment of patients with high or moderate disease activity, the use of a short course (<3 months) of oral GCs is indicated during the period of initiation or escalation of therapy. Such a therapy regimen may be most useful in cases of significant dysfunction and / or severe symptoms of inflammation [4]. Systemic therapy with GCs was used less frequently in our study than in other works [6, 12, 20]. The number of patients who received GEBDs was higher than in the study by E. Berthold et al. [12]: 94.2% and 70.6%, respectively. Taking into account the rapidly progressing erosive process and the high activity of the disease, it seems reasonable to prescribe GEBDs early (during the first year of the disease) to most patients, which corresponds to the data of J. Guzman et al. [20]. These authors, when observing 1104 children with JIA, noted a high need for early prescription of DMARDs and GEBDs in seropositive JRA, as well as in JIA with systemic onset, in comparison with other subtypes. It should be emphasized that all patients included in our study received GEBDs in combination with DMARDs. This scheme is consistent with the 2019 ACR recommendations, according to which, in children and adolescents with JIA and polyarthritis, initiation of GEBD therapy in combination with DMARDs is more preferable than therapy with GEBD alone [4]. When choosing a specific drug, the basic activity of the disease, the presence of systemic manifestations, comorbidities, as well as recommendations for the treatment of seropositive RA in adults (given the genetic and clinical identity of these nosologies) were taken into account [1, 5, 7]. Thus, TNF inhibitors were not used in patients with secondary Sj?gren's syndrome due to a high risk of subsequent lymphoproliferative disease.

Conclusions. Seropositive JRA is a rare subtype of JIA, which is characterized by initially high activity. Most patients require early prescription of immunosuppressive drugs, including MT and GEBDs, due to rapid progression of erosive arthritis. The presence of systemic manifestations and / or Sjogren's syndrome plays a decisive role in the choice of a particular GEBD. The presence of ACCP does not affect the choice or change of a GEBD.

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Conflict of Interest Statement

The investigation has been conducted within the fundamental topic «The evolution of early arthritis and the development of innovative pharmacotherapy technologies for rheumatic diseases in children and adults», topic №0514-2019-0018 of the Ministry of Education and Science of Russia, topic №AAAA-A19-119021190149-0 of R&D.

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