Musik in bayern

ISSN: 0937-583x Volume 89, Issue 7 (July -2024)

https://musikinbayern.com

DOI https://doi.org/10.15463/gfbm-mib-2024-*256*

УДК: 611.018.74: 616.126.422-053:615.224

INFLUENCE OF THE CYTOKINE SYSTEM ON THE COURSE OF RHEUMATOLOGICAL DISEASES

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To Cite this Article

Babamuradova Z.B., Shodikulova G.Z. (2024). " INFLUENCE OF THE CYTOKINE SYSTEM ON THE COURSE OF RHEUMATOLOGICAL DISEASES". *Musik in Bayern*, *89*(7), 61–72. https://doi.org/10.15463/gfbm-mib-2024-256

Article Info

Received: 27-04-2024 Revised: 21-05-2024 Accepted: 26-06-2024 Published: 15-07-2024

Resume

Today, according to the health organization, rheumatological diseases are one of the leading causes of disability worldwide. The role of polymorphic genes of the autoimmune system (IL17A, IL17F, IL23R) and the cytokine system (TNFα, IL 1β, IL4, IL6, IL10) in the differential clinical course and severity of RD disease and the correlation of polymorphic genes of the cytokines IL1β, IL6, IL17A, TNFα with clinical symptoms have not been studied. Based on the above, it is possible to conduct scientific research aimed at early diagnosis of RA, SLE and AS among RDs, studying the characteristics of clinical, laboratory and immunogenetic manifestations, and increasing the effectiveness of treatment.

Key words: rheumatological diseases, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, cytokines, autoimmune inflammation, genetically engineered biological drugs.

ВЛИЯНИЕ СИСТЕМЫ ЦИТОКИНОВ НА ТЕЧЕНИЕ РЕВМАТОЛОГИЧЕСКИХ ЗАБОЛЕВАНИЙ

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Musik in bayern

ISSN: 0937-583x Volume 89, Issue 7 (July -2024)

https://musikinbayern.com

DOI https://doi.org/10.15463/gfbm-mib-2024-*256*

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Резюме

На сегодняшний день, по данным организации здравоохранения, ревматологические заболевания являются одной из ведущих причин инвалидности во всем мире. Роль полиморфных генов системы аутоиммунных состояний (IL17A, IL17F, IL23R) и цитокиновой системы (TNFα, IL 1β, IL4, IL6, IL10) в дифференциальном клиническом течении и тяжести заболевания РЗ и корреляция полиморфных генов цитокинов IL1β, IL6, IL17A, TNFα с клиническими симптомами не изучена. На основании вышеизложенного возможно проведение научных исследований, направленных на раннюю диагностику РА, СКВ и АС среди РЗ, изучение особенностей клинических, лабораторных и иммуногенетических проявлений, повышение эффективности лечения.

Ключевые слова: ревматологические заболевания, ревматоидный артрит, системная красная волчанка, анкилозирующий спондилит, цитокины, аутоиммунное воспаление, генно-инженерные биологические препараты.

Relevance

Today, according to the health organization, rheumatological diseases are one of the leading causes of disability worldwide. Their origin is manifested by the development of an autoimmune process as a result of disorders in the immune system. Therefore, based on genetic studies, it is necessary to improve the features of early diagnosis, development, prevention and treatment, reduce complications and provide practical assistance to patients on various bases of medical care for rheumatological diseases (RD), including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylarthritis (AS), prevent and reduce complications, provide practical assistance to patients at various stages of medical care and develop principles for timely selection of the most optimal treatment method - one of the main problems solved in medicine.

A number of scientific studies are being conducted around the world aimed at studying the role of cytokines in the mechanisms of the pathogenetic development of cancer, improving methods for early and differential diagnosis, treatment and prevention of the disease. In this regard, an analysis was carried out of the distribution of allelic and genotypic forms of genes for autoimmune conditions IL17A, IL17F, IL 23 and genes of the cytokine system such as TNFα, IL 1β, IL4, IL6, IL10 in RD, which are of particular importance in determining the severity of

ISSN: 0937-583x Volume 89, Issue 7 (July -2024)

https://musikinbayern.com

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the disease in arthritis. The significance of immunogenetic factors, selection of optimal treatment methods taking into account genetic predisposition, prediction of these pathologies and conducting scientific research aimed at early diagnosis. In recent years, a number of studies on RD have been carried out in developed countries of the world. To date, the world has developed certain scientific ideas about its pathogenetic mechanisms: determining the pathogenetic mechanisms of the formation and development of RA, SLE, AS is one of the priorities in a number of large scientific centers in the world (Malysheva I.E., Topchieva L.V., Balan O.V., Marusenko I.M., Barysheva O.Yu., Kurbatova I.V.).

It is known that in the development of rheumatoid arthritis, firstly, the individual characteristics and predisposition of the body, and secondly, immunological (ACCP), rheumatoid factor (RF) and genetic factors, the activity of which was the leading link (Jahid M, Rehan-Ul-Haq, Avasthi R, Ahmed RS. Interleukin10-1082 A/G polymorphism: Allele frequency, correlation with disease markers, messenger RNA and serum levels in North Indian rheumatoid arthritis patients, 2018). In addition, a large study in recent years has shown that the contribution of immunogenetic factors to the mechanisms of SLE is significant (Lewis MJ, Barnes MR, Blighe K. et al. Molecular Portraits of Early Rheumatoid Arthritis Provided Clinical and Treatment Response Phenotypes, 2019).

However, an analysis of the literature shows that the role of polymorphic genes of the autoimmune system (IL17A, IL17F, IL23R) and the cytokine system (TNFα, IL 1β, IL4, IL6, IL10) in the differential clinical course and severity of RD disease and the correlation of polymorphic genes of IL1β cytokines, IL6, IL17A, TNFα with clinical symptoms have not been studied, the level of DAS28 activity and their prognostic significance have not been determined; The effectiveness of treatment with genetically engineered biological drugs (GEBPs) has not been studied depending on the transfer of allelic and genotypic forms of autoimmune system genes (IL17A, IL17F, IL23R) and polymorphic genes of the cytokine system (TNFα, IL-1b, IL4, IL6, IL10).

Based on the above, it is possible to conduct scientific research aimed at early diagnosis of RA, SLE and AS among RDs, studying the characteristics of clinical, laboratory and immunogenetic manifestations, and increasing the effectiveness of treatment.

The purpose of the study is to study the characteristics of the immunological status and develop differentiated approaches to the treatment of rheumatological diseases

Materials and methods

ISSN: 0937-583x Volume 89, Issue 7 (July -2024)

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A total of 379 patients with RD were examined, who were divided into several subgroups, and 98 practically healthy people who voluntarily agreed to the study. The study was conducted for the period 2021-2023y on the basis of the Samarkand City Medical Association and 1 - multidisciplinary clinic No. 1 of the Samarkand State Medical University.

To carry out this work, an integrated approach was used, including clinical, laboratory, ultrasound, radiological and statistical research methods.

• 1 subgroup (n=168), patients diagnosed with rheumatoid arthritis (RA).
• 2 subgroup (n=103) patients diagnosed with systemic lupus erythematosus (SLE).
• 3 subgroup (n=108) patients diagnosed with ankylosing spondylitis (AS).

The diagnosis of RA was established based on the 2010 ACR/EULAR criteria. (American College of Rheumatology/European League Against Rheumatism criteria) and ICD. SLE was established based on the 2019 ACR/EULAR criteria. Ankylosing spondylitis - the diagnosis was established based on the ASAS criteria for axial spondylarthritis (2009) according to the Russian version of the modified New York AS classification criteria 2013.

In accordance with the planned clinical and laboratory examinations, diagnosis and developed criteria for inclusion and exclusion in the study were drawn up. Basically, the disease was typical for the age group of 35-40 years (41.6%), women predominated more than men, by 2.5 times.

Clinical studies consisted of clarifying complaints, familiarizing with medical histories, outpatient records, studying anamnestic data and the protocol of the initial examination, and the characteristics of the course of the disease in different categories of patients. The list of instrumental studies included radiography of joints, ECG, ultrasound of internal organs and Doppler echocardiography (Mindray Resona I9). RA activity was assessed using the international indices of degrees of activity DAS28.

Molecular genetic research was carried out in the laboratory of medical genetics of the Russian National Research Medical Center of Hematology (Republic of Uzbekistan, Tashkent) and consisted of detecting variants of autoimmune cytokine genes (IL17A, IL-17F, IL23R) and cytokine system genes (TNFα, IL 1β, IL4, IL6 , IL10) using standard PCR followed by restriction fragment length polymorphism (RFLP) analysis of PCR products (preliminary denaturation (1 cycle) with a duration of 1 min at a temperature of 940C; 35 amplification cycles, which included denaturation for 10 sec. C temperature mode 930C; annealing of primers for 10 sec at a temperature of 640C; elongation for 20 sec at a temperature of 720C (20 sec) and final synthesis for 1 min at a temperature of 720C; checking the specificity and quantity of amplified fragments by method. electrophoresis in an

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https://musikinbayern.com

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agarose gel; then purified from unincluded nucleotides and subjected to capillary electrophoresis in a 3130 genetic analyzer (Applied Biosystems, USA).

According to the treatment plan, patients were divided into the following subgroups.

-**1 group** is divided into subgroups A and B, where "A" consisted of 50 patients who were treated with DMARDs in the form of methotrexate, and subgroup "B" consisted of 53 patients taking DMARDs in the form of levilimab (LLM);

- **2 group** is also divided into subgroups A and B, where "A" consisted of 19 patients who were using "minor" immunosuppressants (Hydroxychloroquine), and subgroup "B" was 16 patients taking other immunosuppressants (Mycophenolate mofetil);

-**3 group** is divided into subgroups A and B, respectively, where "A" consisted of 16 patients who were using DMARDs in the form of methotrexate, and subgroup "B" was 16 patients taking a DMARD in the form of secukinimab;

The examination was carried out over time: within 6 and 12 months from the start of treatment. The effectiveness was assessed on the basis of clinical, laboratory and instrumental studies.

A mathematical analysis of the results obtained was carried out using the programs "OpenEpi 2009, Version 2.3".

Results and discussions

In the course of a general clinical study of patients with RD, we studied and assessed the activity of RA, SLE and AS depending on the form of the disease, which showed that the level of pain according to VAS was 65.6 mm, 53.2 mm and 78 mm; the number of painful joints (PJ) was 1.6 times more prevalent among patients with RA compared with SLE, and 1.4 times with AS, respectively (20.7 versus 12.6 and 20.7 versus 14.7). A similar pattern was observed in relation to the number of swollen joints (SJN) and morning stiffness. Their values for RD were as follows: For RA - 12.6 and 116.4 min, for SLE - 4.2 and 33.7 min, for AS - only morning stiffness was noted for about 35.8 min. At the same time, assessment of RA activity based on the average values of ESR and DAS28 also showed the highest figures for patients with articular-visceral form of RA. In particular, if the median of these indicators among patients with the articular form was 30.2 mm/h and 3.4, then in the articular-visceral form they were 46.8 mm/h and 4.8, respectively.

When RA was diagnosed, symmetrical arthritis of the hand joints occurred in 90% of the examined patients. In patients with SLE, during dynamic observation, a predominance of the asymmetric variant of damage to the small joints of the hands was noted. The frequency of detection of this symptom in patients in this category

ISSN: 0937-583x Volume 89, Issue 7 (July -2024)

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was significantly lower in comparison with patients with rheumatoid arthritis at the time of diagnosis (p <0.01) (Fig. 1).

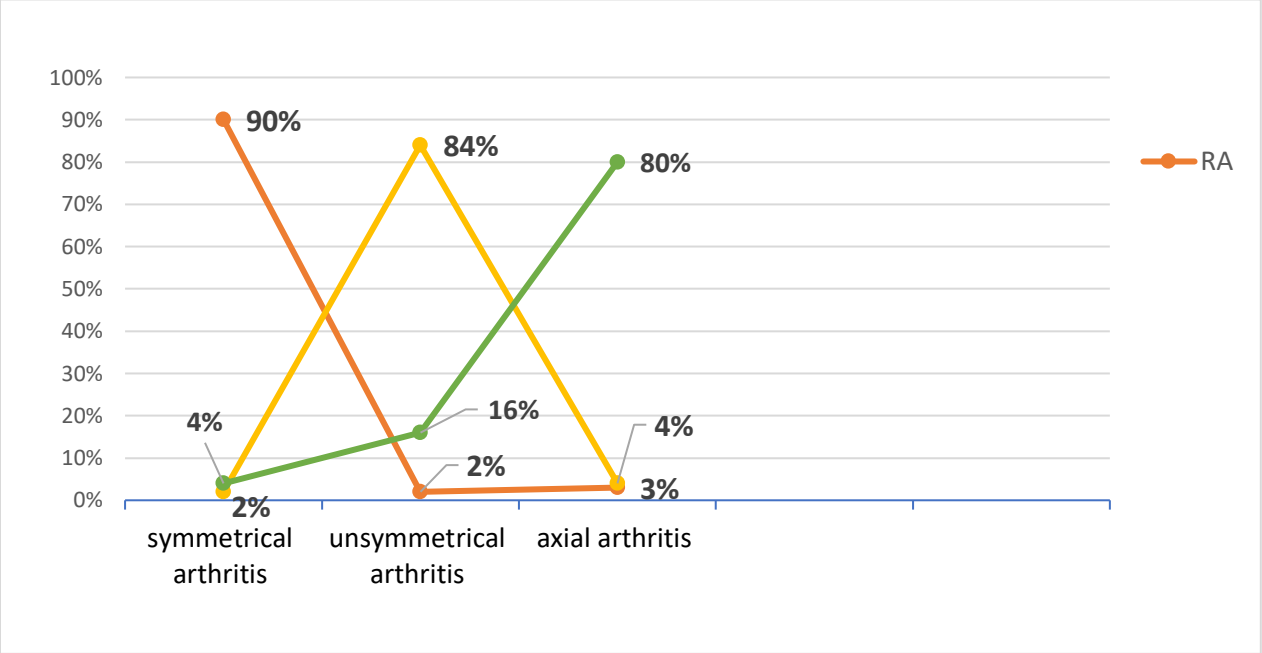

Figure 1. Joint lesions in study groups

Systemic manifestations of RA were recorded in 37 (22%) patients. The most common of them were anemia in 134 (80%), weight loss in 67 (40%), amyotrophy in 142 (85%), fever in 88 (52.5%), rheumatoid nodules in 28 (16.7%).

Among patients with SLE, the most frequently observed lesions were skin lesions in 51 (49%), kidney lesions in 56 (55%), and photosensitivity in 42 (41%), respectively. Among patients with kidney damage, 16 out of 103 people had nephrotic syndrome with proteinuria more than 3 g per day, hypoproteinemia and hypoalbuminemia, hyperlipidemia (cholesterol more than 6.5 mmol/l), 45 of whom had edema. The most common type of AS among our patients was damage to the axial skeleton (sacroiliitis and/or spondylarthritis) - in 73 (79%). The second most common is arthritis of the peripheral joints (mainly the lower extremities) - 23 (24.8%). Much less often, combined damage to the axial skeleton and peripheral joints was observed - in 12 (13%). Among patients with AS, in addition to the most important clinical signs, extra-articular manifestations were also noted, such as uveitis 6 (5.5%), iridocyclitis 14 (12.9%), colitis 11 (10.2%), enthesitis 23 (21 .3%), dactylitis 4 (3.7%), respectively. It is important to know that the course of AS can worsen by involving extra-articular manifestations of this disease.

According to our studies, the limitation of functional activity was also determined by the HAQ index. The results of the study showed that functional

ISSN: 0937-583x Volume 89, Issue 7 (July -2024)

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preservation was observed in 20.8% (35) of patients with RA (0 points), in patients with AS, 0 points were also noted in 39.80% (53), but with SLE many patients - 84 50% (87) retained functional activity, since the severity of joint damage in these patients was milder than in RA and AS. In patients with RA, 41.6% (70) of patients had 1 point, including in patients with AS 33.3% (46) had 1 point, and in SLE, 1 point was noted in only 15.5% (16) patients, also according to the HAQ index, 2 points were identified: with RA in 25% (42) and with AS in 8.3% (9), respectively, these patients could perform physical labor with great difficulty, only in patients with RA 3 points were revealed in 13.5% (21), who did not have the opportunity to perform physical labor and needed the help of others (Fig. 2)

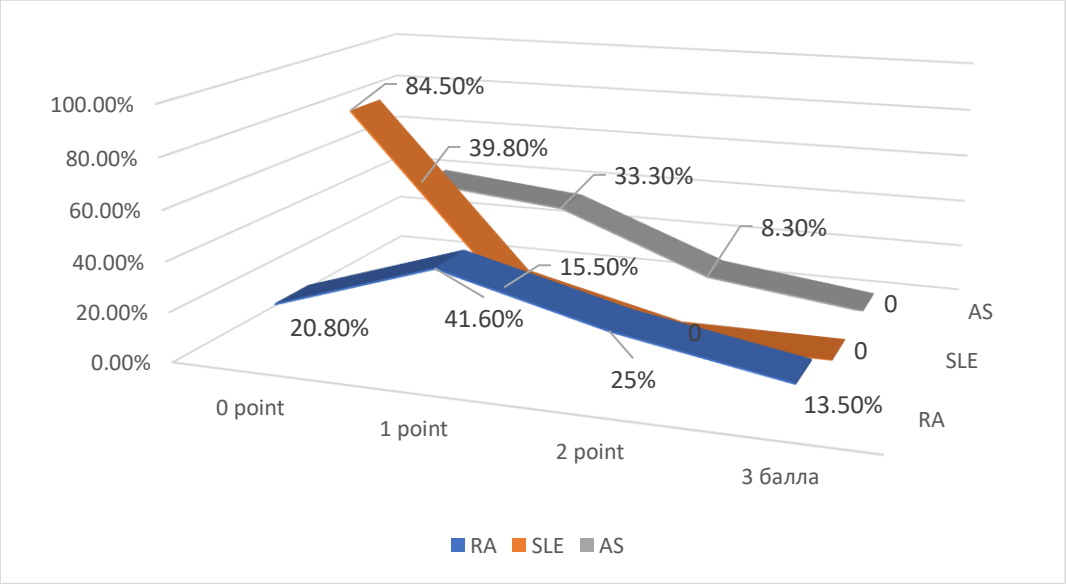

Figure 2. Limitation of functional activity according to the HAQ index

Among patients with RD, seropositivity for antibodies to cyclic citrullinated peptide (ACCP) was detected in 158 (42%) patients, while seronegative was detected in 221 (58%) patients and CG.

An important test for SLE is the test for ANF. In our subjects, the ANA titer was significantly high, in contrast to the CG; in patients with SLE there was an average of 1:640 titers, that is, 4 times more than in the CG. According to our study results, positive indicators according to the ANA definition were among the diagnostic criteria for SLE, which were used to assess the activity, prognosis and characteristics of clinical and laboratory subtypes of the disease, and they also served as predictors of the development of SLE at the preclinical stage. Another important study in AS is HLA-B27 typing in AS. The polymerase chain reaction (PCR) method

ISSN: 0937-583x Volume 89, Issue 7 (July -2024)

https://musikinbayern.com

DOI https://doi.org/10.15463/gfbm-mib-2024-*256*

was used to detect certain sections of DNA molecules of biological objects. The analysis was performed in three stages: isolation, propagation and recognition of DNA fragments. Identification of certain DNA fragments, in particular the HLA-B27 antigen, was carried out using reference genetic detectors. The result of this analysis showed 95% **"detection"** of HLAB27 in the AS group.

To determine the role of cytokine status, the level of cytokines IL-1β, IL-6, IL-17A tumor necrosis factor alpha (TNFA-α) was examined.

As a result of the study, a statistically significant increase in the concentrations of IL-1β, IL-6, IL-17A, TNFA-α was found in patients with RD compared to the control group (p=0.03, respectively). In patients with SLE, decreased concentrations of IL-1β were detected compared to RA and AS, but the level of TNFA-α was increased by 1.5 times in patients with AS compared to SLE and RA (p=0.05). Overproduction of the pro-inflammatory cytokine IL-1β was determined in patients with RA in comparison with SLE (Table 1).

Table 1

Levels of cytokines in patients with RD and CH, M±m, pg/ml

Cytokines	**RD (n=379)**			**Control group (n=98)**	**P value**
	PA (n=168)	**СКВ (n=103)**	**AC (n=108)**		
IL -1β	14,8±8,4	12,3±6,2	17,8±9,3	11,2±3,2	0,037
IL -6	18,40±5,11	14,65±0,43	12,34±4,73	7,4±0,34	0,03
IL -17A	7±4,11	8±2,11	12±5,41	5±0,11	0,05
TNF-α	11,02±0,77	8,50±0,45	12,32±1,25	7,8±3,11	0,039

TNFA-α are powerful inducers of the synthesis of another pro-inflammatory cytokine - IL-6, the concentration of which closely correlates with clinical and laboratory parameters of the activity of the inflammatory process in RD.

Our subjects had improvements in the dynamics of symmetrical, asymmetrical and axial joint damage, where joint swelling, hyperemia, and inflammatory pain decreased, which confirms the DAS28 indicators, disease activity in this table, in patients in subgroup "A" by 1, 2 times, in subgroup "B" 1.5 times the effectiveness of therapy was noted (p<0.03). To determine the effectiveness of basic anti-inflammatory drugs (BAIDs) and GEBDs, in particular the IL6 inhibitor, the level of pro-inflammatory cytokines IL-1β, IL-6, tumor necrosis factor alpha (TNFA-α) and after treatment of RD was examined (Table 2).

Table 1

Indicators of the levels of cytokines IL1β, IL6, IL17A, TNFA-α in patients with RD before and after treatment with BAIDs and GEBDs

ISSN: 0937-583x Volume 89, Issue 7 (July -2024)

https://musikinbayern.com

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Indicators	**1 group patients with RA**		**2 group patients with SLE**		**3 group patients with AS**		**P value**
cytokines	**«A» units/ml n=50**	**«B» units/ml n=53**	**«A» units/ml n=19**	**«B» units/ml n=16**	**«A» units/ml n=17**	**«B» units/ml n=17**	
IL -1β	14,8±8,4	15,8±8,1	12,3±6,2	13,3±5,2	17,8±9,3	17,8±1,3	p<0.03
	12,8±7,4	12,1±0,4	12,3±6,2	11,3±3,2	16,8±3,3	15,8±2,3	
IL -6	18,40±5,11	17,30±4,11	14,65±0,43	14,5±1,3	12,34±4,73	11,41±1,71	p<0.05
	16,20±2,11	15,70±4,11	11,65±0,43	9,45±0,23	11,21±1,8	9,38±1,53	
IL -17A	7±4,11	7,4±3,12	8±2,11	8±2,45	12±5,41	12±4,11	p<0.001
	6,5±3,1	5,4±2,8	7,2±2,21	6±1,25	11±2,32	12±1,08	
TNF -α	11,02±0,77	12,22±2,77	8,50±0,45	8,41±1,23	12,32±1,25	11,82±1,02	p<0.003
	10,02±0,77	9,82±1,17	8,50±0,45	7,10±1,05	11,22±0,54	9,42±1,35	

The analysis showed that as RA progresses, it is accompanied by a higher level of inflammatory and autoimmune reactions, which was confirmed by a significantly higher level of cytokines, so in patients with RA there was an increase in the level of IL -1β by 1.3 times, IL -6 by 2, 5 times and TNF-α by 1.5 times, but in comparison of these indicators after pharmacotherapy, there were relative improvements, in particular in the "B" subgroup, since IL-6 inhibitors in active RA effectively suppress the immunoinflammatory process and have a favorable security profile. The analysis showed that after the use of levilimab, there was a decrease in the level of pro-inflammatory cytokines by 1.4 times, in contrast to the use of methotrexate. A decrease in the level of TNF-α in patients with AS, during the use of secukinumab, indicates the effect of the IL-17A inhibitor directly on the production of immune mediators - TNF-α.

Conclusions

1. The complex of studies carried out allowed us to establish the important role of clinical, laboratory and instrumental analysis of cytokines and specific markers for a differentiated approach to the diagnosis of RD, where DAS28 and VAS (P<0.001), increased levels of RF, ACCP, ANA (P<0.001) were identified (P<0.01), which proves a more severe course of the disease.

2. A significant role has been established for the study of clinical, instrumental, laboratory and immunological parameters depending on the clinical form of RD, which acts as a pathogenetic basis for improving the criteria for predicting the likelihood of an increased risk of development and severity of the disease.

ISSN: 0937-583x Volume 89, Issue 7 (July -2024)

https://musikinbayern.com

DOI https://doi.org/10.15463/gfbm-mib-2024-*256*

3. The effectiveness of GEBD therapy (levilimab for RA and secukinumab for AS) in patients from admission to 6 months from the start of treatment was assessed. The homozygous state of the G allele in the phenotype of a patient with RA, providing a high level of IL-17A production, contributes to the good effectiveness of biological therapy.

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