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Annexin A1 (Anxa1) Levels in Rheumatoid Arthritis: Association with Structural Joint Damage and Changes During Treatment

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Abstract

Background: Since rheumatoid arthritis is one of the most common diseases among the working-age population and significantly affects patients' quality of life, the study of this disease requires in-depth scientific research. The article presents the results of our own research dedicated to studying ANXA1 levels as a biomarker of immune inflammation and joint remodeling in patients with rheumatoid arthritis. Additionally, a significant correlation was demonstrated between ANXA1 levels and disease activity indicators, inflammatory markers, and clinical and laboratory criteria reflecting joint damage.

Objective: The objective is to determine the role of ANXA1 in the progression of the immune inflammatory process in patients with rheumatoid arthritis, as well as its role in assessing structural changes in the joints, and to improve therapeutic and preventive measures.

Methods: In our study, 108 patients with rheumatoid arthritis and 30 healthy individuals were examined. Based on the duration and stage of the disease, the patients were divided into early, established, and late stage groups, and the effect of ANXA1 levels on immune-inflammatory markers and early joint remodeling was determined.

Results: The results of 52 weeks of treatment showed that the combination of basic therapy and baricitinib in patients with rheumatoid arthritis has high clinical and immunological

efficacy. An increase in ANXA1 levels from 2.12 to 9.45 in the main group indicated the activation of its anti-inflammatory protective mechanisms, whereas in the control group, the increase in this indicator was relatively lower. At the same time, the DAS28 index, which reflects disease activity, significantly decreased from 5.08 to 2.7 in the main group, approaching a level of low activity or remission, while in the control group, this indicator remained at 3.5. Although the concentrations of TNF-α and IL-6, the main inflammatory cytokines, decreased in both groups, these changes were much more pronounced in the main group. Specifically, the TNF-α level decreased from 18.9 to 5.4, and the IL-6 level dropped from 14.8 to 5.4, indicating the effective suppression of the immune-inflammatory process. The obtained results demonstrated a close correlation between the restoration of ANXA1 expression, a decrease in cytokine production, and a significant reduction in disease activity in patients receiving baricitinib. This confirms the importance of baricitinib in effectively controlling the immune-inflammatory process and limiting disease progression in rheumatoid arthritis.

Conclusion: It was found that in patients with RA, ANXA1 levels change in correlation with immune inflammatory markers (TNF-α and IL-6). A decrease in ANXA1 levels is accompanied by an increase in inflammatory cytokines and heightened disease activity. Furthermore, ANXA1 levels were associated with early remodeling processes in joint tissues, and their alteration manifested as an early sign of destructive changes. These findings confirm the potential of using ANXA1 as an important biomarker for assessing inflammatory acti.

Keywords: Rheumatoid Arthritis (RA), VAS — visual analog scale, disease-modifying antirheumatic drugs (DMARDs), Annexin A1 (ANXA1), interleukin-6 (IL-6), Disease Activity Score in 28 Joints (DAS28)

Introduction

Background: In recent years, a number of scientific studies dedicated to RA have been conducted in Uzbekistan, mainly focusing on the clinical or immunogenetic disorders associated with this disease. However, the influence of ANXA1 on the clinical course of the disease, changes in immune status, the state of pro-inflammatory cytokines, and disease progression has not been fully studied. Furthermore, treatment and prevention measures for RA have not been developed that take into account ANXA1-related changes in bone and joint structures, along with methods for predicting the development of disability. In recent years, special attention has been paid to studying the mechanisms of not only inflammatory activation but also its resolution in the pathogenesis of autoimmune joint diseases. Within this framework, ANXA1 gains significance as a key endogenous protein that limits inflammation and physiologically regulates the immune response. Fundamental studies have demonstrated that ANXA1 limits the migration of neutrophils across the endothelium, accelerates the suppression of the inflammatory process by macrophages, and reduces the expression of pro-inflammatory cytokines—namely TNF-α and IL-6. Clinical observations have shown that a decrease in ANXA1 expression in spondyloarthritis is reliably associated with disease activity, its chronic course, and destructive changes in joint structures. These studies explain that ANXA1 deficiency leads to a loss of control over inflammation and the activation of pathological remodeling processes. Modern research indicates that a decrease in ANXA1 levels precedes morphological changes detected by instrumental examination methods. In particular, it has also been evaluated as an early biological indicator of inflammation and cartilage destruction.

Materials and Methods

Study Design and Participants

For a prospective study, 108 patients diagnosed with RA who received inpatient treatment at Clinical Hospital No. 3 in Tashkent between 2023 and 2026, along with 30 apparently healthy individuals without RA, were examined. During the study, the 108 patients with rheumatoid arthritis were divided into 3 groups based on the clinical stage of the disease. The first group included 31 patients in the early clinical stage with a disease duration of 6 months to 1 year. The second group included 41 patients in the pronounced stage with a disease duration of 1 to 2 years. The third group consisted of 36 patients in the late clinical stage who had irreversible structural changes in the joints and a disease duration of more than 2 years. The effect of ANXA1 levels on immune inflammation (TNF-α, IL-6) in these patients and the resulting early joint remodeling were determined.

Results

Assessment of ANXA1 levels in RA patients according to clinical stages

During the study, ANXA1 levels in patients with rheumatoid arthritis were assessed according to clinical stages.

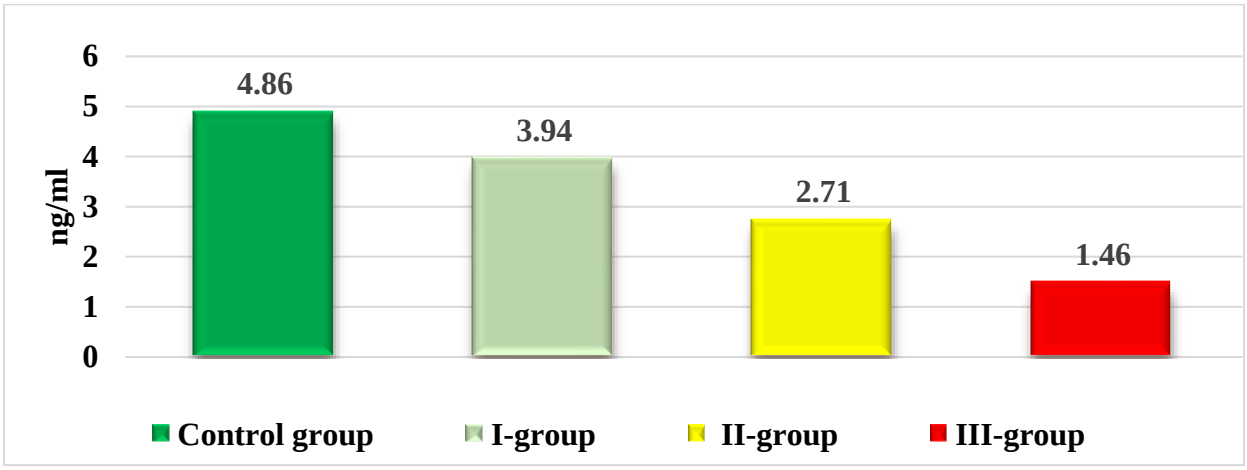

Figure 1. Comparative analysis of Annexin A1 levels by clinical stage (ng/mL)

In the first group, consisting of patients in the early clinical stage, the ANXA1 level averaged 3.94±0.21 ng/mL, which was found to be significantly lower than in the control group ($p<0.05$). Although anti-inflammatory compensatory mechanisms were partially preserved in the body at this stage, a decrease in biomarker levels was observed as a result of the activation of the immune inflammatory process. In the second group of patients in the pronounced clinical stage, the level of ANXA1 decreased further, averaging 2.71±0.18 ng/mL. This parameter was statistically significantly lower than in the first group ($p<0.01$) and was noted to be associated with increased disease activity and the development of erosive-destructive changes. At this stage, an increase in the activity of inflammatory cytokines and a decrease in the activity of anti-inflammatory defense mechanisms were observed. In the third group of patients in the late clinical stage, the lowest levels of ANXA1 were detected, averaging 1.46±0.12 ng/mL. Statistical analysis confirmed that this parameter was significantly lower compared to the control group and patients in the early stage ($p<0.001$). In the late stage, a significant decrease in ANXA1 levels was observed against the background of chronic inflammation, irreversible structural changes in the joints, and functional insufficiency. In the control group, this parameter was within the normal range and averaged 4.86±0.32 ng/mL. The obtained results demonstrated a statistically significant decrease in ANXA1 levels as the clinical stages of rheumatoid arthritis progressed. A continuous decrease in ANXA1 levels was observed with the changing clinical stages of rheumatoid arthritis. This indicates that this biomarker is closely associated with disease activity, the level of inflammation, and destructive changes in the joints. Correlation analysis between ANXA1 and DAS28 scores revealed a decrease in ANXA1 levels as inflammatory activity increases in rheumatoid arthritis. The obtained results demonstrated the diagnostic and prognostic significance of this biomarker in assessing disease activity.

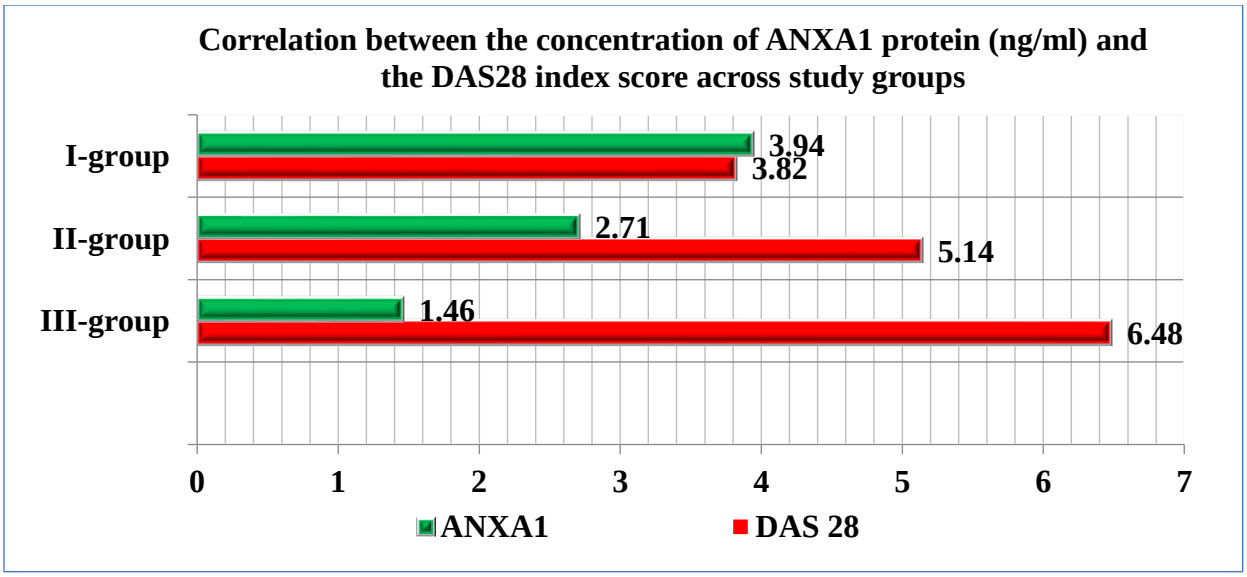

Figure 2. Correlation between ANXA1 protein concentration (ng/mL) and DAS28 index score in the study groups

In the first group of patients at the early clinical stage, the ANXA1 level averaged 3.94±0.21 ng/mL, and the DAS28 index was 3.82±0.24 points. According to the results of the correlation analysis, a moderate inverse relationship was found between the ANXA1 level and the DAS28 index (r=-0.46; p<0.05). This indicated that the anti-inflammatory defense mechanism decreases as disease activity increases. The results of the study showed a clear inverse correlation between an increase in the DAS28 index and a decrease in the ANXA1 level as the clinical stages of rheumatoid arthritis worsened. In the second group at the pronounced clinical stage, the ANXA1 level decreased to 2.71±0.18 ng/mL, while the DAS28 index increased to 5.14±0.31 points. A strong inverse correlation was noted between ANXA1 and DAS28 in this group (r=-0.63; p<0.01). This result was explained by a decrease in ANXA1 levels against the background of inflammatory process activation and increased expression of pro-inflammatory cytokines. In the third group of patients in the late clinical stage, the lowest ANXA1 level was 1.46±0.12 ng/mL, while the DAS28 index was 6.48±0.37 points. Correlation analysis statistically confirmed the presence of a very strong inverse relationship between ANXA1 and the DAS28 index (r=-0.78; p<0.001). This condition indicated that in patients with high disease activity, there is a sharp weakening of the anti-inflammatory defense mechanism and an intensification of destructive processes in the joints. In the control group, the ANXA1 level averaged 4.86±0.32 ng/mL, and the DAS28 index was 2.14±0.16 points. In the control group, no significant correlation was observed (r=-0.18; p>0.05). These changes justify the possibility of using ANXA1 as an important laboratory biomarker in assessing the activity of rheumatoid arthritis and predicting disease progression.

Correlation analysis between ANXA1 and the Larsen Score index showed a decrease in ANXA1 levels as the inflammatory process and destructive changes in the joints increase in rheumatoid arthritis. The results obtained showed that this biomarker is of great importance in assessing radiological progression.

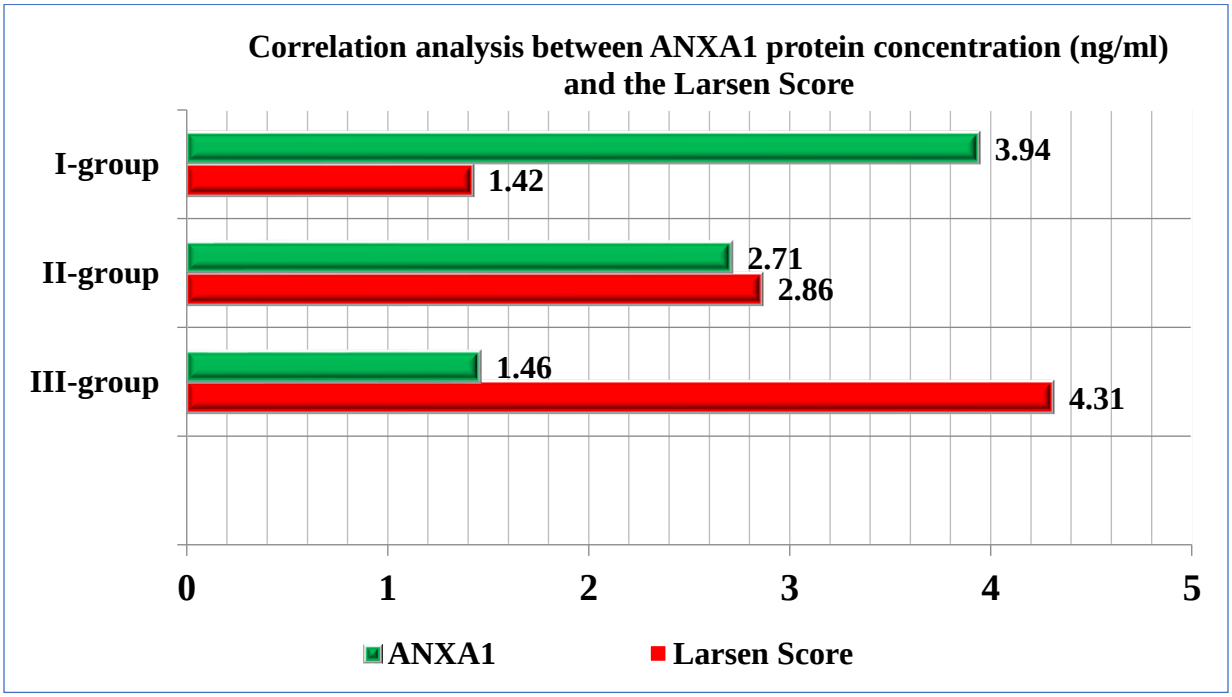

Figure 3. Correlation analysis between ANXA1 protein (ng/ml) and the Larsen Score

In Group I patients at the early clinical stage, the ANXA1 level averaged 3.94±0.21 ng/mL, while the Larsen index was 1.42±0.18 points. According to the correlation analysis results, a moderate inverse correlation was found between these parameters (r=-0.41; p<0.05). This was explained by the development of initial erosive changes in the joints alongside an increase in inflammatory activity and a progressive decrease in the protective effect of ANXA1. In Group II patients at the pronounced clinical stage, the ANXA1 level decreased to 2.71±0.18 ng/mL, and the Larsen index averaged 2.86±0.24 points. In this group, a strong inverse correlation was noted between ANXA1 and the Larsen index (r=-0.64; p<0.01). This result indicates a decrease in anti-inflammatory defense mechanisms against the background of intensified synovial inflammation, pannus formation, and the activation of erosive-destructive processes. In Group III patients at the late clinical stage, the lowest ANXA1 level was found at 1.46±0.12 ng/mL, while the Larsen index was at its highest, averaging 4.31±0.27 points. The correlation analysis results confirmed a very strong inverse relationship between these parameters (r=-0.79; p<0.001). This demonstrated that as the disease duration increases, irreversible structural changes develop in the joints,

and the activity of ANXA1 in anti-inflammatory defense mechanisms sharply decreases. In the control group, the ANXA1 level averaged 4.86±0.32 ng/mL; no radiological destructive changes were observed, and the Larsen index was 0.42±0.06 points. No statistically significant correlation was found in this group (r=-0.12; p>0.05). The study results showed that the decrease in the ANXA1 level in rheumatoid arthritis is inextricably linked with an increase in the Larsen index. It was found that a strong inverse correlation persists between the decrease in this biomarker and the increase in the degree of radiological destruction as the clinical stages of the disease advance. This substantiates the possibility of using ANXA1 as an important laboratory prognostic marker in assessing joint destruction and disease progression in rheumatoid arthritis. The correlation analysis of ANXA1 levels with clinical and functional indices in rheumatoid arthritis was evaluated separately for each clinical stage. The obtained results showed that as the clinical stages of the disease advance, the correlation between the ANXA1 level and the indices assessing disease activity increases.

Table 1. Correlation between ANXA1 levels and clinical indices across clinical stages of RA

Group	CDAI	SDAI	Richie Index	Charcot Index
I-group	0,52 (p<0,01)	0,50 (p<0,01)	0,47 (p<0,05)	0,44 (p<0,05)
II-group	0,68 (p<0,001)	0,66 (p<0,001)	0,62 (p<0,01)	0,59 (p<0,01)
III-group	0,81 (p<0,001)	0,80 (p<0,001)	0,74 (p<0,001)	0,69 (p<0,001)

In Group I patients at the early clinical stage of the disease, a moderate positive correlation was noted between the ANXA1 level and the Charcot index (r=0.44; p<0.05). This was explained by the increase in functional limitations and pain syndrome alongside the activation of the inflammatory process. A positive correlation was found between ANXA1 and the Clinical Disease Activity Index (r=0.52, p<0.01), the Simplified Disease Activity Index (r=0.50, p<0.01), and the Ritchie Articular Index (r=0.47, p<0.05). Due to the relatively low disease activity at the early stage, the correlation indicators were moderate. In Group II patients at the pronounced clinical stage of the disease, the correlation between ANXA1 levels and the clinical indices was observed to be stronger. A positive correlation was noted with the Charcot index (r=0.59, p<0.01), CDAI (r=0.68, p<0.001), SDAI (r=0.66, p<0.001), and the Ritchie index (r=0.62, p<0.01). At this stage, it was found that the intensification of the immune inflammatory process, the exacerbation of the joint syndrome, and the increase in functional impairments strengthened the relationship between ANXA1 levels and the clinical indices. The high correlation with the CDAI and SDAI indices demonstrated that the level of this biomarker changes as disease activity increases. In Group III patients at the late clinical stage of the disease, a strong correlation was observed between the ANXA1 level and the clinical indices. A high degree of positive correlation was found with the Charcot index (r=0.69, p<0.001), CDAI (r=0.81, p<0.001), SDAI (r=0.80, p<0.001), and the Ritchie index (r=0.74, p<0.001). In the late stage, as a result of the chronic immune inflammatory process, irreversible structural changes in the joints, and the worsening of functional insufficiency, a further strengthening of the pathogenetic relationship between ANXA1 levels and clinical indices was noted. In particular, the highest correlation with the CDAI and SDAI indices indicated the maximum activation of the immune inflammatory process in patients with high disease activity.

Clinical and laboratory efficacy of comprehensive treatment for RA

The DAS28 index was calculated to assess the level of rheumatoid arthritis activity in the study groups.

Table 2. DAS28 index indicators in the study groups

Group	Low activity	Moderate activity	High activity
I-group	**8 (25,0%)**	**17 (53,6%)**	**6 (21,4%)**
II-group	**5 (12,5%)**	**17 (41,1%)**	**19 (46,4%)**
III-group	**3 (9,1%)**	**12 (31,8%)**	**21 (59,1%)**
Total (n=108)	**16 (14,8%)**	**46 (42,6%)**	**46 (42,6%)**

According to the analysis results, out of 108 patients, high activity was recorded in 46 (42.6%), moderate activity in 46 (42.6%), and low activity in 16 (14.8%). The findings showed that rheumatoid arthritis activity increased with the duration of the disease. Based on the DAS28 index, the level of disease activity was assessed for each patient, and treatment strategies were formulated individually.

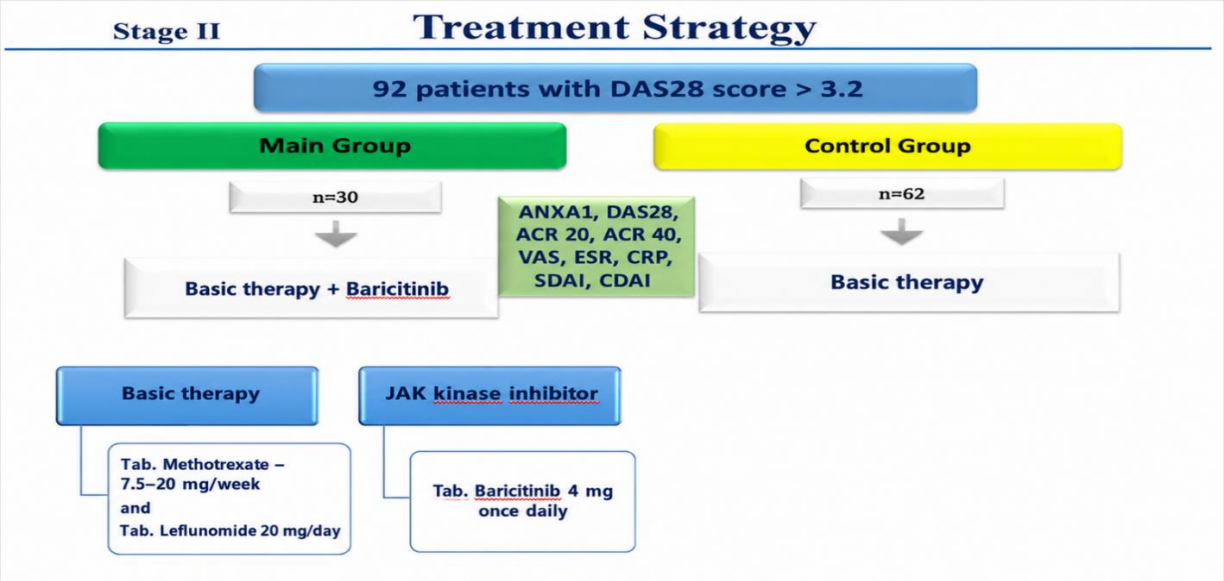

Figure 4. An individualized treatment algorithm based on the DAS28 index

During the study, 92 patients with a DAS28 index greater than 3.2 were identified and, to determine the effectiveness of the treatment, were divided into a main group of 30 patients and a control group of 62 patients. Patients in the main group were prescribed standard therapy with basic disease-modifying antirheumatic drugs (DMARDs) (methotrexate at a dose of 15–25 mg per week, or leflunomide at a dose of 20 mg per day in cases where there are contraindications to methotrexate) in combination with baricitinib, a Janus kinase (JAK1/JAK2) inhibitor, administered orally at a dose of 4 mg per day, and the treatment was observed for 52 weeks. Patients in the control group received standard therapy with basic disease-modifying antirheumatic drugs (DMARDs) (methotrexate at a dose of 15–25 mg per week, or leflunomide at a dose of 20 mg per day in cases of contraindications to methotrexate). The dynamics of the DAS28 index in patients of the study groups after 52 weeks of treatment were analyzed.

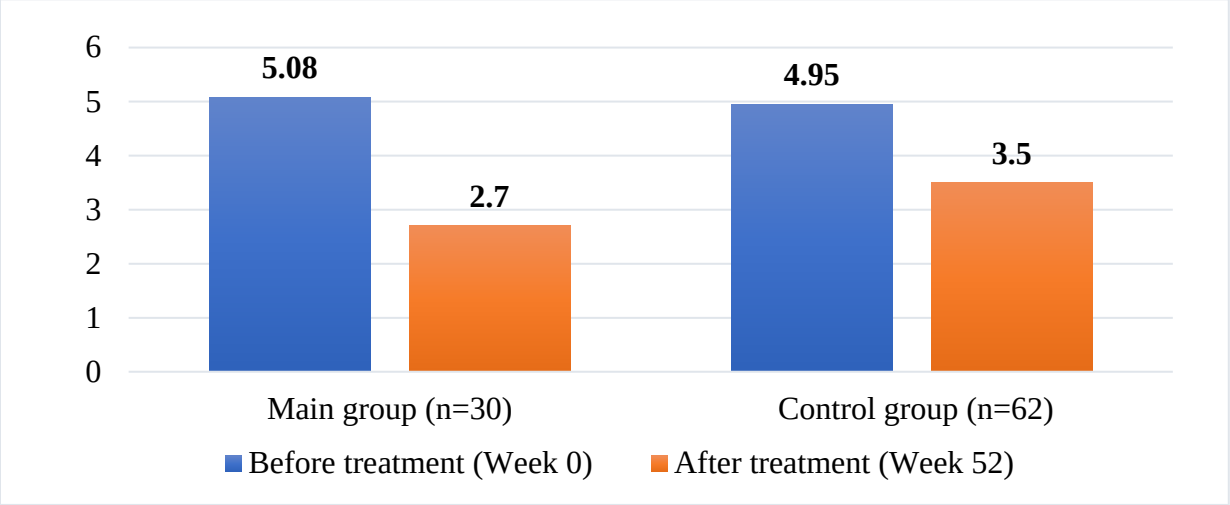

Figure 5. Evaluation of treatment efficacy according to the DAS28 index

To assess disease activity after 52 weeks of treatment, the dynamics of the DAS28 index were analyzed. In both groups of patients, the DAS28 index was 5.08±0.12. In the main group, the DAS28 index decreased from 5.08±0.12 points to 2.70±0.08 points as a result of baricitinib administration in combination with BKMAP. The absolute decrease was 2.38 points, representing a 46.9% decrease compared to the baseline value ($p<0.001$). In the control group, on the background of standard BKMAP therapy, the DAS28 index decreased from 4.95±0.12 points to 3.50±0.09 points. The average decrease in the index was 1.45 points, which was 31.1% relative to the baseline ($p<0.05$). Intergroup comparison revealed that at the end of 52 weeks, the DAS28 score in the control group was statistically significantly lower than in the main control group ($p<0.05$). The obtained results showed that the use of baricitinib in combination with standard BKMAP therapy more effectively reduces rheumatoid arthritis activity.

Assessment of the dynamics of ANXA1 protein levels in the study groups

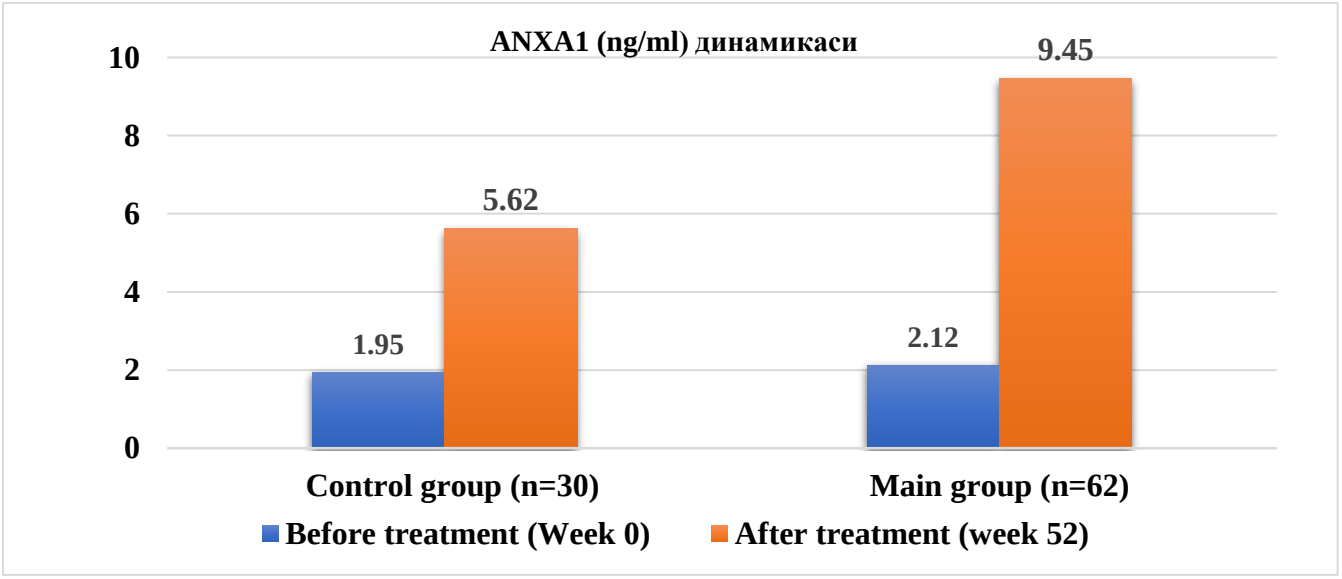

Figure 6. Evaluation of treatment efficacy based on ANXA1 protein levels (ng/ml)

To evaluate treatment efficacy, the dynamics of ANXA1 (ng/mL) were analyzed. The mean ANXA1 level in patients of both groups was 7.60±0.24 ng/mL. In the main group, as a result of using baricitinib in combination with BKMAP, the ANXA1 level increased from 7.60±0.24 ng/mL to 10.45±0.28 ng/mL. The absolute increase was 2.85 ng/mL, representing a 37.5% increase compared to the baseline ($p<0.001$). In the control group, the ANXA1 level increased from 7.60±0.24 ng/mL to 8.62±0.26 ng/mL during standard BKMAP therapy. The mean increase in this indicator was 1.02 ng/mL, which equated to 13.4% of the baseline value ($p<0.05$). Based on the results of the intergroup comparison, it was determined that at the end of 52 weeks, the

ANXA1 level in the main group was statistically significantly higher than in the control group ($p<0.05$). The obtained results demonstrated that the use of baricitinib in combination with standard BKMAP therapy activates endogenous anti-inflammatory mechanisms and serves to control rheumatoid arthritis activity more effectively. The dynamics of interleukin-6 (IL-6) levels before and after treatment were evaluated in the study groups.

Table 3. Assessment of Treatment Efficacy Based on Interleukin-6 (pg/ml) Levels

Group	Before treatment (Week 0)	After treatment (Week 52)	Statistical confidence level
Main group	**13,4±1,5 pg/ml**	**6,12±0.76**	**(p<0,001)**
Control group	**13,4±1,5 pg/ml**	**7,94±1.12**	**p<0,05)**

After treatment, the dynamics of IL-6 concentration, an important laboratory marker of inflammatory activity, was evaluated. Before treatment, the mean IL-6 level in the main and control groups of the study was 13.4±1.5 pg/ml. In the main group, as a result of using baricitinib in combination with BKMAP, the IL-6 level decreased from 13.4±1.5 pg/ml to 6.12±0.76 pg/ml, showing a 54.3% reduction compared to baseline. The observed change was assessed as statistically highly significant ($p<0.001$). In the control group, under standard BKMAP therapy, the IL-6 concentration decreased from 13.4±1.5 pg/ml to 7.94±1.12 pg/ml. According to the results of the intergroup comparison, it was found that at the end of 52 weeks, the IL-6 level in the main group was significantly lower than in the control group. The 54.3% decrease in IL-6 concentration in the main group is explained by baricitinib's effective inhibition of inflammatory cytokine production. The obtained results confirm that the use of baricitinib in combination with standard BKMAP therapy provides more effective control of inflammatory activity in rheumatoid arthritis and reliably reduces IL-6 levels.

Conclusion

In patients with rheumatoid arthritis (RA), serum levels of ANXA1 are characterized by fluctuations that correlate with the course and duration of the disease. A decrease in ANXA1 levels is observed alongside an increase in disease activity. Concurrently, dynamic changes in ANXA1 levels are detected at all stages of the disease's clinical course. In patients with RA, ANXA1 levels were found to change in correlation with immune inflammatory markers (TNF-α and IL-6). A decrease in ANXA1 levels is accompanied by an increase in inflammatory cytokines and heightened disease activity. Furthermore, ANXA1 levels were associated with early remodeling processes in joint tissues, and its fluctuation manifested as an early sign of destructive changes. These findings confirm the potential of using ANXA1 as an important biomarker for assessing inflammatory activity and early joint remodeling in RA.

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