ORIGINAL INVESTIGATIONS

Relationship between laboratory biomarkers and ultrasonographic signs of inflammation in patients with rheumatoid arthritis treated with a rituximab biosimilar

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Objective: *to assess the relationship between laboratory biomarkers and ultrasonographic signs of inflammation in patients with rheumatoid arthritis during therapy with a rituximab (RTM) biosimilar.*

Patients and methods. *20 patients with definite diagnosis of RA were examined. All patients received 2 infusions of RTM (Acellbia®), at a dose of 600 mg intravenously 2 weeks apart during therapy with methotrexate, non-steroidal anti-inflammatory drugs and glucocorticoids. Clinical and laboratory parameters were analyzed immediately before the start of therapy, and then 12 and 24 weeks after the first infusion of the drug.*

Results and discussion. *By the 24th week of RTM therapy, a good/moderate effect according to the EULAR criteria was registered in 17 (85%) patients; remission according to DAS28 (<2.6) was achieved in 4 (20%) patients, SDAI (≤3.3) – in 2 (10%), CDAI (≤2.8) – in 1 (5%). Prior to the start of treatment, active synovitis was detected in 13 (65%) patients by power Doppler imaging (PD), and in 20 (100%) patients by gray scale scanning. During therapy with the RTM biosimilar, a significant decrease in inflammatory changes in the joints was observed, and by the 24th week after the start of treatment, the median PD was 0.5; active inflammation persisted in 7 (35%) patients. As shown by ROC analysis, the initial level of interleukin (IL) 6 >100.0 pg/ml is associated with the persistence of inflammatory activity according to PD by the 24th week of therapy with the RTM biosimilar, while the sensitivity was 85% and the specificity was 62% (AUC 0.78, 95% CI 0.57–0.99)*

Conclusion. *An association was found between an increased level of pro-inflammatory cytokines, mainly IL6, and the activity of synovial inflammation according to ultrasound data. IL6 is the most promising marker for predicting persistent inflammatory activity based on the results of PD; other analyzed parameters have worse sensitivity and specificity parameters.*

Key words: *rheumatoid arthritis; disease activity; sonography; pro-inflammatory cytokines; rituximab biosimilar.*

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Ultrasonography is successfully used to assess the structure of small joints of the hands and feet. When performing ultrasonography of the joints, various scanning options are used, the main of which are the gray scale mode (GS), which provides information about the anatomy and morphological changes of the joints, and power Doppler imaging (PD), which allows visualizing microcirculatory blood flow in the area under study. Thus, GS reflects the proliferation of the synovium, and PD reflects the microcirculatory blood flow in the inflamed synovium [1–4].

Modern principles of pharmacotherapy of RA are based on the early prescription of disease-modifying anti-inflammatory drugs (DMARDs), primarily methotrexate (MT), at the onset of the disease (the "window of opportunity" concept), as well as on the use of various classes of genetically engineered biological drugs (GEBD), which in some cases leads to stable remission [5–7]. Several studies have shown that short-term, as well as long-term, prognosis in RA is much more favorable if remission is achieved in the early stages of the disease [8, 9]. After a wide introduction of biologics into clinical practice, the issue of an objective assessment of the activity of the disease and detection of subclinical inflammation of the joints has become more actively discussed. It is believed that ultrasound of the joints can be a useful method for determining subclinical inflammation in the absence of clinical activity [10]. Thus, ultrasound assessment is now included in a number of large clinical studies to detect latent inflammatory activity [11–15]. A large meta-analysis that combined 19 studies and a total of 1,618 patients with RA, of whom 1,368 were in clinical remission, has shown that according to GS and PD, inflammatory changes in the joints were absent (GS-, PD-) in only 15% of patients, the remaining patients had subclinical inflammation (GS+, PD+ at 84%; GS+, PD- at 41% GS-, PD+ at 44%). Patients with ultrasound signs of active synovitis (GS+, PD+) had a high risk of exacerbation of the disease (odds ratio, OR 3.2) and progression of destructive changes in the joints (OR 9.13) [14]. Active synovitis according to ultrasound findings was associated with certain immunological disorders, the study of which may allow a more objective assessment of the inflammatory activity [16, 17].

Table 1. Clinical and immunological characteristics of RA patients before the administration of RTM (n=20)

Parameters	Results
Men/women, n (%)	2 (10)/18(90)
Age (years), Me [25-й; 75-й percentiles]	h
Disease duration (months) Me;IQR [25; 75 percentiles]	39.5 [20.0; 84.0]
X-ray, stage, n (%): I /II/III/IV	2 (10)/13 (65)/4 (20)/1 (5)
Functional disorders (%): I /II/III/IV	4 (20)/11 (55)/5 (25)/0
DAS28-ESR, Me;IQR [25; 75 percentiles]	5.6 [4.9; 6.8]
HAQ, Me;IQR [25; 75percentiles]	1.7 [1.2; 2.3]
ESR (Westergren), mm/h, Me;IQR [25; 75 percentiles]	45.0 [19.5; 80.0]
CRP, mg/ml Me;IQR [25; 75 percentiles]	12.3 [8.9; 42.5]
IgM RF, IU/ml, Me;IQR [25; 75 percentiles]	197.0 [83.2; 492.5]
IgM RF+, n (%) IgM RF-, n (%)	18 (90) 2 (10)
Anti-CCP, U/ml, Me;IQR [25; 75percentiles]	161.8 [98.3; 300.0]
Anti-CCP +, n (%)	20 (100)

On the one hand, the implementation of biologics in clinical practice increased the effectiveness of the therapy and improved the prognosis of the disease for patients with the most severe forms of RA, and on the other hand, led to a significant increase in the cost of treatment [18]. Reducing the cost of treatment with effective but expensive GEBD and, as a result, increasing the availability of innovative therapy for patients living in countries with limited economic resources is a priority task of healthcare systems worldwide. This problem has been partially solved thanks to the development of biosimilars of biologics, broad use of which in clinical practice has become possible due to the expiration of patents for many original GEBDs [19, 20].

The purpose of this study is to assess the relationship between laboratory biomarkers and ultrasound signs of inflammation in patients with RA against the background of the therapy with a rituximab biosimilar (RTM, Acellbia®).

Patients and methods. 20 patients with a reliable diagnosis of RA were examined according to the criteria of ACR/EULAR (American College of Rheumatology / European Alliance of Associations for Rheumatology) 2010; Table 1).

According to the Table 1, most of the patients were female, middle–aged, with a long course of the disease (median, [Me] duration of RA - 39.5 months), seropositive for IgM rheumatoid factor (RF) and antibodies to cyclic citrullinated peptide (Anti-CCP), had high activity of the inflammatory process, radiological stage II or III, functional disorders class II, moderate impairment of vital activity. Before the start of the therapy with the RTM biosimilar, patients received MT at a stable dose for at least 4 weeks (Me 15 mg; [10; 17.5] mg), as well as nonsteroidal anti-inflammatory drugs (NSAID) and glucocorticoids (GC) up to 10 mg /day without sufficient therapeutic effect.

All patients received 2 infusions of RTM biosimilar at a dose of 600 mg intravenously with an interval of 2 weeks during the therapy with MT, NSAID and GC. Clinical and laboratory indicators were analyzed immediately before the start of the therapy, 12 and 24 weeks after the first infusion. EULAR criteria were used to evaluate the effectiveness of the treatment [21]. Remission of the disease was assessed by the DAS28-ESR.

The study was approved by the local ethical committee of the Federal State Budgetary Scientific Institution "V.A. Nasonova Research Institute of Rheumatology" (protocol №32 dated 12/20/2018).

ESR was determined by the standard international Westergren's method (normal value ≤30 mm/h). Serum concentration of CRP, IgM RF was determined by immunonephelometric method on BN ProSpec analyzer (Siemens, Germany), and a high-sensitivity latex-enhanced test (sensitivity 0.175 mg/L) was used to estimate CRP level. A value of ≤5.0 mg/L was considered a normal level of CRP in blood serum, and the upper limit of normal IgM RF according to the manufacturer's instructions was 15.0 IU/ml. The quantitative assessment of serum anti-CCP level was performed by enzyme immunoassay (IFA) using commercial Axis-Shield reagent kits (UK). The upper limit of normal values was 5.0 U/ml. The level of matrix metalloproteinase 3 (MMP3) in blood serum was measured by ELISA using a commercial reagent set from Invitrogen (USA). According to the manufacturer's recommendations, the upper limit of the norm is 28.8 ng/ml. In healthy donors the upper limit of normal values did not exceed 19.4 ng/ml (n=30). The concentration of 27 cytokines in serum: Interleukin (IL) 1β, IL1Pa, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IL13, IL15, IL17, Eotaxin, FGF-basic, G-CSF, GM-CSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFbb, RANTES, tumor necrosis factor (TNF) α, VEGF were determined using multiplex xMAR technology on a Bio-Plex array system analyzer (BIO-RAD, USA). The upper limit of the norm (pg/ml) in the study of sera of 30 healthy donors was: IL1β – 10.2; IL1Pa – 1287.4; IL2 – 153.6; IL4 – 10.9; IL5 – 10.6; IL6 – 39.6; IL7 – 287.7; IL8 – 50.2; IL9 – 307.5; IL10 – 554.6; IL12 – 53.6; IL13 – 110.4; IL15 – 66.8; IL17 – 471.3; Eotaxin – 1616; FGF-basic – 71.8; G-CSF – 52.5; GM-CSF – 261.1; IFNγ – 4298.7; IP10 – 20219.7; MCP1 – 280.1; MIP1α – 42.7; MIP1β – 165.9; TNFα – 145.9; VEGF – 7693.1. The sera under study were stored at -70 °C.

Ultrasound examination of seven articular zones of the hands and feet of the clinically dominant side (wrists, II–III metacarpophalangeal, II-III proximal interphalangeal, II, V metatarsophalangeal joints) was performed on Logiq 9 (GE, USA) and MyLabTwice (ESAOTE, Italy) devices using a multi–frequency linear sensor (10–18 MHz) with the PD technique, whose parameters have been adapted to register low–speed streams (PRF 300–600 Hz, low filter, dynamic range – 20–40 dB). Ultrasound signs of synovitis were intraarticular effusion and proliferation of the synovium in the GS mode (B-mode) and hypervascularization of the synovium in the PD mode according to the criteria of OMERACT (Outcome Measures in Rheumatology Clinical Trials) [22]. In the GS and PD modes, synovitis was registered on the basis of a semi-quantitative assessment of the thickness of the synovium and its hypervascular flows, which was also expressed in points from 0 to 3.

Statistical evaluation of the results was performed using Statistica 10.0 software package (StatSoft, USA), including generally accepted methods of parametric and nonparametric analysis. Mann–Whitney test was used to compare two groups of parameters whose distribution was different from normal, and Kruskal–Wallis

test was used to compare three or more groups; the results were presented as Me with interquartile range [25th percentile; 75th percentile]. Correlational analysis was performed using the Spearman method. Differences were considered statistically significant at $p<0.05$.

Results. Before RTM therapy, DAS28-ESR (5.6 [4.9; 6.8]), SDAI (Simplified Disease Activity Index; 27.17 [23.08; 39.9]), and CDAI (Clinical Disease Activity Index; 26.6 [22.25; 37]) indices corresponded to high RA activity. By the 24th week of RTM treatment, a good/moderate effect according to EULAR criteria was recorded in 17 (85%) patients; remission according to DAS28-ESR (<2.6) was achieved in 4 (20%) patients, SDAI (≤3.3) in 2 (10%), and CDAI (≤2.8) in 1 (5%).

The levels of the studied cytokines in RA patients and healthy donors are presented in Table 2.

According to Table 2, RA patients had statistically significantly higher concentrations of proinflammatory cytokines (IL1β, IL6, IL12, IL15, TNFα), chemokines (IL8, MIP1β, MCP1) and growth factors (G-CSF, FGF) compared with healthy donors ($p<0.05$). Patients with RA had higher levels of several anti-inflammatory cytokines (IL4, IL5, IL9, IL10, IL1Pa, Eotaxin) ($p<0.05$), while the levels of individual growth factors (IL7, VEGF), chemokines (MIP1α, IP10) and anti-inflammatory cytokines (IL13) were either lower or not different from those of the controls.

Table 2. Initial cytokine profile of patients with RA and healthy donors, Me [25th; 75th percentiles], pg/ml

Parameters	Patients with RA (n=20)	Healthy donors (n=30)
IL1β	14.4 [4.8; 41.3]*,#	4.1 [2.6; 4.9]
IL1Pa	1808 [461.8; 3285.3]*,#	150.6 [111.2; 253.8]
IL 2	45.3 [0.01; 201.9]#	10.8 [5.5; 13.9]
IL 4	7.3 [6.4; 9.5]*,#	3.3 [0.2; 5.9]
IL 5	11.9 [2.6; 28.9]*,#	2.9 [0.2; 5.2]
IL 6	105.5 [38.5; 381.7]*,#	7.8 [4.5; 13.1]
IL 7	9.2 [5.1; 72.2]	8.2 [0.5; 21.5]
IL 8	41.5 [34.4; 53.0]*,#	12.5 [4.8; 16.3]
IL 9	131.8 [58.7; 354.5]*,#	34.2 [26.3; 42.4]
IL 10	103.3 [20.2; 466.9]*,#	13.2 [5.8; 37.5]
IL 12	123.5 [43.9; 365.3]*,#	5.8 [2.2; 9.9]
IL 13	11.8 [5.5; 102.5]	16.7 [9.9; 22.4]
IL 15	132.9 [40.9; 290.4]*,#	6.7 [3.9; 17.4]
IL 17	76.1 [66.3; 100.1]	22.9 [5.2; 90.3]
Eotaxin	502.8 [223.6; 1373.8]*,#	102.4 [19.4; 585.7]
FGF basic	43.2 [35.7; 51.4]*,#	27.3 [19.3; 44.3]
G-CSF	117.8 [92.8; 332.2]*,#	10.9 [2.4; 21.3]
GM-CSF	0.01 [0.01; 115.9]	39.9 [21.6; 61.3]
IFNγ	493.3 [181.3; 1294.5]	285.4 [112.3; 1037.9]
IP10	2545.3 [1878.9; 3070.4]	717.8 [188.7; 4064.8]
MCP1	181.9 [45.4; 511.5]*,#	48.6 [22.3; 120.7]
MIP1α	5.1 [4.4; 7.8]*,#	10.8 [8.8; 18.1]
MIP1β	94.4 [74.4; 134.5]*,#	66.0 [49.4; 99.4]
PDGFbb	3548.5 [2771.3; 4248.2]*,#	26024.5 [5854.8; 58715.0]
RANTES	8584.2 [7304.3; 9665.5]	–
TNFα	546.4 [170.6; 1751.9]*,#	38.9 [17.2; 64.9]
VEGF	111.4 [67.4; 370.5]	205.6 [63.9; 312.8]

*p<0.05 relative to the control group; #level change ≥30% relative to the control group.

Table 3. Dynamics of inflammatory changes in the joints according to ultrasound examination, Me [25th; 75th percentiles], points

Mode	Initially	After 24 weeks
GS	9.5 [7.0; 15.0]	9.0 [6.0; 11.5]#
PD	2.0 [1.0; 3.5]	0.5 [0.0; 2.0]*

* p<0.05; # p=0.05 compared to baseline.

Before the start of the therapy, active synovitis according to PD was detected in 13 (65%) patients, and when scanning in the GS mode – in all patients. Against the background of the use of the RTM biosimilar, a statistically significant decrease in inflammatory changes in the joints was observed. By the 24th week of treatment, the Me of PD was 0.5 (Table. 3), active inflammation persisted in 7 (35%) patients.

At baseline a positive correlation was found between PD findings and the levels of CRP (r=0.54, p=0.02), IL6 (r=0.46, p=0.04), IL13 (r=0.47, p=0.03); and between GS findings and the levels of IL2 (r=0.45, p=0.04), IL5 (r=0.53, p=0.02), IL13 (r=0.46, p=0.03), IL15 (r=0.45, p=0.04), MIP1a (r=0.45, p=0.04) and TNFa (r=0.46, p=0.04).

Depending on the presence of active inflammation according to PD data at the baseline, all patients were divided into two groups in which laboratory indicators of inflammatory activity were evaluated (Table 4).

Patients with inflammation according to PD at baseline, were found to have statistically higher disease activity according to DAS28, CRP level and ESR. There were no significant differences in cytokine profile, however, a tendency to an increase in the levels of IL5, IL6 and MMP3 was found in the presence of active inflammation.

For evaluation of the role of laboratory biomarkers in predicting the persistence of active inflammation during anti B-cell therapy, the baseline level of laboratory indicators was assessed in relation to ultrasound changes after 24 weeks of treatment (Table 5).

Patients with persistent inflammation detected by PD after 24 weeks of the therapy had a higher initial concentration of IL6 compared with patients without inflammation according to the ultrasound findings.

ROC analysis has shown that initial IL6 levels >100.0 pg/mL are associated with the persistence of inflammatory activity detected by PD after 24 weeks of treatment with the sensitivity of 85% and specificity of 62% (AUC 0.78; 95% CI 0.57-0.99; see illustration; Figure 1).

Discussion. Ultrasound methods are increasingly being implemented in clinical practice. Ultrasound can be used to assess joint inflammation, including subclinical inflammation, as well as to monitor disease activity against the background of therapy. We analyzed the relationship between ultrasound signs of inflammatory activity and the level of immunological markers.

Table 4. The disease activity and immunological indicators in patients' groups depending on the presence of inflammation according to PD before the start of the therapy, Me [25th; 75th percentiles]

Parameters	With inflammation (n=13)	Without inflammation (n=7)	p*
DAS28-ESR, points	6.6 [5.6; 6.9]	5.2 [4.3; 5.4]	0.01
SDAI, points	39.4 [25.5; 44.6]	24.9 [22.6; 27.5]	–
CDAI, points	35.0 [22.0; 38.5]	24.0 [22.5; 26.5]	–
ESR, mm/h	70.0 [40.0; 95.0]	17.0 [8.0; 30.0]	0.0001
CRP, mg/l	39.5 [10.2; 48.7]	8.6 [1.9; 10.0]	0.0001
IgM RF, IU/ml	283.0 [170.0; 414.0]	150.0 [9.5; 699.0]	–
IgA RF, U/ml	69.8 [53.4; 200.4]	25.7 [15.1; 164.0]	–
Anti-CCP, U/ml	120.4 [71.2; 265.1]	51.9 [14.2; 264.5]	–
Anti-MCV, U/ml	399.6 [111.4; 1000.0]	225.9 [13.84; 1000.0]	–
MMP3. ng/ml	154.3 [72.9; 200]	42.9 [25.1; 81.4]	0.06
IL1β, pg/ml	10.5 [6.2; 44.0]	18.0 [4.3; 30.5]	–
IL1Pa, pg/ml	1522.5 [849.2; 3355.7]	2093.8 [339.3; 2682.3]	–
IL 2. pg/ml	46.1 [5.89; 253.1]	18.9 [0.01; 131.2]	–
IL 4. pg/ml	7.1 [6.5; 9.4]	7.5 [5.9; 9.6]	–
IL 5. pg/ml	15.2 [5.3; 37.7]	2.7 [0.01; 15.6]	0.05
IL 6. pg/ml	111.6 [95.1; 476.9]	80.2 [18.6; 104.1]	0.06
IL 7. pg/ml	10.6 [5.3; 110.3]	7.8 [2.6; 28.8]	–
IL 8. pg/ml	37.2 [34.7; 51.2]	45.4 [31.5; 54.9]	–
IL 9. pg/ml	136.5 [61.4; 248.9]	63.4 [37.1; 569.1]	–
IL 10. pg/ml	140.5 [32.0; 478.2]	64.5 [13.6; 332.1]	–
IL 12. pg/ml	154.4 [59.3; 278]	60.0 [29.0; 452.6]	–
IL13. pg/ml	14.6 [9.9; 160.2]	6.2 [0.01; 21.1]	–
IL 15. pg/ml	155.9 [69.7; 317.6]	85.9 [0.01; 243.9]	–
IL 17. pg/ml	74.6 [67.9; 98.5]	77.8 [60.8; 105.4]	–
Eotaxin, pg/ml л	632.8 [299.1; 1889.9]	492.7 [174.1; 584.3]	–
FGF basic, pg/ml	44.9 [38.8; 52.3]	37.8 [34.6; 50.5]	–
G-CSF, pg/ml	123.8 [99.6; 379.9]	106.3 [80.5; 258.5]	–
GM-CSF, pg/ml	0.01 [0.01; 79.0]	0.01 [0.01; 152.8]	–
IFNγ, pg/ml	450.9 [284.9; 1578.1]	714.6 [181.3; 892.2]	–
IP10. pg/ml	2555.2 [2135.1; 3289.9]	1990.3 [1764.3; 2850.8]	–
MCP1. pg/ml	150.4 [73.5; 714.3]	213.3 [35.0; 246.7]	–
MIP1α, pg/ml	5.5 [4.6; 8.2]	4.8 [4.0; 5.7]	–
MIP1β, pg/ml	92.6 [67.9; 130.9]	110.9 [84.9; 138.1]	–
PDGFbb, pg/ml	3817.9 [2925.9; 4220.9]	3418.5 [2451.4; 4468.2]	–
RANTES, pg/ml	8509.7 [7398.6; 8998.5]	9833.9 [7210.0; 11677.6]	–
TNFα, pg/ml	447.7 [221.5; 1936.8]	645.1 [159.5; 705.4]	–
VEGF, pg/ml	121.6 [78.2; 599.6]	102.7 [33.1; 133.9]	–

*Differences between groups of RA patients with and without inflammation; AMCV - antibodies to modified citrullinated vimentin.

Patients with inflammation detected by PD had significantly higher disease activity according to DAS28, high levels of CRP and ESR, as well as a tendency to an increase in the concentration of IL5, IL6 and MMP3. To predict continuing inflammatory activity according to PD, IL6 can be considered the most promising marker; its baseline level >100.0 pg/ml was associated with persistent inflammation shown by PD by the 24th week of the therapy with a RTM biosimilar with the sensitivity of 85% and specificity of 62%. Other analyzed indicators have worse sensitivity and specificity parameters.

Similar data were obtained by A. Baillet et al. [17], who in the study of a large group of patients (cohort Etude et Suive des POlyarthrites Differenciees Recentes, ESPOIR) with early RA (n=126), analyzed the relationship between the baseline level of IL6, inflammatory activity by ultrasound and radiological progression of joint destruction during the 3-year follow-up period. A relationship was found between the baseline level of IL6, the number of swollen joints (NSJ) and synovitis according to PD and GS, as well as the presence of erosions. Interestingly, the concentration of CRP correlated only with NSJ ($p<0.001$). These results allow us to regard the baseline level of IL6 as a ultrasonographic biomarker of inflammation. A. Fazaa et al. [18] found a higher level of soluble IL17 receptors in a group of patients with active inflammation detected by ultrasound. There is information about another promising ultrasound marker of synovitis, chemokine CXCL13, whose concentration correlates with the clinical activity of RA and the presence of inflammation detected by ultrasound. Statistical analysis revealed that baseline level of CXCL13 >100 pg/ml was the only independent predictor of residual joint inflammation revealed by ultrasound examination [23]. It should be noted that the results of PD and GS correlate well with the expression of genes of a wide range of proinflammatory mediators (TNFa, IL1Я, VEGF, and to a lesser extent IL6) in the synovial tissue of patients with RA obtained by biopsy [18].

It is interesting to note the important role of MMP3 in predicting persistence of active inflammation detected by PD. L. Zhou et al. [24] revealed a positive association between the level of MMP3 and ultrasound signs of joint inflamma-

tion, as well as more pronounced inflammatory changes in the joints of patients with elevated serum MMP3 levels. Since the level of serum MMP3 directly reflects the degree of synovitis activity, the assessment of this indicator is highly relevant and promising. In our work, we found a tendency to a higher level of MMP3 in the groups of patients with active inflammation.

F.B.G. Lamers-Karnebeek et al. [25] evaluated the role of ultrasound in predicting disease exacerbation after withdrawal of TNFα inhibitors (IFNα). The authors presented the results of the 9-month follow-up of 248 patients with RA who achieved low disease activity during treatment with TNFα and discontinued treatment with GEBD (data from the Potential Optimalisation of Expediency of TNF-I study, POET). An exacerbation was registered in 43% of patients, and arthritis of >1 joint was detected by ultrasound at the time of discontinuation of GEBD in 156 patients. Predictors of exacerbation included longer duration of the disease, seropositivity for RF and Anti-CCP, and the presence of arthritis of >1 joint on ultrasound (OR 1.77; 95% CI 1.16-2.7).

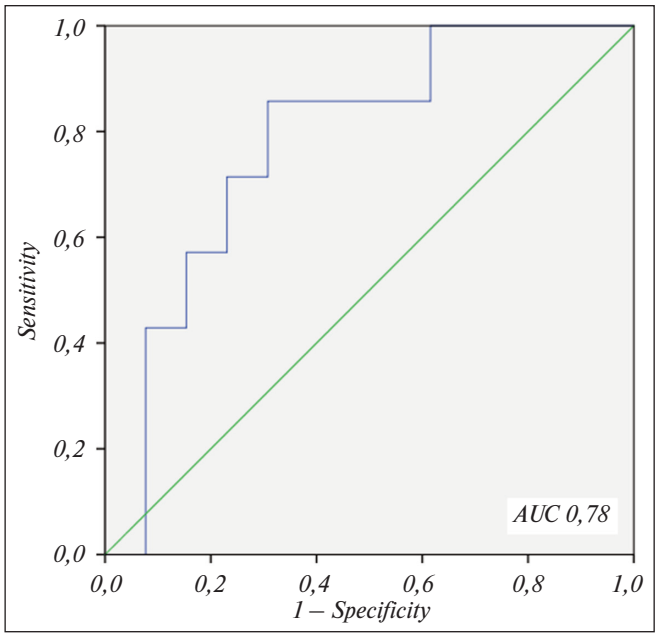
Slightly different data were obtained by H. Kameda et al. [26], in the study of 36 patients with RA who had discontinued biologics therapy and were in remission. Initially, the patients had no painful and swollen joints, and the median value of PD was 0. During the 2-year follow-up period, 20 (55.6%) patients had an exacerbation of the disease, which did not correlate with the results of instrumental methods of examination. In 2 patients with active inflammation according to PD results, an exacerbation was registered 55 and 105 days after the beginning of the follow-up. Having considered a wide range of laboratory indicators, the authors concluded that initially increased levels of IL2 and lower levels of sTNFRI (soluble TNF receptors type I) are predictors of sustained disease remission.

In general, the analysis of the relationship between inflammatory changes of the joints according to ultrasound examination and laboratory indicators of inflammatory activity allows us to suggest the presence of an association between increased levels of CRP, ESR, proinflammatory cytokines, mainly IL6, and the activity of synovial inflammation according to ultrasound examination. Thus, IL6 is the most promising marker for predicting

Table 5. Initial clinical and laboratory indicators of patients depending on ultrasound changes after 24 weeks of the therapy, Me [25th; 75th percentiles]

Parameters	With inflammation according to PD (n=7)	Without inflammation according to PD (n=13)
DAS28-ESR, points	6.6 [5.4; 7.2]	5.4 [4.7; 5.7]
SDAI, points	39.6 [23.2; 47.9]	26.3 [22.9; 31.9]
CDAI, points	36.5 [23.0; 47.0]	25.5 [22.0; 31.0]
ESR, mm/h	62.0 [22.0; 130.0]	40.0 [17.0; 73.0]
CRP, mg/l	37.1 [9.2; 46.0]	10.0 [8.6; 44.4]
IgM RF, IU/ml	318.0 [170.0; 519.0]	201.0 [79.3; 502.0]
IgA RF, U/ml	58.3 [53.4; 147.2]	104.7 [16.9; 200.4]
Anti-CCP, U/ml	159.6 [17.2; 265.1]	119.3 [51.9; 264.5]
Anti-MCV, U/ml	225.9 [86.9; 1000.0]	580.4 [60.8; 1000.0]
MMP3. ng/ml	154.3 [56.1; 200.0]	75.9 [26.7; 123.4]
IL1β, pg/ml	18.5 [4.5; 63.3]	10.5 [4.8; 30.5]
IL1Pa, pg/ml	3355.7 [448.5; 14548.3]	953.2 [475.1; 2206.7]
IL 2. pg/ml	253.1 [0.01; 850.9]	18.9 [0.01; 75.8]
IL 4. pg/ml	7.0 [5.9; 9.3]	7.8 [6.5; 9.6]
IL 5. pg/ml	15.2 [2.7; 30.8]	5.3 [2.7; 27.0]
IL 6. pg/ml	286.4 [106.8; 590.7]	95.1 [31.5; 108.5]*
IL 7. pg/ml	10.6 [3.8; 361.5]	8.5 [5.3; 28.8]
IL 8. pg/ml	47.0 [36.4; 54.9]	39.2 [33.9; 46.2]
IL 9. pg/ml	127.0 [50.8; 385.9]	192.3 [62.2; 323.2]
IL 10. pg/ml	148.2 [21.2; 1877]	66.1 [19.2; 332.1]
IL 12. pg/ml	154.4 [35.7; 1064.4]	72.1 [46.1; 237.7]
IL13. pg/ml	22.7 [6.2; 275.5]	11.6 [2.7; 21.1]
IL 15. pg/ml	317.6 [23.5; 845.3]	94.9 [58.5; 176.5]
IL 17. pg/ml	67.9 [64.0; 74.6]	77.8 [74.9; 101.6]
Eotaxin, pg/ml л	857.7 [423.2; 3681.3]	340.9 [216.1; 584.3]
FGF basic, pg/ml	40.9 [35.7; 54.1]	43.9 [35.7; 48.2]
G-CSF, pg/ml	102.3 [94.1; 258.5]	130.6 [91.4; 382.5]
GM-CSF, pg/ml	0.01 [0.01; 418.7]	0.01 [0.01; 72.7]
IFNγ, pg/ml	535.7 [175.2; 2939.2]	317.5 [181.3; 892.2]
IP10. pg/ml	2555.2 [1934.8; 3289.9]	2471.0 [1764.3; 2850.8]
MCP1. pg/ml	308.7 [42; 1119.3]	90.7 [48.7; 246.7]
MIP1α, pg/ml	5.0 [4.4; 7.7]	5.1 [4.4; 8.0]
MIP1β, pg/ml	83.7 [63.6; 99.1]	110.9 [84.9; 151]
PDGFbb, pg/ml	2925.9 [2656.1; 3308.7]	3975.8 [3418.5; 4275.6]
TNFα, pg/ml	1566.9 [169.9; 3472]	324.6 [171.2; 705.4]
VEGF, pg/ml	116.2 [73.6; 599.6]	106.6 [61.2; 200.6]

*p<0.05 among the groups.



ROC curve information value for determining the basal level of IL6 for predicting the persistence of inflammatory activity after 24 weeks of therapy with the RTM biosimilar

persistent inflammatory activity based on PD results, other analyzed indicators have worse sensitivity and specificity parameters.

Conclusion. In summary, the disease remission is a broader concept and includes not only clinical data, but also a number of instrumental and laboratory indicators, which should be evaluated as a whole when deciding whether to discontinue a particular drug, or modify the therapy scheme. Ultrasound can be considered a promising method for a more objective evaluation of inflammatory changes in the joints, which can improve the assessment of disease activity.

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Conflict of Interest Statement

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