ORIGINAL INVESTIGATIONS

Expression of interferon-stimulated genes in patients with rheumatoid arthritis on anti-B-cell therapy (preliminary results)

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Objective: *to evaluate the expression of interferon-stimulated genes (ISG) – interferon (IFN) signature – in patients with rheumatoid arthritis (RA) and its dynamics during anti-B-cell therapy.*

Patients and methods. *We examined 20 patients with RA who received two infusions of the biosimilar rituximab (RTM) Acellbia® in a total dose of 1200 mg. Five genes were selected to evaluate IFN signature: IFI44L, MX1, IFIT1, RSAD2, EPSTI1. The expression of IFI44L and IFIT1 could not be determined for technical reasons, and further analysis included three genes – MX1, EPSTI1, RSAD2. IFN signature was calculated as the average value of the expression of three selected genes (IFN-score).*

Results and discussion. *The initial expression level of MX1 was 11.48 (5.45–19.38), EPSTI1 – 12.83 (5.62–19.64), RSAD2 – 5.16 (2.73–10.4) and IFN-score –10.3 (5.18–17.12), in patients with RA it was statistically significantly higher than in healthy donors: 1.26 (0.73–1.6); 1.06 (0.81–1.48); 0.93 (0.72–1.19) and 1.09 (0.92–1.42), respectively ($p<0.05$). The IFN-score was high in 15 (75%) patients, low in 5 (15%). The use of RTM was accompanied by a statistically significant decrease in disease activity and the level of acute phase parameters (ESR, CRP) after 12 and 24 weeks of therapy ($p<0.05$). In the group as a whole, as well as in patients with a moderate effect of therapy or its absence, by the 24th week of treatment, an increase in the expression of RSAD2 ($p<0.05$) and a tendency to an increase in the IFN-score level ($p=0.06$) were observed.*

Conclusion. *In patients with RA, an increased expression of ISH was found compared to healthy donors. An increase in the expression of RSAD2 and IFN-score is observed both in patients with a satisfactory effect of RTM and with no effect. The obtained results can be important for predicting the course of the disease and personalizing therapy.*

Key words: *rheumatoid arthritis; interferon-stimulated genes; interferon signature; disease activity; the effectiveness of therapy.*

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Rheumatoid arthritis (RA) belongs to a broad class of immune-mediated inflammatory rheumatic diseases (IIRDs), which stem from abnormal immunological tolerance to one's own tissues leading to inflammation and irreversible organ damage [1]. Lately, it has been proposed that an important role in the pathogenesis of IIRDs is played by the so-called interferonopathies, i.e., abnormal regulation of type I interferon (IFN) production. The assessment of these abnormalities may be useful for determining the clinical disease phenotypes and predicting treatment outcomes.

IFNs are a group of molecules with pleiotropic effects on the immune system, which ensure the interaction between innate and adaptive immune responses [2, 3]. There are type I, II and III IFNs with different properties and structures, produced by different cells [3]. Type I IFN is the largest group, which includes IFNα, β, ω, ε, κ; the best known are IFNα and β. Type II IFNs include IFNγ; type III IFNs include IFNγ1, γ2, γ3, γ4. Type I and III IFNs activate intracellular signaling pathways mediating antiviral and anti-tumor immune response [2–5]. Type I IFNs are primarily produced by plasmacytoid dendritic cells (DCs) [3]. Plasmacytoid DCs produce type I IFNs after the interaction of virus antigens or endogenous nucleic acids with pattern recognition receptors (PRR) or toll-like receptors (TLR), predominantly type 7 or 9 [6]. Type I IFNs act on all nucleated cells for the inhibition of viral replication and have immune-stimulating properties, including those related to myeloid DC maturation induction and activation, Th1 polarization of the immune response, B cell activation, antibody production and immunoglobulin class switching [7–10]. Type I IFN activity is usually assessed based on the expression of IFN-stimulated genes (ISG), which is called IFN-signature [7–9, 11]. Unlike type I IFNs, type II IFNs induce the expression of other genes primarily produced by NK cells and certain T cell subpopulations. The main role of type II IFN is to regulate certain aspects of the immune reaction: phagocytosis and antigen presentation [11].

The importance of type I IFN hyperproduction in the pathogenesis of IIRDs was confirmed both in laboratory animal models of rheumatic diseases (RDs) and in patients with hereditary monogenic disorders with a specific inflammatory phenotype, which, in 2011, were proposed to be merged into a group of congenital type I interferonopathies [12–14].

In patients with RA, type I IFNs can potentially become prognostic biomarkers of response to biological therapy. A series of papers demonstrated that a low expression of the type I IFN

Table 1. Clinical and immunological characteristics of RA patients (n=20)

Parameter	Value
Sex, n (%): males/females	2 (10)/18(90)
Age, years, Me [25th; 75th percentile]	61.5 [54.0; 66.5]
Disease duration, months, Me [25th; 75th percentile]	39.5 [20.0; 84.0]
Radiographic stage, n (%):	
I	2 (10)
II	13 (65)
III	4 (20)
IV	1 (5)
PK, n (%):	
I	4 (20)
II	11 (55)
III	5 (25)
IV	0
DAS28, Me [25th; 75th percentile]	5.6 [4.9; 6.8]
HAQ, Me [25th; 75th percentile]	1.7 [1.2; 2.3]
ESR (Westergren), mm/h, Me [25th; 75th percentile]	45.0 [19.5; 80.0]
CRP, mg/mL, Me [25th; 75th percentile]	12.3 [8.9; 42.5]
IgM RF, IU/mL, Me [25th; 75th percentile]	197.0 [83.2; 492.5]
IgM RF, n (%):	
positive	18 (90)
negative	2 (10)
ACCPA, U/mL, Me [25th; 75th percentile]	161.8 [98.3; 300.0]
ACCPA positive, n (%)	20 (100)

Note. HAQ – Health Assessment Questionnaire.

system prior to rituximab (RTM) therapy is associated with high efficacy of this drug [15, 16].

The goal of this study was to evaluate ISG expression in RA patients and its changes with anti-B cell therapy.

Patients and methods. A total of 20 patients with a confirmed RA diagnosis according to ACR/EULAR criteria (American College of Rheumatology/European Alliance of Associations for Rheumatology 2010) followed up at V.A. Nasonova Research Institute of Rheumatology were investigated, most of whom were female, middle-aged, with long-term disease (median, Me 39.5 months), with positive IgM rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACCPA), high inflammatory activity, radiographic stage II or III, functional class (FC) II, and moderate disability status (Table 1). Prior to starting anti-B cell therapy, patients received methotrexate (MTX) at stable doses (Me 15 [10; 17.5] mg) for at least 4 weeks as well as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs) up to 10 mg prednisone equivalent per day with inadequate therapeutic efficacy.

All patients received two infusions of biosimilar RTM (Acellbia®) at a dose of 600 mg intravenously, 2 weeks apart, while continuing MTX, NSAID and GC therapy. Clinical parameters were assessed immediately prior to therapy and at 12 and 24 weeks after the first infusion. EULAR criteria were used to assess treatment efficacy (DAS28). Disease remission was assessed using DAS28, SDAI (Simplified Disease Activity Index) and CDAI (Clinical Disease Activity Index). All patients signed the informed consent form at enrollment.

ESR was measured using the standard international Westergren method (reference values ⩽30 mm/h). Serum concentrations of CRP and IgM RF were measured using the BN ProSpec immunonephelometry analyzer (Siemens, Germany); a latex-enhanced high-sensitivity test was used for the assessment of CRP level (sensitivity 0.175 mg/L). Serum CRP values ⩽5.0 mg/L were within the reference range. According to the manufacturer's instructions, the upper limit of the norm for IgM RF was set at 15.0 IU/mL. Serum ACCPA quantification was performed using an enzyme-linked immunosorbent assay with commercially available reagent kits (Axis Shield, United Kingdom; upper limit of normal 5.0 U/mL).

Literature data were reviewed, and five genes (*IFI44L, MX1, IFIT1, RSAD2, EPSTI1*) were selected for IFN signature assessment, and their expression was evaluated. Total RNA was isolated from whole blood using the RIBO-sol-A commercial kit (InterLabService, Moscow). The reverse transcriptase (RT) reaction was performed using the Reverta commercial kit (InterLabService, Moscow). Real-time polymerase chain reaction (PCR) was performed using Quant Studio 5 (Applied Biosystems) and gene expression kits (Applied Biosystems, USA): *IFI44L* (Hs00915292_m1), *MX1* (Hs00895608_m1), *IFIT1* (Hs01675197_m1), *RSAD2* (Hs00369813_m1), *EPSTI1* (Hs01566789_m1); β-actin was used as endogenous control. When setting real-time reverse transcriptase PCR for each determination of the expression of each gene, complementary DNA (cDNA) of 20 control individuals and cDNA of patients with RA were placed onto the plate, therefore, expression in the controls was studied at each expression determination [17].

For technical reasons, the expression of *IFI44L* and *IFIT1* could not be determined and the expression of only three genes was included in the subsequent analysis: *MX1, EPSTI1, RSAD2.* The IFN signature was calculated as the mean expression of the three selected genes (IFN score). The control group included 20 healthy donors matched with the RA patients by sex and age.

The results were statistically processed using the Statistica 10.0 software package (StatSoft Inc., USA), including generally accepted methods of parametric and non-parametric analysis. For non-normally distributed data, Mann–Whitney test was used to compare the groups and the results were presented as Me with interquartile range (Me [25th; 75 percentile]). The differences were considered statistically significant at $p<0.05$.

Results. Prior to RTM therapy, DAS28 (5.6 [4.9; 6.8]), SDAI (27.17 [23.08; 39.9]) and CDAI (26.6 [22.25; 37]) scores indicated high RA activity. A reduction in disease activity was observed at 12 and 24 weeks of therapy ($p<0.05$; Table 2). At week 24 of RTM therapy, a good response according to EULAR criteria was observed in 5 patients, a moderate response in 12 patients and no response in 3 patients; DAS28 remission (<2.6) was achieved in 4 (20%) patients; SDAI remission (⩽3.3) was achieved in 2 (10%) patients; CDAI remission (⩽2.8) was achieved in 1 (5%) patient. At week 12 of the study, 20% improvement in ACR was observed in 70% of patients, ACR50 in 55% of patients, ACR70 in 5% of patients; at Week 24 these parameters were 75, 45 and 15%, respectively.

Baseline expression levels in RA patients were 11.48 [5.45; 19.38] for *MX1*, 12.83 [5.62; 19.64] for *EPSTI1*, and 5.16 [2.73; 10.4] for *RSAD2* and were statistically significantly higher than in healthy donors: 1.26 [0.73; 1.6], 1.06 [0.81; 1.48] and 0.93 [0.72; 1.19], respectively ($p<0.05$). The IFN score in RA patients was statistically significantly higher than in healthy donors: 10.3 [5.18; 17.12] and 1.09 [0.92; 1.42], respectively ($p<0.05$). The IFN signature was detected in 15 (75%) patients and was not different from healthy donors in 5 (15%) patients.

In the group in general, and in patients with moderate or lack of treatment efficacy in particular, an increase in *RSAD2* expression ($p<0.05$) and a trend of increasing IFN score ($p=0.06$) were observed at Week 24 of therapy. Changes in expression were statistically significant in patients with good response to therapy which is likely related to the small number of patients in this group ($p>0.05$; Table 2).

In patients with no IFN signature (n=5), the reduction in disease activity was more pronounced at Week 24 than in the group of patients with IFN signature: ΔDAS28 – 3.45 [2.94; 3.69] and 1.02 [0.5; 2.02], respectively ($p<0.05$). All patients who did not respond to therapy had an increased ISG expression.

Discussion. These results indicate a higher ISG expression in RA patients compared with healthy donors: IFN signature was detected in 75% of these patients. Literature data suggest that IFN signature is detected in the peripheral blood of more than 50% of RA patients and can also be found at the preclinical stage of the disease [18, 19]. The relative ISG expression in RA patients is lower compared with patients with systemic lupus erythematosus (SLE) or other IIRDs [20]; however, certain genes associated with increased activation of type I IFN system in SLE (*IRF5, IRAK1, STAT4* and *PTPN22*) are also associated with a risk of RA [20]. Identification of a specific polymorphism correlates with the risk of some RDs, which may suggest that a large group of disorders may share the same pathogenetic mechanisms [20].

The IFN signature can be a potential predictive marker of response to biological therapy. Several studies demonstrated that a low expression of the type I IFN system prior to RTM therapy is associated with a high efficacy of this treatment [15, 16]. R.M. Thurlings et al. [15] analyzed the expression of type I IFN in two cohorts of RA patients treated with RTM (n=20 and n=31, respectively). Depending on the level of type I IFN expression in mononuclear cells, all patients were divided into two groups: with high and low IFN levels. A more pronounced reduction in the disease activity according to DAS28 was observed in the group with low IFN levels, and response to RTM therapy according to EULAR criteria was also observed more frequently in these patients. The authors concluded that there is an inverse relationship between the efficacy of RTM therapy and type I IFN expression. Similar results were obtained by H.G. Raterman et al. [16], who investigated the expression of several genes (*LY6E, HERC5, IFI44L, ISG15, MxA, MxB, EPSTI1* and *RSAD2*) in the peripheral blood of RA patients using real-time PCR. ROC-analysis showed that efficacy of RTM therapy can be predicted with a probability of 87% using the baseline expression of the genes associated with type I IFN system (authors proposed several gene combinations: *EPSTI1, RSAD2* and *MxA; HERC5, RSAD2, MxA and LY6E; HERC5, IFI44L, EPSTI1, RSAD 2, MxA* and *LY6E*). We obtained similar evidence of an inverse correlation of the IFN signature level with the efficacy of RTM therapy: in the absence of IFN signature, a more pronounced reduction in the disease activity was observed at week 24 of therapy compared with IFN signature presence: ΔDAS28 3.45 [2.94; 3.69] and 1.02 [0.5; 2.02], respectively ($p<0.05$). In the group of patients with moderate efficacy of RTM therapy or lack of efficacy, an increase in ISG expression was observed at Week 24, whereas changes in this parameter were not statistically significant in patients with a good response to RTM therapy.

Table 2. Dynamics of disease activity and ISH expression during RTM therapy, Me [25; 75th percentile]

Parameter		Overall group	Moderate response/ no response at Week 24 (n=15)	Good response at Week 24 (n=5)
DAS28:	baseline	5.6 [4.9; 6.8]	5.64 [4.68; 6.99]	5.6 [5.2; 6.57]
	12 weeks	4.28 [3.24; 4.75]	4.4 [3.3; 5.05]*	4.17 [2.6; 4.4]*
	24 weeks	4.14 [3.11; 4.66]	4.47 [3.8; 4.8]*	2.5 [2.33; 2.6]*
ESR, mm/h:	baseline	45.0 [19.5; 80.0]	50.0 [14.0; 87.0]	40.0 [40.0; 70.0]
	12 weeks	20.0 [16.0; 38.0]*	22.0 [18.0; 40.0]*	16.0 [12.0; 18.0]*
	24 weeks	21.5 [12.0; 31.0]*	28.0 [14.0; 36.0]#	12.0 [10.0; 12.0]*
CRP, mg/L:	baseline	12.3 (8.9; 45.2)	14.4 [9.2; 46.0]	10.2 [8.6; 37.1]
	12 weeks	4.9 [2.2; 11.3]*	5.7 [2.4; 13.3]*	3.9 [1.6; 5.1]*
	24 weeks	4.9 [2.3; 21.9]*	10.4 [2.7; 24.1]#	2.6 [1.2; 4.2]*
EPST1:	baseline	12.83 [5.62; 19.64]	13.1 [5.4; 19.9]	12.6 [9.8; 14.2]
	24 weeks	14.4 [3.38; 43.9]	12.4 [2.9; 49.5]	16.4 [10.3; 19.9]
RSAD2:	baseline	**5.16 (2.73; 10.4)**	**5.12 [2.3; 9.7]**	8.34 [3.7; 18.2]
	24 weeks	**14.97 [5.04; 42.1]***	**14.6 [1.3; 43.9]***	15.4 [5.9; 40.3]
MX1:	baseline	11.48 [5.45; 19.38]	10.6 [5.3; 18.8]	13.5 [5.8; 19.9]
	24 weeks	12.49 [3.4; 69.1]	10.4 [3.2; 80.4]	56.5 [9.7; 57.7]
IFN score:	baseline	**10.3 [5.18; 17.12]**	**11.7 [4.4; 18.9]**	8.9 [8.3; 15.3]
	24 weeks	**16.5 [5.05; 55.8] p=0.06**	**14.8 [2.8; 60.8], p=0.06**	27.4 [11.6; 38.1]

*$p<0.05$ versus baseline; #$p<0.05$ for moderate response/no response versus good response groups

Assessment of IFNα/IFNβ ratio may be useful for predicting the efficacy of tumor necrosis factor α inhibitors [21, 22]. T. Having analyzed the serum levels of IFNα and IFNβ in 124 RA patients, T. Wampler Muskardin et al. [22] demonstrated that a higher baseline level of IFNβ was associated with lack of response to therapy ($p=0.013$). According to ROC-analysis results, an IFNβ/IFNα ratio >1.3 allows to predict lack of response to therapy (odds ratio 6.67; $p=0.018$) with a sensitivity of 77% and specificity of 45%.

The causes of the differences in IFNα/IFNβ ratios in the bloodstream are not known. IFNα predominates in SLE, whereas IFNβ predominates in RA [22, 23]. This phenomenon remains unclear, especially considering various anti-inflammatory effects of IFNβ and the lack of improvement with recombinant IFNβ therapy in RA patients, as well as worse response to TNFα inhibitors in patients with higher levels of this type of IFN. Considering the complex regulation of type I IFN signaling, it can be assumed that IFNβ effects likely depend on the amount, duration, location of activity (peripheral blood or tissues) and other factors.

Conclusions. Thus, the foregoing results suggest an increased ISG expression in patients with RA compared with healthy donors. IFN signature assessment may help to predict the efficacy of treatment with genetically engineered biological drugs and develop personalized management strategies. However, further studies are needed in different patient groups for a better understanding of the role of type I IFN system in the pathogenesis of RA.

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