The association between genetic characteristics and treatment failure when switching from biologic disease-modifying antirheumatic drugs/Janus kinase inhibitors in patients with rheumatoid arthritis

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Single-nucleotide polymorphisms (SNP) of genes may determine the response to therapy with biological disease-modifying antirheumatic drugs (bDMARDs) and Janus kinase inhibitors (JAKi) in patients with rheumatoid arthritis (RA).

Objective. *The aim of this study was to find the association between polymorphisms of IL-6 (rs1800795), IL-6R (rs2228145), TNFAIP3 (rs10499194, rs6920220), TNFA (rs1800629), CTLA-4 (rs231775), TNFSF13B (BAFF) (rs9514828), KCNS1 (rs734784), COMT (rs4633), IL-10 (rs1800872) and STAT4 (rs7574865) genes and poor response of RA patients to switching from ineffective bDMARD or JAKi to another type of bDMARD/JAKi therapy.*

Materials and methods. *The study group consisted of 94 patients with RA (85.1% were females, mean age 47.2±13.8 years) with moderate to high disease activity (DAS28-CRP – 5.38±0.90) despite bDMARDs/JAKi therapy. All patients were switched to another bDMARD/iJAKi, including 12 (12.8%) to TNFα, 27 (28.7%) to iIL-6, 46 (48.9%) to rituximab, and 9 (9.6%) to JAKi. After 6 months, RA activity was assessed by DAS28-CRP, SDAI and CDAI indices. Two groups were distinguished: responders (achievement of remission or low disease activity – DAS28-CRP 3,2, SDAI 11, CDAI<10) and non-responders (maintenance of moderate/high disease activity according to the same indices). Polymerase chain reaction genotyping for SNPs of the above genes was performed in all patients.*

Results and discussion. *The bDMARD/JAKi responder and non-responder groups consisted of 47 (50%) patients each. Carrying the variant T (TT+CT) allele of the TNFAIP3 SNP (rs10499194) and the T (GT+TT) allele of STAT4 (rs7574865) independently increased the risk of non-response to bDMARDs/JAKi (TT+CT vs CC: odds ratio (OR)=2.84 [95% confidence interval (CI): 1.23–6.56]; p=0.013; OR=3.18 [95% CI: 1.36–7.46]; p=0.007, respectively). The presence of T minor alleles of the TNFSF13B (BAFF) gene SNP (rs9514828) and the G (AG+GG) KCNS1 gene (rs734784) were independently associated with a reduced risk of treatment failure (CC vs. CT+TT: OR=0.25 [95% CI: 0.10 – 0.66]; p=0.004; OR=0.29 [95% CI: 0.12–0.74]; p=0.008, respectively). The multiplicative model (G vs A) was statistically significant for the TNFA gene SNP (rs1800629) (OR=3.12 [95% CI: 1.1–9.03] p=0.037); the super-dominant model was statistically significant for the CTLA-4 gene (rs231775) – (AA+GG vs AG: OR=2.6 [95% CI: 1.14–6.25] p=0.022).*

Conclusions. *TNFAIP3 (rs10499194), STAT4 (rs7574865), TNFA (rs1800629), TNFSF13B (BAFF) (rs9514828), KCNS1 (rs734784) and CTLA-4 (rs231775) were identified as six genetic predictors of treatment inefficiency in bDMARDs/JAKi switching.*

Keywords: *inefficiency, SNPs, gene, TNFAIP3 (rs10499194), TNFA (rs1800629), TNFSF13B (BAFF) (rs9514828), KCNS1 (rs734784), STAT4 (rs7574865), bDMARDs, JAKi, switching.*

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Rheumatoid arthritis (RA) is an autoimmune inflammatory disease described by progressive joint damage and extraarticular involvement of internal organs [1–3]. In recent years, the treatment of RA has undergone significant changes due to the widespread introduction of biological disease-modifying antirheumatic drugs (bDMARDs) and Janus kinase inhibitors (JAKi), which have significantly increased the likelihood of achieving remission or low disease activity (LDA) [4–8]. However, the problem of a personalized approach to prescribing bDMARDs and JAKi based on the use of reliable biomarkers remains unresolved [9–14]. Age, gender, concomitant therapy, body mass index, smoking, duration and activity of RA, functional status, presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) have been evaluated as predictors of treatment response. However, it is not possible to effectively personalize therapy using prognostic models based on these parameters [15–18].

In this regard, the evaluation of genetic features of patients with RA is of great interest. Single-nucleotide polymorphisms (SNPs) of a number of genes have been found to be associated with changes in RA activity and progression [19–27], as well as with variability of response to bDMARDs/JAKi. Therefore, the detection of certain SNPs may be a valuable method for predicting response to antirheumatic therapy [16, 28–35]. However, despite numerous studies, no universally accepted genetic markers of response to bDMARDs/JAKi have been identified.

The aim of this study was to investigate the potential role of SNPs such as *IL-6 (rs1800795)*, *IL-6R (rs2228145)*, *TNFAIP3 (rs10499194, rs6920220)*, *TNFA (rs1800629)*, *CTLA-4 (rs231775)*, *TNFSF13B (BAFF) (rs9514828), KCNS1 (rs734784)*, *COMT (rs4633)*, *IL-10 (rs1800872)* and *STAT4 (rs7574865)* genes as predictors of response to bDMARDs/JAKi in a population of RA patients with prior non-response to bDMARDs/ JAKi with another mechanism of action.

Material and methods. The study group consisted of 94 patients with a confirmed diagnosis of RA fulfilling the 2010 ACR/EULAR (American College of Rheumatology/European Alliance of Associations for Rheumatology) criteria. The patients were admitted to V.A. Nasonova Research Institute of Rheumatology between October 2022 and October 2023 due to RA exacerbation and ineffectiveness of previous therapy. The majority of patients were middle-aged women, seropositive for RF and ACPA, with moderate or high disease activity (Table 1).

Table 1: Patient characteristics (n=94)

Parameter	Value
Age, years, M±σ	47.2±13.8
Female/male, %	85.1/14.9
Duration of RA, years, Me [Q1–Q3]	11.0 [6.0; 16]
RF+, n (%)	75 (79.8)
ACPA+, n (%)	69 (73.4)
TJC, Me [Q1–Q3]	10.0 [7.0; 15]
SJC, Me [Q1–Q3]	5.0 [4.0; 9.0]
PtGA (VAS, mm) Me [Q1–Q3]	70.0 [60.0; 80.0]
PhGA (VAS, mm) Me [Q1–Q3]	70.0 [60.0; 70.0]
ESR, mm/h, Me [Q1–Q3]	35.0 [14.0; 64]
CRP, mg/L, Me [Q1–Q3]	14.6 [3.70; 33.0]
DAS28-ESR, M±σ	5.87±1.10
DAS28-CRP, M±σ	5.38±0.90
SDAI, Me [Q1–Q3]	32.5 [25.17; 41.83]
CDAI, Me [Q1–Q3]	31 [23.5; 38.0]
Treatment at the current admission, n (%):	
TNFα	39 (41.5)
iIL6	12 (12.8)
RTX	9 (9.6)
ABT	13 (13.8%)
JAKi	21 (22.3)

Note. TJC – tender joint count; SJC – swollen joint count; PtGA – patient global assessment; PhGA – physician global assessment; VAS – visual analogue scale; DAS28-ESR – Disease Activity Score by ESR level; DAS28-CRP – Disease Activity Score by C reactive protein level; SDAI – Simplified Disease Activity Index; CDAI – Clinical Disease Activity Index; TNFα – tumor necrosis factor inhibitors; iIL6 – interleukin 6 inhibitors; RTX – rituximab; ABT – abatacept.

At the time of recruitment, all patients were reviewed by a bDMARD/JAKi prescribing committee to decide which drug the patient should be switched to, based on the failure of the previous therapy. Of the patients, 12 (12.8%) were prescribed TNFi, 27 (28.7%) – iIL6, 46 (48.9%) – RTX, 9 (9.6%) – JAKi.

The efficacy of the bDMARDs/JAKi treatment was assessed after 6 months. The treatment was considered effective if remission or LDA (DAS28–CRP≤3.2; SDAI≤11; CDAI<10) was achieved, otherwise patients were assigned to the non-responder group. Forty-seven patients were enrolled in each group. The resulting groups were comparable in terms of gender, age, presence of RF and ACPA.

Venous blood samples were taken from all patients on admission for genotyping of SNPs: *IL-6R (rs2228145)*, *TNFAIP3 (rs10499194, rs6920220)*, *TNFA (rs1800629)*, *CTLA-4 (rs231775)*, *TNFSF13B (BAFF) (rs9514828)*, *KCNS1 (rs734784)*, *COMT (rs4633)*, *IL-10 (rs1800872)* and *STAT4 (rs7574865)*. The *IL-6 gene (rs1800795)* was only investigated in 84 patients. Genotyping was performed with real-time polymerase chain reaction using original sequencing specific primers and samples labelled with different fluorescent tags (Syntol Research and Development Company). Automatic registration and interpretation of the obtained results were performed on a detection amplifier DT-96 (DNA-Technology LLC, Russia). Genotyping was performed according to the manufacturer's instructions.

SNPs of each studied gene were compared in the responding and nonresponding groups.

The *data were statistically analyzed* using the standard statistical analysis package IBM SPSS Statistics 27 (IBM Corp., USA) and MedCalc MedCalc statistical software version 20.030 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2024). Quantitative variables are presented as mean and standard deviation (M±σ). Median and interquartile range (Me [Q1-Q3]) were used when there was no normal distribution in the groups. Normality of distribution was tested using the Shapiro–Wilk test. Qualitative variables were presented as absolute values and their relative frequencies (%). Pearson's χ^2 test and Fisher's exact test were used to evaluate the results obtained. The Hardy–Weinberg equilibrium was verified for all SNPs by the Pearson χ^2 test. The Chi-squared criterion was used to assess the differences in the distribution of gene SNPs genotypes and alleles between the groups. The odds ratio (OR) and 95% confidence interval (CI) were calculated using logistic regression analysis to estimate the measure of risk of

treatment ineffectiveness. Analyses were performed according to three inheritance models: dominant, recessive, and multiplicative. Statistical significance was defined as $p<0.05$.

All patients provided written consent to participate in the study. The present study was approved by the local ethics committee of V.A. Nasonova Research Institute (protocol number 23 from 17.11.2022).

Results. The distribution of genotypes of SNPs such as *TNFAIP3 (rs10499194)*, *TNFSF13B (BAFF) (rs9514828)*, *KCNS1 (rs734784)* and *STAT4 (rs7574865)* were statistically significantly different in patients according to their response to bDMARDs/JAKi therapy (p=0.041, p=0.008, p=0.033 and p=0.019, respectively). The distribution of genotypes of *TNFA (rs1800629)* and *CTLA-4 (rs231775)* SNPs tended to be statistically significantly different (p=0.065, p=0.083 respectively), and the genotype distribution of *IL-6 (rs1800795)*, *IL-6R (rs2228145)*, *TNFAIP3 (rs6920220)*, *COMT (rs4633)* and *IL-10 (rs1800872)* did not differ in two groups (p=0.22, p=0.77, p=0.81, p=0.57 and p=0.76 respectively; Table 2).

A statistical analysis was conducted to examine the correlation between the studied SNPs and the efficacy of bDMARDs/JAKi following the change of the initial drug class, utilizing various genetic models. This analysis identified several statistically significant associations for polymorphic variants of the *TNFAIP3 (rs10499194)*, *TNFSF13B (BAFF) (rs9514828)*, *KCNS1 (rs734784)* and *STAT4 (rs7574865)*. The presence of minor T (CT + TT) allele of the *TNFAIP3 (rs10499194)* was found to increase the risk of treatment ineffectiveness according to the dominant model (CC vs. CT + TT: OR=2.84; 95% CI 1.2–6.56; p=0.013; see Table 2). In patients with the CT + TT genotype, the ineffectiveness of bDMARDs/JAKi was observed in 63% of cases, compared to 37.5% of patients with the homozygous CC genotype (p=0.03). Furthermore, the multiplicative genetic model (C vs. T) revealed that the minor T allele increased the risk of treatment ineffectiveness twofold (OR=2.0; 95% CI: 1.0–3.8; p=0.036).

Conversely, the presence of the mutant T allele of the TNFSF13B (BAFF) (rs9514828) was associated with a reduced risk of treatment ineffectiveness according to the dominant model (CC vs. CT + TT: OR=0.25; 95% CI 0.10–0.66; p=0.004;

Table 2. Distribution of genotypes and alleles of gene polymorphisms depending on response to bDMARD/JAKi therapy, n (%)

Characteristics		Response to therapy yes (n=47)	Response to therapy no (n=47)	p
	***IL-6 (rs1800795)*, n=84**			
Genotype	GG	9 (21,4)	13 (31)	0,216
	CG	22 (52,4)	24 (57,1)	
	CC	11 (26,2)	5 (11,9)	
Alleles	G	40 (47,6)	40 (47,6)	1,0
	C	44 (52,4)	44 (52,4)	
	***IL-6R (rs2228145)*, n=94**			
Genotype	AA	17 (36,2)	20 (42,6)	0,772
	AC	21 (44,7)	20 (42,6)	
	CC	9 (19,1)	7 (14,9)	
Alleles	A	55 (58,5)	60 (63,8)	0,456
	C	39 (41,5)	34 (36,2)	
	***TNFA (rs1800629)*, n=94**			
Genotype	GG	42 (89,4)	34 (72,3)	0,065
	AG	5 (10,6)	12 (25,5)	
	AA	0	1 (2,1)	
Alleles	G	89 (94,7)	80 (85,1)	**0,037**
	A	5 (5,3)	14 (14,9)	
Dominant model	GG	42 (89,4)	34 (72,3)	**0,036**
	AG + AA	5 (10,6)	13 (27,7)	
	***TNFAIP3 (rs10499194)*, n=94**			
Genotype	CC	30 (63,8)	18 (38,3)	**0,041**
	CT	14 (29,8)	25 (53,2)	
	TT	3 (6,4)	4 (8,5)	
Alleles	C	74 (78,7)	61 (64,9)	**0,036**
	T	20 (21,3)	33 (35,1)	
Dominant model	CC	30 (63,8)	18 (38,3)	**0,013**
	CT + TT	17 (36,2)	29 (61,7)	
	***TNFAIP3 (rs6920220)*, n=94**			
Genotype	GG	28 (59,6)	32 (68,1)	0,809
	AG	17 (36,2)	13 (27,7)	
	AA	2 (4,3)	2 (4,3)	
Alleles	G	73 (77,7)	77 (81,9)	0,47
	A	21 (22,3)	17 (18,1)	
	***CTLA-4 (rs231775)*, n=94**			
Genotype	AA	14 (29,8)	20 (42,6)	0,083
	AG	26 (55,3)	15 (31,9)	
	GG	7 (14,9)	12 (25,5)	
Alleles	A	54 (57,4)	55 (58,5)	0,88
	G	40 (42,6)	39 (41,5)	
Super dominant model	AA + GG	21 (44,7)	32 (68,1)	**0,022**
	AG	26 (55,3)	15 (31,9)	
	***TNFSF13B (BAFF) (rs9514828)*, n=94**			
Genotype	CC	8 (17)	21 (44,7)	**0,008**
	CT	32 (68,1)	18 (38,3)	
	TT	7 (14,9)	8 (17)	
Alleles	C	48 (51,1)	60 (63,8)	0,078
	T	46 (48,9)	34 (36,2)	
Dominant model	CC	8 (17)	21 (44,7)	**0,004**
	CT + TT	39 (83)	26 (55,3)	
	***KCNS1 (rs734784)*, n=94**			
Genotype	AA	9 (19,1)	21 (44,7)	**0,033**
	AG	31 (66)	20 (42,6)	
	GG	7 (14,9)	6 (12,8)	
Alleles	A	49 (52,1)	62 (66)	0,055
	G	45 (47,9)	32 (34)	
Dominant model	AA	9 (19,1)	21 (44,7)	**0,008**
	AG + GG	38 (80,9)	26 (55,3)	

Characteristics		Response to therapy yes (n=47)	Response to therapy no (n=47)	p
		COMT (rs4633), n=94		
Genotype	CC	9 (19,1)	13 (27,7)	0,57
	CT	25 (53,2)	24 (51,1)	
	TT	13 (27,7)	10 (21,3)	
Alleles	C	43 (45,7)	50 (53,2)	0,31
	T	51 (54,3)	44 (46,8)	
		IL-10 (rs1800872), n=94		
Genotype	CC	25 (53,2)	29 (61,7)	0,76
	AC	21 (44,7)	17 (36,2)	
	AA	1 (2,1)	1 (2,1)	
Alleles	C	71 (75,5)	75 (79,8)	0,48
	A	23 (24,5)	19 (20,2)	
		STAT4 (rs7574865), n=94		
Genotype	GG	33 (70,2)	20 (42,6)	**0,019**
	GT	12 (25,5)	24 (51,1)	
	TT	2 (4,3)	3 (6,4)	
Alleles	G	78 (82,9)	64 (68,1)	**0,019**
	T	16 (17,1)	30 (31,9)	
Dominant model	GG	33 (70,2)	20 (42,6)	**0,007**
	GT + TT	14 (29,8)	27 (57,4)	

see Table 2). Data on the frequency of ineffective therapy according to depending on the presence of the minor T allele (p=0.005) are shown in Figure 1.

According to the dominant model (see Table 2), the presence of variant allele G (AG +GG) of the *KCNS1 (rs734784)* reduced the risk of treatment ineffectiveness compared to patient with carrying the AA genotype (OR=0.29; 95% CI 0.12–0.74; p=0.008). Among the carriers of minor G allele (AG+GG) the therapy was ineffective in 40.6% of cases, compared to 70.0% of AA genotype patients (p=0.01).

The presence of variant T allele (GT + TT) allele of the *STAT4 (rs7574865)* increased the risk of treatment ineffectiveness compared to the GG genotype (OR=3.18; 95% CI 1.36–7.46; p=0.007) according to the dominant model (see Table 2). The incidence of ineffectiveness depending on the presence of the minor T allele (p=0.01) is shown in Figure 2. The multiplicative model (G vs T) was statistically significant (OR=2.29; 95% CI 1.15–4.56; p=0.019).

The multiplicative model (G vs A) was statistically significant for the *TNFA (rs1800629)* (OR=3.12; 95% CI 1.10–9.03; p=0.037). The patients carrying variant allele A (AG+AA) of the *TNFA (rs1800629)* have an increased the risk of treatment ineffectiveness compared to carriers of the GG genotype: OR=3.21 (95% CI 1.04–9.90; p=0.036) according to the dominant model (see Table 2). In carriers of minor A allele (AG+AA), treatment ineffectiveness occurred in 72.2% of cases and in 44.7% of patients with the GG genotype (p=0.04).

Statistically significant differences were also observed when examining the super dominant model of *CTLA-4 (rs231775)*, p=0.022. The presence of the homozygous genotype (AA + GG) increased the risk of treatment ineffectiveness (OR=2.6; 95% CI 1.14–6.25) compared to the heterozygous genotype (see Table 2). In carriers of the homozygous (AA + GG) genotype, treatment ineffectiveness occurred in 60.4% of cases and in 36.6% of cases with the AG genotype (p=0.03).

The *IL-6 (rs1800795)*, *IL-6R (rs2228145)*, *COMT (rs4633)* and *IL-10 (rs1800872)* were not associated with the risk of treatment ineffectiveness in the studied group of patients requiring bDMARDs/JAKi switching.

Discussion. The present study evaluated the contribution of *IL-6R*, *TNFAIP3*, *TNF-α*, *TNFAIP3*, *CTLA-4*, *TNFSF13B (BAFF)*, *KCNS1*, *COMT*, *IL-10* and *STAT4* genes SNPs to the development of ineffectiveness of bDMARDs/JAKi in RA patients. Carrying the T minor allele for *TNFAIP3 (rs10499194)*, *STAT4 (rs7574865)* and the A allele for *TNFA (rs1800629)* has been shown to be associated with an increased risk of ineffectiveness after switching to another drug, whereas the presence of the G and T minor alleles of the *KCNS1 (rs734784)* and *BAFF (rs9514828)*, respectively, and the AG genotype of the *CTLA-4 (rs231775)* were associated with a reduction in this risk.

In our study, we found that the mutant T allele of the *TNFA1P3 gene (rs10499194)* increased the risk of ineffective bDMARDs/JAKi therapy (OR=2.84; p=0.013). We could not find any data in the literature on the association of this SNP with poor response to bDMARDs/JAKi. At the same time, the *TNFAIP3* gene is known to encode the ubiquitin-modifying enzyme A20, a critical regulator of the NF-κB pathway, which suppresses the development of the

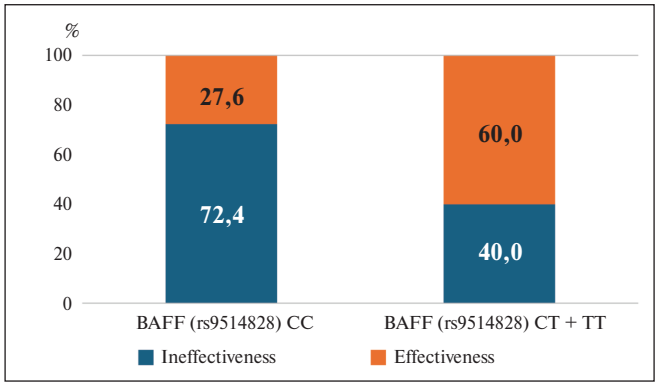

Fig. 1. *Frequency of treatment failure depending on the presence of the minor T allele (CT + TT) of the TNFSF13B (BAFF) polymorphism (rs9514828)*

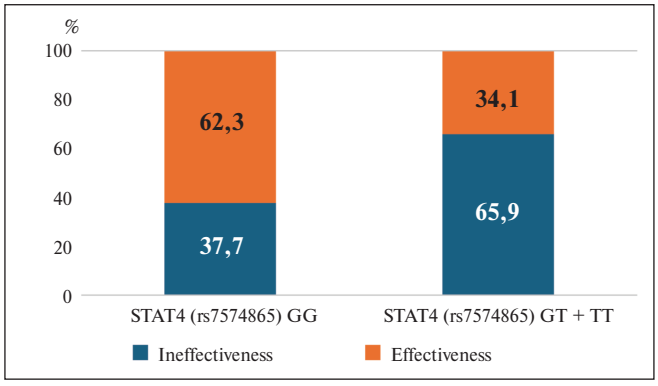

Fig. 2. *Frequency of treatment failure depending on the presence of the minor T allele (GT + TT) of the STAT4 polymorphism (rs7574865)*

inflammatory cascade in RA [36]. Most international studies have shown a protective role of the *rs10499194* SNP in the development of RA [36–39]. It can be assumed that the presence of SNP *rs10499194* in patients with established RA may determine resistance to treatment as a result of diminished production of proinflammatory cytokines, which are the target of bDMARDs.

According to our data, the presence of variant allele T (GT + TT) of the *STAT4 (rs7574865)* in the genotype increased the risk of non-response to treatment threefold compared with carrying the GG genotype according to the dominant model. The influence of the STAT4 SNP on the risk of developing RA has been widely discussed in the international literature [21, 40–42]. The association of this polymorphism with the response to bDMARDs has also been established. For example, in the study by P. Conigliaro et al [43] in an Italian cohort of RA patients, the *STAT4 (rs7574865)* was associated with no response to TNFα by EULAR criteria (OR=0.38; p=0.05). These findings were confirmed when examining the association between the *rs7574865* and response to treatment according to EULAR. Carriers of the variant allele had worse response at 2 years (OR=0.16; p=0.013). However, P.A. Juge et al [44] found no statistically significant association between the STAT4 (rs7574865) and response to RTX after 6 months of treatment (p=0.284) according to the recessive model (GG+GT vs. TT). The effect of STAT4 gene mutation on the efficacy of bDMARDs therapy may be determined by the fact that the protein it encodes is a cytoplasmic transcription factor for interleukin (IL) 12 and IL23. These determine the differentiation and proliferation of Th1 and Th17 cells [20]. Accordingly, mutation of the STAT4 gene can lead to their increased activation, thereby increasing the severity of immune-mediated inflammation [45].

We showed that the minor allele A of the *TNFA* gene *(rs1800629)* is associated with a high risk of bDMARD/JAKi inefficiency (OR=3.21; 95% CI 1.04–9.90), which is consistent with the results of most studies. For example, a recent meta-analysis by R.F. Al-Sofi et al [46] investigating the prognostic significance of this SNP showed that the A allele of the *TNFA -308G> A* gene was associated with an overall poor response to TNFα (OR=0.71; 95% CI 0.55–0.92) in 25 studies encompassing 4,341 patients, including those with RA. One study not included in this meta-analysis found that lack of response to TNFα was more common in carriers of the AG genotype than the GG genotype (p<0.05); in this study no homozygous variant genotype (AA) was identified [47]. J.R. Maxwel et al [48] found an association between the response to TNFα (p=0.001) and the TNFA gene *SNP -308G> A (rs1800629)* in the whole cohort of patients (n=1050). After stratifying by the drug used, the variant AA genotype was found to be associated with a significantly worse response compared to the G allele in patients treated with etanercept – ETN (p=0.001). A Russian team led by I.A. Guseva obtained very interesting results. They found that patients with the GG and AG genotypes had good or satisfactory response to tocilizumab (OR=8.0; 95% CI 1.2–52.8; p=0.03) when investigating the association of *TNFA -308G>A* gene *SNPs* with primary response to tocilizumab therapy. At the same time, the AA genotype was not detected in the study group, which may be due to the small number of patients who did not respond to treatment [49]. We showed that the presence of a variant T allele of *TNFSF13B (rs9514828)* was associated with a reduced risk of bDMARD/JAKi non-response (OR=0.25; p= 0.004). At the same time, R.A. Juge et al [44] found that CC and CT genotypes of *TNFSF13B (rs9514828)* were associated with good response to RTX (p=0.035). Though our findings show the opposite Contrary to the findings of the present data, it is important to note that the non-responder group in the above-mentioned study was small (n=22). In this group, BAFF levels prior to the initiation of RTX therapy were lower than in the responder group. This may indirectly indicate reduced BAFF production due to the presence of the mutant allele. BAFF is a B-cell activating factor that modulates the processes of activation and differentiation of B-cells that produce anti-drug antibodies (ADAs) [50]. It reduces the response to bDMARDs therapy in RA [44]. Increased BAFF gene expression has also been associated with increased autoantibody production [51] in RA patients with a high rate of disease progression [52]. Thus, the presence of the mutant allele may result in a decrease in BAFF production and, therefore, a decrease in the production of ADAs and proinflammatory mediators.

We found an association between the *KCNS1 (rs734784)* and response to bDMARDs/JAKi. We showed that the presence of mutant G allele (AG + GG) reduced the risk of ineffective therapy by 3.45 times compared with carrying the AA genotype. A review of the literature revealed no data on the impact of this gene on the effectiveness of bDMARDs/JAKi. The *KCNS1* gene encodes a subunit of the neuronal potassium channel Kv9.1, modulating its function and contributing to chronic pain development [53]. According to recent data, the presence of the G allele of the *KCNS1* gene *(rs734784) (A>G)* was associated with an increased risk of postoperative pain [54, 55]. The difference between our results and the literature data may be explained by different pathogenesis of inflammatory pain in patients with RA and postoperative pain.

When examining the *CTLA-4 (rs231775)*, we found that the AG genotype (AA+GG vs. AG) reduced the risk of ineffectiveness of bDMARDs/JAKi (OR=0.38; 95% CI 0.16–0.88), which is in agreement with the results of the study by N. Pete et al. [28], that the G allele was associated with a more favorable EULAR response after 12 months of ABT therapy (G vs AA; OR=3.48; 95% CI 1.20 – 10.09).

In contrast, the *IL-6 (rs1800795)*, *IL-6R (rs2228145)*, *TNFAIP3 (rs6920220)*, *COMT (rs4633)* and *IL-10 (rs1800872)* SNPs were not associated with the risk of treatment ineffectiveness in the bDMARD/JAKi switch group. It should also be noted that in the research of H. Schotte et al. [34], who analyzed the response to ETN depending on four polymorphisms of the IL10 gene, in particular, no correlation of the *rs1800872* with the outcome of ETN therapy was found.

This study has several limitations. Firstly, only one SNP was analyzed for each selected gene. Other SNPs (or combinations of SNPs) may be involved in treatment response. Furthermore, there are certain limitations related to the relatively small sample size. Given the small number of observations, we did not correct for multiple comparisons. Therefore, our results should be considered preliminary.

Conclusion. Our findings suggest six genetic predictors of bDMARD/JAKi treatment failure: *TNFAIP3 (rs10499194)*, *STAT4 (rs7574865)*, *TNFA (rs1800629)*, *TNFSF13B (BAFF) (rs9514828)*, *KCNS1 (rs734784)* and *CTLA-4 (rs231775)*. The identification of these polymorphisms may facilitate the selection of patients for whom the prescription of bDMARDs/JAKi is particularly relevant, especially following the failure of first-line therapy. However, given the limited predictive capacity of individual polymorphisms, the identification of combinations of SNPs that are important in the development of RA and the response to bDMARD/JAKi may provide a more personalized treatment approach. Such a study would require a significant increase in sample size, including different ethnic groups of patients and stratification by drug class.

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