Research Institute of Clinical and Experimental Lymphology –
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IL1b T-31C and VEGFA C+936T SNPs may be used as prognostic markers of rheumatoid arthritis treatment inefficiency

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Rheumatoid arthritis (RA) is a chronic progressive inflammation joint disease. Now the treatment of RA is mainly empirical and some patients save inflammation activities despite standard treatment.

Biological disease-modifying antirheumatic drugs (bDMARDs) open new opportunities in rheumatology. These drugs are prescribed in case of inefficiency of treatment by conventional synthetic disease-modifying antirheumatic drugs. They act on the main parts of the inflammatory process and have a good response, but they also have negative sides.

Inflammation mediators lie in basis of RA pathogenesis, so mutations in regulatory regions of their genes may influence to response to treatment.

Because genetic predisposition to RA is well known, constant genetic markers may be useful in a comprehensive assessment of the course of the disease and for the selection of therapy

The aim of our study was to analyze the association between some SNPs and treatment of rheumatoid arthritis with biological drugs.

Patients and methods.

•We studied 368 Russian patients with rheumatoid arthritis. All of them were treated in accordance with the standard recommendations.

- 57 patient received biological disease-modifying antirheumatic drugs (predominantly, rituximab).

•RA was verified by the 2010 criteria of American Rheumatism Association/European League against rheumatism.

Patients were 64 yrs [54; 71], 321 (87.2%) women.

The disease duration - 14 yrs [8; 21].

•All participants provided informed consent before enrollment. Investigation protocol was approved by the Local Ethic Committee of the RICEL (number 107 from 27.02.2015)

•Single nucleotide polymorphisms

- *TNFA C-863A, TNFA G-308A, TNFA G-238A,*
- *IL1B T-31C,*
- *IL4 C-590T,*
- *IL6 G-174C,*
- *IL10 A-1082G, IL10 C-592A,*
- *VEGFA C+936T, VEGFA C-2578A*

were determined by restriction fragment length polymorphism analysis of PCR-amplified fragments (PCR-RFLP) or RT-PCR.

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Results

Patients treated with bDMARDs had earlier disease onset (36 y.o. [26; 51] vs 48 y.o. [36; 58], p<0,001), that may indicate an unfavorable prognosis.
Hardy-Weinberg equilibrium (HWE) test revealed significant deviation only for *IL10 A*-1082G (Xi2=6.357; p=0.0117) and *IL10 C-592A* (Xi2=7.080; p=0.0078). The remaining genotypes corresponded to the HWE.

Analyze revealed the significant prevalence of the mutation homozygotes *IL1B -31CC* in patients received bDMARDs (28.1% vs 17.1%, p=0.044) (Table 1).

Table 1 - Association of IL1b T-31C with biological drug treatment

Treatment	***IL1B T-31C***			**Sum**
	IL1B -31 TT	***IL1B -31 TC***	***IL1B -31 CC***	
Not bDMARDs	117 (37.6%)	141 (45.3%)	53 (17.1%)	311
bDMARDs	13 (22.8%)	28 (49.1%)	16[a] (28.1%)	57

Contrariwise, dominant homozygotes *VEGFA +936 CC* were more commonly found among bDMARDs group patients (80.4% vs 66.6%, p=0.041) (Table 2).

Table 2 - Association of VEGFA C+936T with biological drug treatment

Treatment	***VEGFA C+936T***		**Sum**
	VEGFA +936 TT+CT	***VEGFA +936 CC***	
Not bDMARDs	103 (33.3%)	205 (66.6%)	308
bDMARDs	11 (19.6%)	45 (80.4%)[b]	56

Other polymorphisms didn't demonstrate any significant associations.

Conclusion

Our data suggest, that *IL1B T-31C* and *VEGFA C+936T* SNPs can be used as part of a comprehensive assessment of the prognosis of the treatment effectiveness.