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The potential pathogenic role of glucocorticoid receptor polymorphisms in systemic lupus erythematosus and rheumatoid arthritis

Glucocorticoids (GC) have been widely discussed about their physiological and pathological effect, however, they are still the most cost-effective drugs and suggested as the first therapeutical option in many autoimmune disorders including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [1,2]. Besides of their anti-inflammatory and immunosuppressive benefit, there are some potential risk in the GC management as adverse effects or non-response to the therapy. Endogenous and synthetic GC act via glucocorticoid receptors (GCR) which a member of the nuclear hormone receptor superfamily is encoded by the NR3C1 gene. The polymorphisms of GCR genes contribute in the diversity of the glucocorticoid receptor sensitivity [3].

In the patomechanisms of the autoimmune diseases could be identified the role of the GC and polymorphisms of GCR, also. The most extensively studied and identified single nucleotid polymorphisms (SNPs) in NR3C1 gene known as N363S, Bcl-I, 9β, ER22/23EK. Results of case-control, cross-sectional and cohort studies studies which analysed the relationship between the GCR SNPs and the systemic autoimmune disorders showed that *BclI* and N363S polymorphisms are associated with reduced risk of SLE and RA, altough, the 9β and ER22/23EK have a potential risk for onset of diseases and the various symptoms [4,5].

Until now, both for clinicians and researchers there is still a great arguement to evaluate or stand an evidence of implication of GCR polymorphisms and sensitivity or resistency for GC in the various autoimmune diseases. To face with the previous data, systemic reviews and meta-analysis there are some differences of GCR polymorphisms among the populations have been investigated in the latest decades [3].

In order to explore the association between the *BclI*, N363S and A3669G (9β) GR gene polymorphisms, parameters and clinical manifestations of SLE and RA we analysed results of 104 SLE and 146 RA patients compared to 160 healthy subjects from the Hungarian population. We have found that the prevalence of *BclI* polymorphism was significant lower both in the SLE and RA group as compared to healthy controls. In agreement with the previous studies these findings confirmed that fact the *BclI* polymorphism increases glucocorticoid sensitivity and may contribute as a preventive role in the development of SLE and RA. Another interesting co-existence in the SLE study was found, between *BclI* carrier and neuro-psychiatric symptoms. Consequently, these symptoms developed more frequently in the BclI positive SLE group and, however, the neuro-psychiatric symptoms less apparent in the A3669G (9β) carriers. Interesingly, there were not found statistically significant differences between the *BclI* polymorphism and other clinical parameters of SLE. Also, we have not found other association between the SLE and control population in the prevalence of N363S and A3669G (9β) alleles. Table 1. The tender joint counts tended to be lower in homozygous than in heterozygous *BclI* carriers of RA patients. These findings are explained by the higher tendency of glucocorticoid sensitivity of *BclI*. Surprisingly, in the RA group 9ß carriers were older, but not significantly, at the onset of the disease than controls, contrary to *BclI* and N363S polymorphisms. Homozygous BclI patients in the RA population showed a significantly higher aDNA level compared to heterozygous carriers and higher aDNA was observed in patients without anti-TNFα therapy, while anti-TNFα-treated patients showed only tendency. Furthermore, the other controversial result was that anti-CCP level was significantly lower in heterozygous 9β patients treated with anti-TNFα contrary to the non-

Table 1
The BclI, N363S, 9β allele frequency in SLE and RA patients and control population.

Genotype	SLE patients (n = 104)	Control (n = 160)	p-Value	RA patient (n = 146)	Control (n = 160)	p-Value
BclI						
Non- carriers	58	62		83	62	
Heterozygous carrier	38	82		50	82	
Homozygous carrier	8	16		13	16	
Allele frequency	0,26	0,36	0,025	0,26	0,36	0,0104
N363S						
Non-carriers	98	150		134	150	
Heterozygous carrier	6	10		12	10	
Homozygous carrier	0	0		0	0	
Allele frequency	0,03	0,031	0,873	0,041	0,031	0,5054
9β						
Non-carriers	74	100		90	100	
Heterozygous carrier	27	48		56	48	
Homozygous carrier	3	12		0	12	
Allele frequency	0,16	0,22	0,179	0,192	0,225	0.8775

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carriers. However, knowing that fact, 9β SNP decrease the GC sensitivity, anti-TNFα treatment is indicated more frequently, and the anti-CCP levels could be reduced in these patients compared to those not treated with anti-TNFα. There was not any correlation between other immunserological, disease specific parameters, co-morbiditate diseases and the SNPs in case of SLE and RA patient.

There are some controversial phenomen in our research detailed below. Understanding the results, we should take into consideration the snp patterns may be only a slice factor of patomechanism and development of autoimmunity. In the SLE group, *Bcl*I polymorphism increases, while the A3669G polymorphism decreases the sensitivity of glucocorticoid receptors and both SNPs may contribute to the development of psychiatric syndromes. Altough, in RA study population the *Bcl*I polymorphism and the increased anti-DNA, the lower anti-CCP level in heterozygous 9β patients also support to arise some hypothesis. The background of autoimmune diseases (AID) are triggered by environmental, hormonal and the wide genetic variations. The alteration of the steroid level, hormones, the stress, could be a prominent factor in the development of AID. Besides the external factors (e.g. anti-TNF alpha therapy, stress situation) the inner factors (e.g. dysregulation of HPA-axis, daily circle of cortisol, synovial cell or other cells apoptosis) have a deep influence on inflammatory process [6,7].

Our results reveal that, however, the development of autoimmunity is triggered and catalyzed by many factors and molecular patterns the endogen glucocorticoid receptor polymorphisms play a critical point in the inflammatory mechanisms and may modify the response to the glucocorticoids. For the future – with respect to the previous studies findings- we believe that to evaluate the glucocorticoid polymorphisms in the autoimmune disease may insert in the clinical practice.

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