Glucocorticoid receptor polymorphisms in rheumatoid arthritis: results from a single centre

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Abstract

Objective

Until now, glucocorticoids (GCs) with their anti-inflammatory and immune suppressive effects are one of the most effective agents in therapy of several autoimmune disorders including rheumatoid arthritis (RA). Glucocorticoid receptor (GR) polymorphisms may result in variable sensitivity to glucocorticoids playing an important role in the development and control of symptoms in RA. We aimed to test whether the functional polymorphisms of the GR encoding gene (NR3C1) are associated with susceptibility to RA and with various clinical signs and symptoms.

Methods

146 patients were enrolled at the National Institute of Reumatology. Clinical diagnosis was based on the criteria of the American College of Rheumatism (ACR) 2010. Complex clinical, routine laboratory and immunological laboratory evaluations were performed. For genotyping of the GR polymorphisms N363S (rs6195), BclI (rs41423247) and 9β (rs6198) peripheral blood DNA was used, extracted with commercially available reagents. Genotyping was performed with routine molecular biological methods. Genetic data were compared to those obtained in a healthy control group (n=160) using Chi square or Fisher tests. Associations between GR genotypes and clinical and immunological parameters were determined with ANOVA.

Results

The main finding of the present study is the lower frequency of the BclI in RA patients. Furthermore, regarding the laboratory and immunoserological parameters, the level of anti-DNA antibody was significantly higher in homozygous BclI carriers compared to heterozygous carriers, irrespective of the anti-TNF-alpha therapy.

Conclusion

Our results reveal that although GR polymorphisms are not key players in development or clinical course of RA, they might affect glucocorticoid action and, together with other endogenous and exogenous factors, interfere with the pathomechanism of RA. Our results reveal some possible factors (including BclI polymorphism), and therefore contribute to elucidate the implication of the combination of GR functional variants.

Key words

glucocorticoid receptor, rheumatoid arthritis, BclI, anti-DNA, pathophysiology

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Introduction

Until now, due to their anti-inflammatory and immunosuppressive effects, glucocorticoids (GCs) are one of the most effective agents in the therapy of several autoimmune disorders including rheumatoid arthritis (RA) (1). Although the exact aetiology is unknown, rheumatoid arthritis as a chronic, inflammatory disorder is mediated by several pathways. Dysregulation of the hypothalamic-pitutiary-adrenal (HPA) axis, the relatively low cortisol level, high concentrations of proinflammatory cytokines – mainly tumour necrosis alpha (TNF-alpha), interleukin-6 (IL-6), interleukin-17 (IL-17) – might contribute to the pathogenesis of RA (2). Glucocorticoid receptors (GR) are important elements in determining the sensitivity and effects of GC at cellular level, and probably play a role both in the pathomechanism and the response to therapy of RA. Despite the benefit in the early and prolonged therapy, the adverse effects of the glucocorticoids are a potential risk in the managment of RA. Moreover, observations suggest that a great proportion of the RA population fails to respond to exogeneous GC administration (3). Studies highly recommend determining the individual glucocorticoid sensitivity apart from the glucocorticoid dose (4). GCs manifests their effect by binding to membrane and intracellular receptors. The glucocorticoid receptor alpha (GRα) is known to be the active isoform. The precise function of glucocorticoid receptor beta (GRß) is still not detailed clearly, but it seems to exert a negative dominant effect on GRα and it may also have independent transcriptional activity (5). GRß could contribute to the GC resistence in RA. However, several GR gene variants exist, the minor alleles of the GR polymorphisms N363S and BclI are associated with increased sensitivity to GCs, while ER22/23EK and 9ß polymorphisms are associated with a relative GC resistence (6).

Based on our previous as yet unpublished data on glucocorticoid receptor polymorphisms in systemic lupus erythematosus (SLE) (7), our aim in this study was to analyse the role of GR single nucleotid polymorphisms (SNPs) in the pathogenesis and clinical course of rheumatoid arthritis (RA). We also aimed to investigate their possible interaction with anti-TNF-α therapy.

Materials and methods

Patients and controls

One-hundred and fourty-six Caucasian patients who met the classification criteria of the American College of Rheumatism (ACR) 2010 were included in the study (8). The control group consisted of 160 healthy individuals from the Hungarian population, with no personal history of RA (9). The percentage of females was 90.41% and 69.38% in the RA population and in controls, respectively. The patients' age was 58.28±12.04 years, while 52.7±14.7 in the control population. Age at onset of RA was 50.44±14.62. Additionally, all patients were either rheumatoid factor (RF) positive and anti-cyclic citrullined peptide (anti-CCP) positive and/or had joint erosions. Radiographic data and RF were avaiable in 100%, anti-CCP were avaiable 95.21%, and anti-DNA data were available in 93.81% of patients. Patients were divided into two groups according to therapy: those treated only with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (n=81, 55.48%) and those also receiving anti-TNF-α therapy (n=65, 44.52%). Anti-TNF-α therapy was initiated after treatment failure with at least 2 csDMARDs and still with active RA, as indicated by the disease activity score (DAS28> 3.2). The research was approved by the local Ethics Committee of Semmelweis University (SE TUKEB 12/2013). Written informed consent was obtained from all patients.

Clinical and immunoserological analysis

Clinical data of the 146 RA patients containing detailed disease parameters, such as tender and swollen joint counts, visual analogue score (VAS), disease activity score (DAS28-ESR) and Health Assessment Questionnaire (HAQ) were documented at the time of the study. At the time of this cross-sectional study every patient reached the therapeutic

Table I. Demographic and clinical characteristics of patients and control groups.

	Control (n=160)	RA (n=146)	RA patients with anti-TNF-alpha (n=65)	RA patients without anti-TNF-alpha (n=81)	*p*-value (TNFw *vs*. TNFwo)
Mean age (SD)	52.7±14.7	58.28 ± 12.04	58.35 ± 12.49	58.23 ± 11.76	0.952
Mean disease duration (years)	NA	7.84 ± 7.60	11.49 ± 9.08	4.91 ± 4.37	**<0.001**
Age at the onset of disease (years)	NA	50.44 ± 14.62	46.86 ± 16.16	53.32 ± 12.64	**0.008**
Gender (female/male)	111/49	132/14	62/3	70/11	0.058
Anti-CCP level (U) (mean ± SD)	NA	499.7 ± 617.4	584.9 ± 619.8	431.0 ± 610.8	0.145
>40U		81/139 (58.3%)	44/62 (71.0%)	37/77 (48.1%)	**0.003**
20-40U		10/139 (7.2%)	6/62 (9.7%)	4/77 (5.2%)	
<20U		48/139 (34.5%)	12/62 (19.4%)	36/77 (46.8%)	
RF level (IU/ml) (mean ± SD)	NA	165.1 ± 412.0	214.5 ± 474.3	125.4 ± 352.1	0.206
>20 IU/ml		69/139 (49.6%)	38/62 (61.3%)	31/77 (40.3%)	**0.014**
≤20 IU/ml		70/139 (50.4%)	24/62 (38.7%)	46/77 (59.7%)	
Anti-DNA level (IU/ml) (mean ± SD)	NA	11.5 ± 17.9	11.3 ± 16.6	11.7 ± 19.1	0.892
>30 IU/ml		10/137 (7.3%)	3/62 (4.8%)	7/75 (9.3%)	0.252
≤30 IU/ml		127/137 (92.7%)	59/62 (95.2%)	68/75 (90.7%)	

RA: rheumatoid arthritis; anti-TNFα: anti-tumour-necrosis factor alpha; anti-CCP: anti-citrullinated protein; RF: rheuma factor; anti-DNA: anti-deoxyribonucleic acid; SD: standard deviation; TNFw and wo: with and without anti-TNF-α; IU: intenational unit.

target (remission or LDA (low disease activity)) as defined by the European League Against Rheumatism (EULAR) committee (9). According to clinical charts, 34% and 71% of patients never received systemic or local GC treatment in a short period respectively, however, 52% and 0% received systemic or local GC at the time of the study. Patients received <7.5 mg equivalent dose of prednisolon (PED) GC at the time of the study. The cumulated GC doses of patients were averaged from the onset of disease to the time of the study and the doses were converted to hydrocortizone for comparison purposes.

Apart from the basic inflammatory labor parameters (erythocyte sedimentation rate (ESR), C-reactive protein (CRP)), autoantibodies were also measured. In addition to rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), the anti-double stranded deoxyribonucleic acid (anti-dsDNA) and anti-cardiolipin immunoglobulin M and G (a-CL IgM and IgG) antibodies were also measured in all patients with RA. Anti-dsDNA was tested using ELISA (ORGENTEC Diagnostika GmbH, Mainz, Germany). Anti-CCP, anti-Cardiolipin IgM and IgG antibodies were tested with ELISA (INOVA Diagnostics, San Diego, CA, USA).

DNA extraction and genotyping

Genotyping of the BclI, N363S and A3669G polymorphisms was performed from peripheral blood DNA isolated with a commercially available DNA Isolation kit (QIAamp DNA Blood Mini Kit Qiagen, USA). Genotypes of the BclI and the N363S variants were determined by allele-specific polymerase chain reaction (PCR) (10). The A3669G polymorphism was analysed using a primer-probe set purchased as predesigned Taqman allelic discrimination assay and performed according to the manufacturer's instructions (Applied Biosystems, Applied Biosystems Group 850 Lincoln Center Drive Foster City, CA) on a 7500 Fast Real Time PCR System (Applied Biosystems) (11-12). Genotypes of the BclI, N363S and A3669G SNPs were compared between RA patients and the control group consisting of 160 healthy individuals (10-12).

Statistical analysis

Dell Statistica (data analysis software system), v. 13. (Dell Inc. (2016), software.dell.com) was used for statistical analysis. Distribution of allele frequencies was calculated with χ^2 and Fisher's exact test. To examine the differences of coninuous variables, Student's independent samples' t-test was used. In all comparisons, *p*-value <0.05 was considered statistically significant.

Results

Demographic and disease-specific characteristics

In this study the mean age was similar in the RA and control group. Not surprisingly, the percentage of females in the RA group was significantly higher than in the control group (90.41% and 69.38%, respectively, $p<0.00001$).

Anti-TNF-alpha was administered in 44.52% of the RA cases. The age at disease onset in anti-TNF-α-treated patients was significantly lower compared to the patients without anti-TNF-alpha treatment. Both RF and anti-CCP were present in 95.20% of the RA patients.

Neither aDNA, nor aCCP or RF levels differed significantly between the anti-TNF-alpha-treated and non-treated group. However, when grouping patients according to their antibody levels, significantly more patients had higher aCCP and RF levels in the patients treated anti-TNF-alpha (584.9±619.8; 214.5±474.3) than those not treated (431.0±610.8; 125.4±352.1) and ($p=0.003$ and $p=0.014$, respectively). The characteristics of the study and control population are presented in Table I.

The allele frequencies of the GR gene SNPs

The BclI allele frequency was significantly lower in RA patients compared to controls (p=0.0104). The higher proportion of BclI in the control population suggests that the increased sensitivity to endogenous glucocorticoids associated with this polymorphism results in a lower risk of developing RA (Table II). There were no significant associations regarding N363S or 9β allele frequencies and development of RA (Table II).

Associations between genotypes and clinical and immunoserological parameters

There was no difference in age between carriers and non-carriers of the BclI and N363S polymorphisms. 9ß carriers were older, but not significantly, at the onset of the disease than controls (53.00 *vs*. 48.85, respectively, p=0.095). There was no significant correlation between the GR SNP carrier status and the RA disease activity measures as the patients were treated to target. However, the tender joint counts tended to be lower in homozygous than in heterozygous BclI carriers (2.69±3.07 *vs*. 6.18±6.16; respectively, p=0.053). Interestingly, patients with the homozygous BclI allele had significantly higher level of aDNA than heterozygous BclI carriers (20.15±26.65 IU *vs*. 7.63±7.73 IU, p=0.005). This difference was maintained when considering only patients without anti-TNF-alpha therapy (22.75±33.40 IU *vs*. 7.20±7.85 IU, p=0.0345), while anti-TNFα-treated patients showed only tendency (16.00±11.98 IU *vs*. 8.083±7.73, p=0.069). (Table III). The anti-CCP level was significantly lower in case of heterozygous 9β patients treated with anti-TNF-alpha contrary to the non-carriers (388.7±485.1 U *vs*. 708.8±668.1 U, p=0.0467) while there was not significant differences in the group without TNF-alpha therapy.

Since the duration of the average glucocorticoid therapy in RA patients was quite short, we did not find any unequivocal correlation between the duration of GC therapy or the average GC dose and the GR polymorphisms.

Table II. The allele frequency of BclI, N363S and 9β gene polymorphism in patients with RA and in healthy controls.

Genotype	Control population (n=160)	RA patients (n=146)	RA patients with anti-TNF-alpha (n=65)	RA patients without anti-TNF-alpha (n=81)
BclI				
non-carrier	62 (38.75%)	83 (56.84%)	36 (55.38%)	47 (58.02%)
heterozygous carrier	82 (51.52%)	50 (34.24%)	24 (44.52%)	26 (32.09%)
homozygous carrier	16 (0.1%)	13 (8.90%)	5 (7.69%)	8 (9.87%)
allele frequency	**0.356**	**0.260**	0.262	0.259
N363S				
non-carrier	150 (0.93%)	134 (91.78%)	59 (90.76%)	75 (92.59%)
heterozygous carrier	10 (6.25%)	12 (8.21%)	6 (9.23%)	6 (7.40%)
homozygous carrier	0	0	0	0
allele frequency	0.031	0.041	0.046	0.037
9ß				
non-carrier	100 (62.50%)	90 (61.64%)	396 (60%)	51 (62.96%)
heterozygous carrier	48 (30%)	56 (38.35%)	26 (40%)	30 (37.03%)
homozygous carrier	12 (7.50%)	0	0	0
allele frequency	0.225	0.192	0.200	0.185

RA: rheumatoid arthritis; anti-TNF-alpha: anti-tumour-necrosis factor alpha.

Table III. The association of BclI carrier status and anti-DNA level.

	anti-DNA level (IU/ml)	p-value
non-carrier	12.53 ± 20.32	
heterozygous BclI carrier	7.63 ± 7.73	0.005
homozygous BclI carrier	20.15 ± 26.65	
patients without anti-TNF-alpha treatment		
non-carrier	12.26 ± 19.86	
heterozygous BclI carrier	7.20 ± 7.85	0.035
homozygous BclI carrier	22.75 ± 22.4	
anti-TNF-alpha treated patients		
non-carrier	12.88 ± 21.19	
heterozygous BclI carrier	8.08 ± 7.73	0.069
homozygous BclI carrier	16.0 ± 11.98	

anti-TNF-α: anti-tumour-necrosis factor alpha; anti-DNA: anti-deoxyribonucleic acid

Similarly, there was no association between body mass index (BMI) or BMI change during GC therapy and the SNPs (not shown).

Discussion

Based on previous studies, in this research we actually examined the functional polymorphisms of the GR gene (BclI, N363S and 9β), associated with increased or decreased GC sensitivity, which could enhance or suppress pro-inflammatory pathyways, anti-inflammatory mechanisms in RA. In this cross-sectional study we examined whether functional polymorphisms of the GCR gene are associated with susceptibility to RA and the different serological, clinical parameters and anti-TNF-alpha therapy.

Firstly, our findings – similarly to the observations of Oosten *et al*. (13) – show that the more frequent appearance of the minor allele of BclI polymorphism is associated with a lower risk of developing RA by increasing GC sensitivity. In contrast to previous studies, we did not find associations between other investigated GR polymorphisms (N363S, 9β) and the susceptibility to RA. The age at disease onset of RA patients without anti-TNF-alpha was significantly higher compared to the patients with anti-TNF-alpha treatment. It suggests that patients with higher disease activity, anti-CCP positivity and

poor prognostic factors predispose to initiate an anti-TNF-alpha treatment earlier in life. However, the age of 9β carrier RA patients was higher but not significantly, than the controls, which is controversial knowing its effect causes relative GC resistance. Otherwise, carrying the 9β SNP may result in the need for anti-TNF-alpha treatment, which may contribute to the significantly lower anti-CCP levels in these patients compared to those not treated with anti-TNF-alpha. However, these results could only partially be explained by the minor effects of the SNPs. On the other hand, individual and enviromental factors of our studied population may also contribute to the differences with respect to previous studies (14-15). The genetic predisposing factors in RA are complex and mediate or determine the heterogenous disease activity or response to the therapy (4, 16). Cytokine networks in the pathogenesis of RA play a major role in the diversitiy of biological processes and the phenotype of RA, however, a final common pathway is widely represented by many researches (15). Glucocorticoids (GC) via glucocorticoid receptors (GR) have a relatively high impact in cytokine networks. Pro-inflammatory cytokines also influence the tissue-specific (paracrin) GC effect. Therefore, a prominent correlation is established by synovial and other inflammatory cells that produce cytokines in ongoing disease activity and GC sensitivity (17). Also, the GR polymorphisms – as BclI, ER22/23EK, N363S and 9ß – may constitutionally determine GC sensitivity and thus the susceptibility to develop RA (18)

Secondly, the most interesting key points of our research are represented by two unexpected findings. Homozygous BclI patients in the RA population and also in the subgroup of patients not treated with anti-TNF-alpha showed a significantly higher aDNA level compared to heterozygous carriers. Homozygous BclI patients treated with anti-TNF-α showed only the same tendency. Knowing the fact that anti-TNF-alpha could induce antinuclear antibodies (ANA) including anti-DNA antibodies (19), moreover drug-induced lupus is developed by anti-TNF-alpha therapy in a smaller proportion of patients (20), our results were somewhat unexpected. In the study population, the anti-DNA level did not differ significantly between patients with or without anti-TNF-alpha therapy in the analysed gene polymorphisms. There was no significant differences in the DNA titres between the patients with and without anti-TNF-alpha therapy independently of the analysed genotypes. Also, there was no significant association of the TNF-alpha therapy and the three genotypes.

Finally, there was no correlation between the aDNA and aCCP levels in the two (anti-TNF-alpha treated and not-treated) populations, either. This finding potentially excludes the role of polyclonal B-cell activity in the background. According to the GC sensitising effect of BclI, the results indicated a lower tender joint count in homozygous carriers, altough this association did not reach satistical significance (21). However, this tendency was consequent regardless of anti-TNF-alpha therapy. We did not find any correlation between the other documented clinical immunoserological and laboratory parameters and also the csDMARD therapies.

Our findings reveal some debatable hypotheses. To the best of our knowledge, there are no studies regarding GR polymorphisms and their association with aDNA antibody. In particular, the positive correlation between the BclI polymorphism and the aDNA is uncommon. The BclI polymorphism is associated with increased sensitivity for GCs and an enhanced anti-inflammatory activity (22). However, in our study population the BclI polymorphism and the increased anti-DNA level is a controversial phenomenon.

The increased anti-DNA level may indicate the development of lupus. However, the development of lupus usually is rare in RA patients with elevated DNA. In RA, tumour necrosis factor-alpha *(*TNF-alpha) is one of the proinflammatory cytokines that plays a pivotal role in the pathogenic changes in the synovium. Anti-TNF-alpha therapy has been successfully exerted in the treatment of several autoinflammatory conditions, mainly in RA. Anti-TNF-alpha suppresses the production of Th1 cytokines, therefore it leads to a triggered Th2 cytokine production, IL-10, and IFN-α and could induce lupus-like syndrome (23). The other hypothesis is that systemic inhibition of TNF-α could interfere with apoptosis by decreasing CD44 expression. This affects immune and synovial cell apoptosis and autoantibody production against DNA and other nuclear antigens (24-25). However, the result in our cohort, that the anti-DNA level was high in homozygous BclI carriers both with and without anti-TNF-alpha therapy, suggests that susceptibility to autoimmunity is processed by more gene loci or polymorphisms. Therefore, induction of antibodies is common in patients with anti-TNF-alpha, but only a minority of the patients experienced it and were and treated for lupus-like syndrome (25).

In summary, in the present study on RA patients we have found that carrying a BclI allele showed a lower risk of developing RA. The age of patients treated with anti-TNF-alpha at the diagnosis of RA was significantly lower than those without anti-TNF-alpha. Interestingly, patients with the homozygous BclI gene had significantly higher aDNA levels than heterozygous BclI carriers. This latter finding was inconsistent with the previous results indicating an increased GC sensitivity of BclI carriers. However, other gene polymorphisms and external factors could also interfere with the pathomechanism of RA and the response to glucorticoid therapy (26). These results reveal some preliminary hypotheses and, in the future, a higher number of RA patients, functional variants and combinations of polymorphisms could elucidate further biological mechanisms.

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