Influence of Interleukin 10 Promoter Polymorphisms in Susceptibility to Giant Cell Arteritis in Northwestern Spain

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ABSTRACT. ***Objective.*** Proinflammatory cytokines such as interferon-γ (IFN-γ) play an important role in the pathogenesis of giant cell arteritis (GCA). Interleukin 10 (IL-10) is a Th2 cytokine with a suppressor effect on IFN-γ production. We assessed the influence of functional *IL-10* gene promoter polymorphisms in susceptibility to GCA in individuals from Northwestern Spain.

Methods. One hundred three patients with biopsy-proven GCA and 226 matched controls from the Lugo region of Northwest Spain were genotyped for IL-10 –1082 G/A (rs1800896) and –592 C/A (rs1800872) promoter single nucleotide polymorphisms (SNP) by Taqman 5' allelic discrimination assay using Taqman predesigned SNP genotyping assays (numbers C_1747360_10 and C_1747363_10, respectively).

Results. A significant difference in the distribution of –1082 G/A genotypes between GCA patients and controls was observed (p = 0.034). It was mainly due to a decreased number of GCA patients carrying the –1082 A/A genotype (23.3%) compared with controls (36.7%) [p = 0.01, corrected p (p_c) = 0.03; OR 0.53, 95% CI 0.31– 0.90]. In addition, haplotype analysis showed that the ATA haplotype frequency was slightly decreased (p = 0.05, p_c = 0.2; OR 0.6, 95% CI 0.4–1.0), whereas the uncommon GTA haplotype was significantly increased in GCA patients compared with controls (p = 0.00005, p_c = 0.0002; OR 8.7, 95% CI 2.2–34.8).

Conclusion. Our results suggest a potential implication of IL-10 –1082 promoter polymorphism in susceptibility to GCA in Northwestern Spain. (First Release June 1 2007; J Rheumatol 2007:34:1535–9)

Key Indexing Terms:
GIANT CELL (TEMPORAL) ARTERITIS
INTERLEUKIN 10
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GENE POLYMORPHISMS

Giant cell arteritis (GCA) is the most common systemic vasculitis in elderly individuals from Western countries[1,2]. It is characterized by the granulomatous involvement of large and medium-size blood vessels of the aorta with predilection for the extracranial arteries of the carotid artery[2,3]. Cranial ischemic events, in particular blindness, constitute the most feared complications of this vasculitis. These severe ischemic complications are the result of inflammation of the arterial wall, which leads to intimal hyperplasia, fragmentation of internal elastic laminae, and luminal occlusion[4].

The immune response leading to GCA encompasses all the features of a Th1 pattern[5]. Besides elevated tissue expression of proinflammatory cytokines such as interleukin 1ß (IL-1ß) and tumor necrosis factor-α[6], tissue levels of interferon-γ (IFN-γ), a prototypic Th1 cytokine, play an important role in the development of this granulomatous vasculitis[5]. A direct correlation between these levels and the occurrence of lumen-occlusive intimal hyperplasia has also been described[5].

GCA is a polygenic disease, and additional evidence suggests that different gene expression patterns may modulate the incidence and clinical spectrum[7]. In this regard, a microsatellite dinucleotide (CA) repeat polymorphism in the first intron of the IFN-γ gene was found to be associated with differences between biopsy-proven GCA with and without visual ischemic manifestations[8]. IL-10 is a Th2 cytokine with suppressor effects on IFN-γ production[9]. Three biallelic polymorphisms, localized at positions –1082, –819, and –592 of the *IL-10* gene promoter region, have been identified. These polymorphisms have been reported to be functionally important, since they influence the plasma concentrations and production of IL-10[10-16]. They are in strong linkage disequilibrium, and in particular, –819 and –592 genetic variants are in complete linkage disequilibrium. Interestingly, the *IL-10* gene –592 C/A promoter polymorphism has recently been associated with susceptibility to GCA in Northern Italy[17]. Consequently, we have assessed the potential implication of two IL-10 promoter polymorphisms, –1082G/A and –592C/A, in the sus-

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ceptibility to and severity of biopsy-proven GCA in a large series of patients from the Lugo region of Northwestern Spain.

MATERIALS AND METHODS

Study population. The study group included 103 patients diagnosed with biopsy-proven GCA in the Division of Rheumatology of the Hospital Xeral-Calde, Lugo, and 232 ethnically matched controls from the same region. All GCA patients met the 1990 American College of Rheumatology criteria for the classification of GCA[18]. Only patients who had a positive temporal artery biopsy showing disruption of the internal elastic laminae with infiltration of mononuclear cells into the arterial wall with or without giant cells were included.

GCA patients were considered to have an associated polymyalgia rheumatica (PMR) if they had severe bilateral ache and pain involving the neck, shoulder, and/or pelvic girdle, associated with morning stiffness[19,20]. As described[21,22], patients were considered to have severe ischemic manifestations if they had at least one of the following complications: visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia), cerebrovascular accidents (stroke and/or transient ischemic attacks), jaw claudication, or large-artery stenosis of the extremities that caused signs of occlusive manifestations (limb claudication) of recent onset. The main clinical features of this series of 103 patients are shown in Table 1.

All patients and controls provided written informed consent. We obtained approval for the study from the local ethics committee.

IL-10 promoter genotyping. DNA from patients and controls was obtained from peripheral blood using standard methods.

IL-10 –1082 G/A (rs1800896) and –592 C/A (rs1800872) promoter single nucleotide polymorphisms (SNP) were genotyped by Taqman 5' allelic discrimination assay using Taqman predesigned SNP genotyping assays (part numbers C_1747360_10 and C_1747363_10, respectively; Applied Biosystems, Foster City, CA, USA). PCR was carried in a total reaction volume of 5 μl with the following amplification protocol: denaturation at 92°C for 10 min, followed by 40 cycles of denaturation at 92°C for 15 s and annealing and extension at 60°C for 1 min. Post-PCR, the genotype of each sample was attributed automatically by measuring the allelic specific fluorescence on an ABI-Prism 7500 sequence detection system using the SDS 1.2.3 software for allelic discrimination (Applied Biosystems).

Table 1. Main clinical features of a series of 103 patients with biopsy-proven GCA from the Lugo region. Data in parentheses indicates total proportion of patients with a particular variable.

Feature	
Age (yrs) at time of diagnosis	
Mean ± SD	74.5 ± 6.0
Median	75
Range	60–92
Women:men	59:44
Headache	87 (84)
Abnormal temporal artery on examination	77 (75)
Polymyalgia rheumatica	41 (40)
Jaw claudication	41 (40)
Visual manifestations*	23 (22)
Permanent visual loss	10 (10)
Stroke	1 (1)
Arm claudication due to ischemia of the humeral artery	1 (1)
Severe ischemic manifestations**	53 (51)
ESR 40 mm/h	103 (100)

* Transient visual loss including amaurosis fugax, permanent visual loss, or diplopia. ** At least one of the following features: visual manifestations, cerebrovascular accidents (stroke and/or transient ischemic attacks), jaw claudication, or limb claudication of recent onset.

Statistical analysis. The strength of associations between patient groups and controls and alleles or genotypes of the *IL-10* promoter polymorphisms was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables by either chi-square or Fisher's exact analysis. Statistical significance was defined as $p \leq 0.05$. P values were corrected by the number of comparisons. Calculations were performed with the Stata v6 statistical package. Pair-wise linkage disequilibrium measures were investigated and haplotypes constructed using the expectation-maximization algorithm implemented in Unphased 2.403 software[23].

RESULTS

Clinical features of patients. Table 1 shows the main clinical features of this series of 103 patients with biopsy-proven GCA. Briefly, women outnumbered men; 53 (51%) experienced severe ischemic manifestation, including visual loss in 10; and 41 (40%) had PMR.

Genotypic and allelic frequencies of IL-10 –1082 G/A and –592 C/A promoter polymorphisms. The control population was found to be in Hardy-Weinberg equilibrium for both –592 C/A and –1082 G/A IL-10 promoter polymorphisms. Although no significant differences in allelic frequency between GCA patients and controls for the IL-10 polymorphisms were seen, a significant difference in the –1082 G/A genotype distribution in GCA patients compared with controls was observed ($p = 0.034$), although this difference was not significant after correction by the number of comparisons ($p_c = 0.1$). It was mainly due to a decreased number of GCA patients carrying the –1082 A/A genotype (23.3%) compared with controls (36.7%) ($p = 0.01$, $p_c = 0.03$; OR 0.53, 95% CI 0.31–0.90; Table 2). However, when the IL-10 –592 C/A genotype frequencies were assessed, no significant differences between GCA patients and controls were found (Table 2).

Haplotype distribution of IL-10 promoter polymorphisms. In keeping with the significantly reduced frequency of the –1082 A/A genotype in GCA patients, the frequency of the ATA haplotype was slightly decreased in GCA patients compared with controls ($p = 0.05$, $p_c = 0.2$; OR 0.6, 95% CI 0.4–1.0). To our surprise, while the frequencies of the ACC and GCC haplotypes were similar in both groups (Table 3), the GTA haplotype, uncommon in Caucasian populations[11,24], was found to be significantly increased in patients compared with controls ($p = 0.00005$, $p_c = 0.0002$; OR 8.7, 95% CI 2.2–34.8; Table 3).

Influence of IL-10 promoter polymorphisms in the clinical spectrum of GCA. In a further step we investigated whether IL-10 promoter polymorphisms might influence the clinical spectrum of the disease. However, no allelic or genotype differences according to sex or the presence of PMR or severe ischemic complications were seen for either single-point or haplotype analysis (data not shown).

DISCUSSION

IL-10 is an antiinflammatory cytokine inhibiting Th1 functions. Since SNP in the regulatory sequences of genes are con-

Table 2. Genotypic and allelic frequencies of IL-10–1082G → A and IL-10–592C → A promoter polymorphisms among GCA patients and controls.

IL-10 Promoter Polymorphisms	GCA Patients	Controls	p	OR (95% CI)
–1082 G/A genotype*	n = 103 (%)	n = 226 (%)		
G/G	15 (14.6)	35 (15.5)	0.79	0.96 (0.50–1.83)
G/A	64 (62.1)	108 (47.8)	0.01**	1.77 (1.10–2.84)
A/A	24 (23.3)	83 (36.7)	0.01	0.54 (0.5–1.07)
G/G + G/A	79 (76.7)	143 (63.3)	0.016***	1.82 (1.13–2.93)
A/A	24 (23.3)	83 (36.7)	0.016	0.53 (0.31–0.90)
Allele				
G	94 (45.6)	178 (39.4)	0.1	1.29 (0.92–1.80)
A	112 (54.4)	274 (60.6)	0.1	0.77 (0.55–1.07)
–592 C/A genotype	n = 102 (%)	n = 232 (%)		
C/C	62 (60.8)	143 (61.6)	0.9	0.96 (0.63–1.43)
C/A	37 (36.3)	83 (35.8)	0.9	1.03 (0.63–1.66)
A/A	3 (2.9)	6 (2.6)	0.9	1.30 (0.34–4.85)
Allele				
C	161 (78.9)	369 (79.5)	0.9	0.96 (0.63–1.43)
A	43 (21.1)	95 (20.5)	0.9	1.05 (0.69–1.56)

* –1082 G/A genotype GCA patients vs controls, p = 0.034, p_c (corrected) = 0.1. ** p_c = 0.03. *** p_c = 0.032.

Table 3. Distribution of IL-10 promoter haplotypes in GCA patients and controls.

Haplotype	GCA, 2N = 193 (%)	Controls, 2N = 424 (%)	p	OR (95% CI)
AT*A	30 (15.5)	91 (21.5)	0.05**	0.6 (0.4–1.0)
AC*C	81 (42.0)	163 (38.4)	0.73	1.1 (0.8–1.5)
GC*C	82 (42.5)	170 (40.1)	1.00	1.0 (0.8–1.3)
GT*A	11 (5.7)	2 (0.5)	0.00005***	8.7 (2.2–34.8)

* The –819 SNP allele was deduced on the basis of its known complete linkage disequilibrium with the IL-10 –592 SNP. The 2 possible haplotypes between these SNP are –819T–592A and –819C–592C. ** p_c = 0.2. *** p_c = 0.0002.

sidered to be associated with the differential production of cytokines, the implications of polymorphisms in the promoter region of the *IL-10* gene may be of potential interest in our understanding of the mechanisms leading to the development of GCA. Polymorphisms at the –1082 G/A, –819 T/C, and –592 A/C *IL-10* promoter region have been associated with an increased risk for conditions such as cardiovascular diseases[25-27], Alzheimer's disease[28-30], sepsis susceptibility[31], and cancer[32]. IL-10 gene promoter polymorphisms have also been associated with the development of rheumatic diseases such as rheumatoid arthritis[33], Sjögren's syndrome[34-36], systemic lupus erythematosus[37,38], systemic sclerosis[39], and Wegener's granulomatosis and microscopic polyangiitis[40,41].

Interestingly, a recent report showed a significant association with IL-10 –592 C/A but not with IL-10 –1082 G/A promoter polymorphism in GCA patients from Reggio Emilia in Northern Italy[17]. However, our study exclusively included patients with histopathologically confirmed GCA, and no significant IL-10 –592 C/A or IL-10 –1082 G/A allelic differences were observed between patients and controls from Northwestern Spain. The possibility that these results could have arisen due to type II error seems unlikely, since we estimated that the study population had 75% power to detect the effect of the *IL-10* –1082 polymorphisms and 79% power to detect the effect of the *IL-10* –592, considering an odds ratio of 1.7 at the 5% significance level.

Although the –1082 A allele has been associated with low and the –1082 G allele with high *in vitro* IL-10 production[33], paradoxically, in GCA patients from Northwestern Spain the *IL-10* –1082 G/A genotype distribution disclosed a decreased frequency of the low IL-10 secretor *IL-10* –1082 A/A genotype in the group of patients. Similarly, the haplotype analysis yielded a significantly reduced frequency of the ATA haplotype, also associated with low IL-10 production, and an increase of the GTA haplotype. These results are not in accord with a potential influence of *IL-10* promoter polymorphisms to downregulate IL-10 secretion, and favor a Th1 response leading to the development of GCA. Therefore, it would be very interesting to elucidate the exact role of IL-10 in the pathogenesis of GCA and its implications in regulating the inflammatory response.

GCA appears to be a polygenic disease and different genes

may influence its phenotype and outcome[7,42]. As a result, it is possible that environmental factors, probably infectious agents, may upregulate gene expression, which may be different according to the genetic background of the population, leading to the development of GCA. With respect to this, although the clinical expression of the disease is similar in Reggio Emilia and Lugo[43], incidence rates of GCA are almost 2-fold higher among individuals from Lugo than among individuals from Reggio Emilia[44,45]. In addition, susceptibility to GCA in the 2 populations shows important immunogenetic differences[46]. In this regard, in keeping with reports on GCA in patients of Scandinavian background[47,48], GCA in Lugo is associated with HLA-DRB1*04 alleles[49]. However, this does not seem to be the case for patients in Reggio Emilia[50]. Other immunogenetic differences between the 2 populations in terms of the potential association of this large-vessel vasculitis with other non-HLA alleles have also been emphasized[51-56]. Due to this, although the distribution of *IL-10* promoter polymorphisms is very similar in healthy controls from Lugo and Reggio Emilia, the important immunogenetic differences in terms of disease susceptibility and severity between patients from these 2 Southern European populations may also explain the discordant results observed in the IL-10 gene polymorphism distribution.

The lack of agreement between our findings and those reported by Boiardi, *et al*[17] suggests that the exact role of *IL-10* promoter polymorphisms in GCA is still unclear, and further studies in different populations are needed to clarify the implication of these genetic variants in GCA susceptibility.

Our results from this series of patients with biopsy-proven GCA suggest a potential implication of *IL-10* –1082 promoter polymorphism in susceptibility to GCA in Northwestern Spain.

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