C-reactive protein gene polymorphisms influence susceptibility and outcomes of biopsy-proven giant cell arteritis in Italian patients

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Abstract

Objective

To investigate potential associations between the two functional C-reactive protein (CRP) gene polymorphisms at position 3872C>T (rs1205) and 4741G>C (rs3093068) and susceptibility, clinical expression, laboratory and pathological findings, and outcomes of giant cell arteritis (GCA) in a Nothern Italian population.

Methods

One hundred and seventy Italian patients with biopsy-proven GCA resident in Reggio Emilia area, Italy, and 200 healthy controls from the same geographic area were genotyped for rs1205 and rs3093068 CRP gene polymorphisms by molecular methods. The patients were subgrouped on the basis of the presence or absence of clinical manifestations, histological and laboratory findings, and outcomes.

Results

The distribution of rs1205 genotype was significantly different between GCA patients and controls (p=0.018). Homozygosity for T allele was significantly more frequent in GCA patients compared to controls [p=0.006; odds ratio (OR): 2.28 (95% CI: 1.1, 4.8)]. The distribution of rs3093068 genotype differed significantly between GCA patients and controls (p=0.010). Allele C and the carriers of the C allele (C/C+C/G) of rs3093068 genotype were significantly less frequent in GCA patients compared to controls [p=0.002, OR: 0.39 (95% CI: 0.24-0.73); p=0.002, OR: 0.35 (95% CI: 0.17-0.70), respectively]. No significant associations were found between the two polymorphisms and baseline clinical manifestations. The carriers of the allele C of rs3093068 genotype had significantly higher CRP values at diagnosis (13.2±5.0 vs. 8.3±6.0 mg/dl, p=0.007). Homozygosity for T allele of rs1205 genotype had a significantly more frequent eosinophil infiltration of the temporal artery wall (21.4% vs. 6.0%) (p=0.010, OR 4.28;1.31-13.98) than patients carrying the allele C. Carriers of the allele T of rs1205 genotype had lower glucocorticoid (GC) treatment duration (p=0.041), lower cumulative total GC dose (p=0.017), and higher prevalence of long-term remission (p=0.024).

Conclusion

CRP gene rs1205 and rs3093068 polymorphisms influence GCA susceptibility and its outcomes.

Key words

C-reactive protein gene polymorphism, giant cell arteritis

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Introduction

Giant cell arteritis (GCA) is a vasculitis involving the arteries of medium and large size, affecting elderly people (≥50-year-old), of unknown origin. This vasculitis is characterised by high levels of acute phase reactants at diagnosis. Glucocorticoids (GCs) are the main treatment and acute phase reactants, particularly C-reactive protein (CRP), are currently used to monitor GCA disease activity and treatment response (1-3).

CRP is a protein produced in a pentameric form (pCRP) by liver cells under the influence of IL6 and is degraded at tissue level in a monomeric form (mCRP) (4, 5).

CRP is not only a marker of inflammation, but it has also pro-inflammatory properties (6-8). Monomeric CRP is able to activate endothelial cells with upregulation of the expression of many adhesion receptors, as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). Furthermore, mCRP is also able to activate neutrophils and monocytes activating Mac-1 and upregulating Mac-1 binding, and to bind and activate complement and platelets. Therefore, the "CRP system" can cause activation of different inflammatory components and may play an important role in organ damage in different inflammatory conditions.

CRP gene is mapped in the proximal long arm of chromosome 1 and consists of one intron separating two exons (9). CRP gene is polymorphic and several CRP gene polymorphisms were reported to be associated with differences in CRP blood levels (10, 11).

Some CRP polymorphisms were associated with increased susceptibility, clinical expression and outcomes in different rheumatic conditions such as rheumatoid arthritis (12-14), systemic lupus erithematosus (15-18), ankylosing spondylitis (19, 20), progressive systemic sclerosis (21), abdominal aortic aneurism (22, 23), Kawasaki disease (24) and large vessel vasculitis (25-27).

Aim of our study was to evaluate the prevalence of the functional CRP gene polymorphisms rs1205 and rs3093068, located at exon 2 and at about 900bp upstream of CRP gene, in aNorthern Italian population of GCA temporal artery biopsy (TAB)-positive patients and in healthy controls of the same geopgraphic area. We also evaluated the influence of these two polymorphisms on clinical manifestations at disease onset, laboratory and histological findings, and outcomes.

Patients and methods

Study population

In this retrospective population-based study we reviewed the computerised registry of the Pathology Laboratory at Arcispedale Santa Maria Nuova, which keeps records of the results of all TABs performed in Reggio Emilia, Italy, between 1986 and 2007. GCA positive specimens were reviewed by the same pathologist. A total of 194 GCA patients residing in the Reggio Emilia area were identified. Their median age was 75 years (range 52-92 years). Of these, 170 patients could be contacted, all of whom were willing to participate in this study. Patients were diagnosed as having biopsy-proven GCA if hystologic examination of the TAB specimen showed disruption of the internal elastic lamina, with infiltration of mononuclear cells into the arterial wall, with or without giant cells (28). Temporal artery biopsy procedures in Reggio Emilia have been described in detail elsewhere (28). Temporal artery biopsy was routinely performed in all patients with clinical manifestations of GCA. Segments longer than 1 cm were generally obtained. The clinical findings at diagnosis and during follow-up, the erythrocyte sedimentation rate (ESR) and CRP values at diagnosis, as well as the initial prednisone dosage, were ascertained through interviews with the patients and by reviewing the patients' medical records. At diagnosis and during follow-up, ESR was determined using the Westergren method (since most of our patients were women over the age of 50, the upper limit of normal considered for ESR was 30 mm/hour). CRP was measured by nephelometry (NA latex CRP kit; Behringwerke, Marburg, Germany; upper limit of the normal reference ranges 0.5 mg/dl). A detailed list of clinical parameters eval-

uated is presented in Table I. Patients were subgrouped according to the presence or absence of cranial, visual and systemic manifestations, polymyalgia rheumatica (PMR) (marked aching and early morning stiffness bilaterally without other apparent cause, in at least 2 of the 3 following regions: neck, shoulder girdle, or hip girdle), and severe cranial ischemic events (vision loss and/or cerebrovascular accidents).

Histology

The following pathological findings in TAB specimens were also evaluated (29): the severity of inflammation graded on a semiquantitative scale (mild, moderate and severe) (Fig. 1), the severity of intimal hyperplasia (mild <25% reduction in lumen diameter, moderate from 25% to 75%, and severe >75%), and the presence or absence of the following findings: giant cells, predominantly eosinophilic inflammatory infiltrate, calcifications, intraluminal acute thrombosis and laminar necrosis.

Follow-up

Patients were followed from the time of diagnosis until either their death or until 31 November 2022. All patients with GCA were initially treated with a mean prednisone dose of 47±15 mg/day. Some patients with visual ischaemic manifestations also received intravenous pulses of methylprednisolone (1 g/day for three consecutive days) followed by prednisone 60 mg/day. We used a standardised protocol for prednisone (PDN) treatment in GCA already described in our previous studies (30, 31). Disease-related signs/symptoms, ESR and CRP levels, and PDN dosages were recorded at every follow-up visit (scheduled in most patients every 3 months). Cumulative PDN doses received after 6 months, 1 year and at the end of follow up or at PDN withdrawal were calculated. We diagnosed disease flares if all the following criteria were satisfied: reappearance of signs/symptoms of GCA/PMR; resolution of signs/symptoms after increasing or restarting GCs; increase of acute phase reactant levels(ESR≥40 mm/h or CRP≥0.5 mg/dl); and exclusion of other causes. We also considered relapses the appearance of new lumen changes at follow-up CTA/MRA and CDS or new/increased FDG uptake at follow-up PET/CT associated with a variation in the GC dose and/or immunosuppressive treatment, independently by the value of the inflammatory markers and independently by the association with vascular ischemic manifestations.

In case of asymptomatic increases of ESR and/or CRP the dosage of GCs was maintained stable until the next visit, other possible causes for such increases were investigated and the dosage of GCs was increased only if a clinical flare was documented. Long-term remission (LTR) was defined as permanent discontinuation of PDN without recurrence of symptoms and elevation of inflammatory markers for at least 1 year. We also evaluated the time interval between the beginning of PDN therapy and the first relapse, the duration of long-term remission and the duration of PDN therapy. Controls were randomly recruited from the lists of patients who were under the care of the medical practitioners of the public health service of the same geographic area. Controls had no clinical evidence of GCA and/or PMR. Stratification by the random number method according to age was used to approximately

Table I. Demographic, clinical, laboratory and histological findings in 170 biopsy-proven giant cell arteritis patients*.

Characteristics	n (%)
Females	131/170 (77.1)
Age of onset, years	73.8 ± 7.4
Cranial Symptoms	161/170 (94.7)
Headache	136/170 (80.0)
Abnormalities of temporal arteries**	114/169 (67.5)
Scalp tenderness	68/165 (41.2)
Jaw claudication	84/170 (49.4)
Carotidodynia	16/170 (9.4)
Visual Manifestations	55/170 (32.4)
Amaurosis	19/170 (11.2)
Visual loss	35/170 (20.6)
Diplopia	11/170 (6.5)
Severe ischaemic events***	39/170 (22.9)
Systemic manifestations****	119/170 (70.0)
Fever	26/170 (15.3)
Polymyalgia rheumatica	75/170 (44.1)
Peripheral arthritis	12/168 (7.1)
ESR at diagnosis, mm/hour, mean ± SD	89.3 ± 29.2
CRP at diagnosis, mg/dl, mean ± SD	8.7 ± 6.0
CRP levels ≥5 mg/dl	107/170 (62.9)
Initial prednisone dosage, (mg/day)	51 ± 37
Histologic features	
Calcification	27/154 (17.5)
Intimal thickening	
Mild	14/107 (13.1)
Moderate	38/107 (35.5)
Severe	55/107 (51.4)
Laminar necrosis	41/153 (26.8)
Giant cells	127/161 (78.9)
Eosinophils	13/153 (8.5)
Grading of inflammation	
Mild	33/158 (20.9)
Moderate	52/158 (32.9)
Severe	73/158 (46.2)

*Except where indicated otherwise, values are the number of patients who were positive/number of patients for whom data were available (%).
**Artery tenderness, nodules, and/or decreased or absent temporal artery pulsation.
***Visual loss and/or cerebrovascular ischaemic events.
****Presence of at least one of the following: asthenia, anorexia, weight loss of at least 4 Kg, or fever.

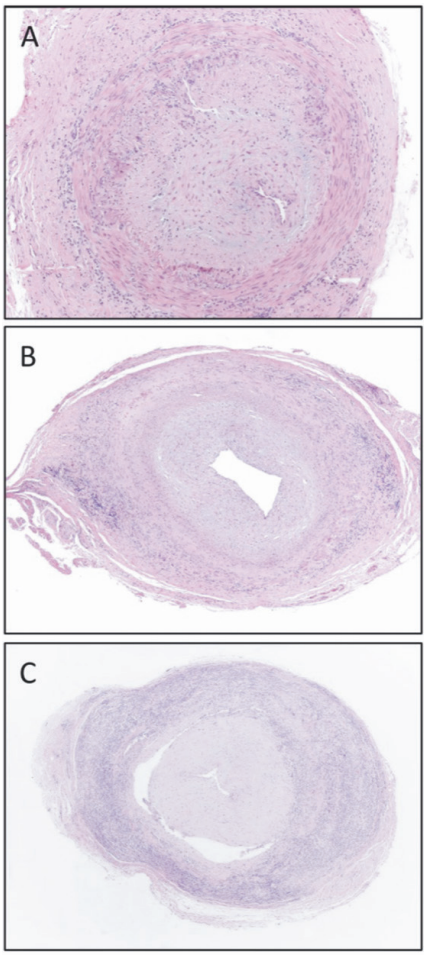

Fig. 1. Different intensity of transmural inflammation in temporal artery biopsy specimens: mild (**A**), moderate (**B**), and severe (**C**).
(A) Hematoxylin-Eosin, 40X; (B, C) Hematoxylin-Eosin, 20X.

match the patients with the controls. Two hundred healthy controls, age- and gender-matched were identified. All study subjects were white, of Italian descent. The study was approved by the Ethics Committee of Reggio Emilia Hospital. Informed consent was obtained from all patients or their relatives.

CRP polymorphism molecular analysis of 3872C>T (rs1205) and 4741G>C (rs3093068)

Genomic DNA was extracted from samples of whole blood by a rapid purification kit (16 LEV DNA BLOOD PURIFICATION) using an automated Maxwell® RSC Instruments (Promega, Madison, USA). Genotyping of 3872G>A (rs1205) and 4741G>C (rs3093068) polymorphisms was carried out using a real-time PCR: Taqman Probes were commercially available, C_7479334_10 for rs1205 and C_27452252_10 for rs3093068. (Life Technologies Corporation 6055 Sunol. Blvd. Pleasanton CA, USA). Reaction was performed in a reaction volume of 12 µl containing template DNA (10 ng), Taqman probes and TaqMan™ Genotyping Master Mix, (Life Technologies Corporation 6055 Sunol. Blvd. Pleasanton CA, USA). Finally, the 10 ng of DNA was added from each sample. For negative control nuclease-free ddH2O was used instead of patient DNA, for positive control DNA of known genotype.

Molecular analysis of 3872C>T (rs1205) was available for 198/200 and 4741G>C (rs3093068) for 185/200 healthy controls (32).

Statistical analysis

Statistical analysis was done using the SPSS statistical package (SPSS, Chicago, IL, USA) and web statistical tool SNPStats (SNPStats [http://bioinfo.iconcologia.net/SNPstats]). Continuous data were described as mean and standard deviation (mean±SD) or median and range, and categorical variables as absolute frequencies and percentages. Continuous variables were compared by using T-test or Mann-Whitney test when the distributions were skewed. Comparison of categorical variables was performed by using chi square or Fischer's exact test.

The frequencies of the alleles and genotypes among the case patients and control group were compared by chi-square test. Odds ratios (ORs) were calculated together with their 95% CI. The cases and controls were tested for conformity to the Hardy-Weinberg equilibrium using a 2X2 chi-square test between observed and expected numbers. We performed power test using Power/Sample Size Calculator: at a significance level of 0.05 power was 0.36 for allelic test and 0.28 for genotypic test (https://www.stat.ubc.ca/~rollin/stats/ssize/caco.html).

Table II. Frequencies of alleles, genotypes and carriage rates of rs1205 CRP gene polymorphism in patients with GCA and controls.

	Giant cell Arteritis (n=162)	Controls (n=198)	*p*	OR (95% CI)
Alleles				
T	129/324 (39.8)	135/396 (34.1)	0.129	1.27 (0.94-1.73)
C	195/324 (60.2)	261/396 (65.9)		
Genotype				
T/T	32/162 (19.8)	19/198 (09.6)		
C/T	65/162 (40.1)	97/198 (49.0)	0.018	
C/C	65/162 (40.1)	82/198 (41.4)		
Carriage rate				
C/T+T/T	97/162 (59.9)	116/198 (58.6)	0.804	1.05 (0.69-1.61)
C/C	65/162 (40.1)	82/198 (41.4)		
C/T+C/C	130/162 (80.2)	179/198 (90.4)	0.006	2.32 (1.26-4.27)
T/T	32/162 (19.8)	19/198 (9.6)		

Values are the number/total number examined (%).
OR: odds ratio; 95% CI: 95% confidence interval.

Table III. Frequencies of alleles, genotypes and carriage rates of rs3093068 CRP gene polymorphism in patients with GCA and controls.

	Giant cell arteritis (n=164)	Controls (n=185)	*p*	OR (95% CI)
Alleles				
C	13/328 (4.0)	37/370 (10.0)	0.002	0.395 (0.24-0.73)
G	315/328 (96.0)	333/370 (90.0)		
Genotype				
C/C	1/164 (0.6)	3/185 (1.6)	0.010	
C/G	11/164 (6.7)	31/185 (16.8)		
G/G	152/164 (92.7)	151/185 (81.6)		
Carriage rate				
C/C+C/G	12/164 7.3)	34/185 (18.4)	0.002	0.351 (0.175-0.703)
G/G	152/164 (92.7)	151/185 (81.6)		
C/C	1/164 (0.6)	3/185 (1.6)	0.626	0.376 (0.039-3.58)
C/G+ G/G	163/164 (99.4)	182/185 (98.4)		

Values are the number/total number examined (%).
OR: odds ratio; 95% CI: 95% confidence interval.
Both GCA population and control population respects HW law.

Results

The demographic and clinical characteristics of the 170 Italian patients with biopsy-proven GCA are reported in Table I.

Populations of cases and controls were tested for Hardy-Weinberg equilibrium: genotype frequencies of all populations did not reject Hardy-Weinberg equilibrium, excepted for rs1205 genotype frequencies of GCA patients which were not in Hardy-Weinberg equilibrium (p=0.0382).

The allele and genotype frequencies of the two functional variants of CRP gene at position rs1205 and rs3093068 in GCA patients and in healthy controls

are shown in Table II and III.

Alleles T and C frequencies were similar in GCA patients and controls (Table II). The distribution of rs1205 genotype polymorphism was significantly different between GCA patients and controls (p=0.018). Homozygosity for T allele was significantly more frequent in GCA patients compared to controls (p=0.006).

Given the sample size (162 GCA and 198 controls) and the allele frequencies of the polymorphism examined, we can exclude with 80% certainty a genetic relative risk of 1.8 at rs1205 CRP gene polymorphism

Regarding rs3093068 CRP gene polymorphism, allele C and carriers of the C allele (C/C+C/G) were significantly less frequent in GCA patients than in controls (p=0.002 for both comparisons) (Table III). The distribution of rs3093068 genotype differed significantly between GCA patients and controls (p=0.010).

Given the sample size (164 GCA and 185 controls) and the allele frequencies of the polymorphism examined, we can exclude with 80% certainty a genetic relative risk of 2.3 at rs3093068 CRP gene polymorphism.

Baseline clinical manifestations. No significant associations were found between these two polymorphisms and baseline clinical manifestations (data not shown).

CRP levels at baseline. Patients homozygous for the allele T of rs1205 genotype compared to carriers of the C allele (CT+CC) had significantly lower baseline serum CRP levels (6.4±5.2 mg/dL *vs*. 9.2±6.1 mg/dL, p=0.018) and a lower frequency of patients with baseline CRP values >5 mg/dl (43.8% *vs*. 66.9%, p=0.015). Considering rs3093068 genotype polymorphism, patients carrying C allele (CC+CG) compared to those homozygous for the allele G had baseline significantly higher levels of CRP (13.2±4.9 mg/dL *vs*. 8.3±6.0 mg/dl, p=0.007) and a significantly higher frequency of baseline CRP values >5 mg/dl (100% *vs*. 60.4%, p=0.004). Furthermore, allele C carriers had also at diagnosis higher ESR levels (105.0±30.6 *vs*. 85.6±29.0 mm/h, p=0.040) and lower hemoglobin values (10.3±1.2 *vs*. 11.3±1.5 g/dl, p=0.044).

Histological examination. At TAB histological examination, patients homozygous for the allele T of the rs1205 CRP gene polymorphism compared to those carrying C allele (TC+CC) had significantly more frequent predominantly eosinophilic infiltrate in the arterial wall [21.4% (6/28 patients) *vs*. 6.0% (7/117), p=0.02]. We did not observe any association of this CRP gene polymorphism with the other histological findings evaluated. No associations between rs3093068 CRP gene polymorphism and the examined TAB histological findings were found (data not shown).

Follow-up. During the follow-up (median duration: 127.5 months, range: 12-304) 71/130 (54.6%) of patients reached long-term remission, while 55/130 (42.3%) had at least one relapse. Mean (±SD) cumulative prednisone dose at the end of follow up was 14034±13910 mg, at 6-month 5178±1563 mg, and at 12 month 7097±2452. Mean (±SD) duration of prednisone therapy was 61.8±65.5 months, mean time to the first relapse 96.2±87.7 months, and mean daily prednisone doses at 6 month and at 1 year were 19.6±11.8 mg and 10.2±9.2 mg, respectively. Baseline serum CRP values were similar in patients with and without relapsing disease (8.3±5.9 mg/dL *vs*. 8.5±5.5 mg/dL, p=0.898) and with and without long-term remission (8.2±5.7 mg/dL *vs*. 8.6±5.7 mg/dL, p=0.721).

Table IV. Prednisone dosages, outcomes and rs1205 CRP gene polymorphism*.

	C/T+T/T N=78	C/C N=48	*p*
Duration of GC therapy, mean (SD), months	52 ± 56	79 ± 78	0.041
Cumulative prednisone dose, 6 months, mean (SD), mg	5262 ± 1409	4848 ± 1667	0.182
Cumulative prednisone dose, 12 months, mean (SD), mg	7201 ± 2559	6715 ± 2253	0.331
Total cumulative prednisone dose, mean (SD), mg	11146 ± 7162	18520 ± 19659	0.017
Mean prednisone dose at 6 months, mean (SD), mg/day	20.4 ± 11.9	16.8 ± 10.6	0.119
Mean prednisone dose at 12 months, mean (SD), mg/day	9.5 ± 9.1	10.7 ± 9.1	0.554
Long-term remission	48/78 (61.5)	19/48 (39.6)	0.024
Patients with at least one relapse	33/78 (42.3)	21/48 (43.8)	0.874
Time to the first relapse, mean (SD), months	90 ± 85	97 ± 88	0.638
Duration of follow-up, mean (SD), months	130 ± 83	133 ± 86	0.887

*Except where indicated otherwise, values are the number of patients who were positive/number of patients for whom data were available (%).

The associations between the rs1205 CRP gene polymorphism and the clinical outcomes evaluated at last follow-up are shown in Table IV. Patients carrying the allele T (CT+TT) had lower PDN treatment duration (p=0.041), lower cumulative total PDN dose (p=0.017), and higher frequency of patients in long-term remission (p=0.024).

We did not find any significant difference in the follow-up outcomes between patients homozyigous for the allele T and those carrying C allele (TC+CC) (data not shown).

No significant associations were oberved between the rs3093068 CRP polymorphism and the clinical outcomes at last follow-up (data not shown).

Discussion

CRP is widely recognised as a marker of inflammation and cardiovascular risk. However, some more recent data demonstrated that pCRP, the dominant isoform in the injured tissues, and mCRP act as direct mediators in inflammatory reactions and have an essential role in innate immune response (6, 8). In large vessel vasculitis, serum CRP levels are used as diagnostic markers and for evaluating disease activity and treatment response (1-3). Different allelic polymorphisms of the CRP gene were demonstrated to be associated with serum CRP levels (10, 11). In particular, patients with the TT allelic variant of

rs1205 CRP gene polymorphism had a reduced production of CRP, while patients carrying the C allelic variant of rs3093068 CRP gene polymorphism were high CRP producer (10, 11).

In our study we found that homozygosity for T allele in rs1205 CRP gene polymorphism was significantly more frequent in GCA patients compared to healthy controls, while allele C in rs3093068 CRP gene polymorphism and its carriage rate were significantly less frequent. We also showed that GCA patients homozygous for the allele T of rs1205 CRP gene polymorphism had significantly lower baseline serum CRP levels compared to carriers of the C allele, while patients carrying the C allele of CRP rs3093068 gene polymorphism compared to those homozygous for the allele G had baseline significantly higher CRP levels.

Only 3 previuos studies have evaluated the prevalence of CRP gene polymorphisms on susceptibility and clinical manifestations in large vessel vasculitis (LVV) (25-27). One indian study analysed the influence of CRP gene polymorphism rs1205 on susceptibility and baseline CRP serum levels in a group of 104 Takayasu's arteritis (TAK) patients as compared to 185 sex-matched healthy controls (26). Differently from our study, they found a reduced frequency of T allele and a higher frequency of homozygosity for the allele C in TAK patients. One chinese study compared the prevalence of 4 CRP gene polymorphisms (rs1809947, rs3093077, rs1205 and rs2808630) in 178 TAK patients and 229 healthy controls of Han ancestry (25). The study was negative, showing no associations between the studied CRP gene polymorphisms and TAK and serum baseline CRP levels. The third study from Northwestern Spain compared 4 CRP gene polymorphsms, including rs1205, in GCA patients and controls (27). The study was negative and the Authors concluded that the functional CRP gene polymorphisms assessed in their study did not seem to play a major role in GCA pathogenesis in individuals from Northwesten Spain. They found no association between clinical manifestations at presentation, particularly severe cranial ischaemic events, and baseline CRP levels with the 4 CRP gene polymorphisms they studied (27). Differences in the genetic between TAK and GCA, in the ethnicity-dependent genetic factors, and in the polymorphism loci which were studied may partially explain the different results observed in different studies. Ethnicity-dependent genetic factors may be responsible for different clinical presentation of LVV in different populations, this point must be considered when designing clinical trials or studies in multiracial populations.

Different studies have evaluated the influence of some genetic polymorphisms on the GCA outcomes (33-43). Two studies from Spain reported an association of interleukin-13 and Toll like receptor-9 gene polymorphisms on the duration of GC treatment, the number of relapses and the cumulative dose of GCs (33, 34). In another study of a different Spanish population that included 210 patients diagnosed with biopsy-proven GCA, the TLR4 +896 G allele was significantly increased in patients with biopsy-proven GCA compared with controls (40). The increase was due to a significantly higher frequency of heterozygosity for the TLR4 -896 A/G genotype in the group of patients with biopsy-proven GCA compared with controls. However, no significant differences were observed when GCA patients were stratified according to the presence of disease-specific clinical features. In the same population, IFN-gamma functional polymorphisms were found to be associated with clinical manifestations of severity (visual ischemic manifestations) rather than susceptibility to biopsy-proven GCA (41). It was also the case for functional variant of vascular endothelial growth factor polymorphisms that were associated with the susceptibility to severe ischemic manifestations in both biopsy-proven GCA and GCA patients with large vessel vasculitis involvement without cranial ischemic manifestations (42, 43).

In our population, patients carrying the allele T of rs1205 CRP gene polymorphism had lower GC treatment duration, lower cumulative total GC dose, and a higher frequency of long-term remission. A link between reduced CRP production mediated by allele T of rs1205 CRP gene polymorphism and a less severe form of disease, likely requiring lower initial glucocorticoid doses, can be speculated.

However, in our study, as observed in other studies, we showed no association between CRP baseline levels with flaring disease and long-term remission (44-48).

Previous studies have revealed the presence of eosinophilic infiltrate in a variable percentage of TAB specimens in GCA patients. Hallgren *et al*. showed in a series of TAB of GCA patients the presence of activated eosinophils and secreted eosinophil cationic protein in all layers of the inflamed vessels indicating a role for eosinophils in GCA vascular damage (49). In the study of Chatelen *et al*. eosinophils in TAB specimens were observed in about 15% of cases, a percentage similar to that observed in our study (8.5%) (50). No previous studies have evaluated the correlation between TA vascular findings and gene polymorphisms in GCA. Our study demonstrated the possible influence of the T allele of the rs1205 CRP gene polymorphism on the cellular infiltrate of the TA wall.

In conclusion, the CRP gene rs2015 and rs3093068 polymorphisms influence GCA susceptibility and its outcomes. However, to confirm these results multicentre collaborations to recruit an adequate number of patients are required.

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