Intercellular Adhesion Molecule-1 Gene Polymorphisms in Isolated Polymyalgia Rheumatica

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ABSTRACT. ***Objective.*** In untreated polymyalgia rheumatica (PMR), high levels of circulating soluble intercellular adhesion molecule-1 (ICAM-1) have been observed. To investigate the clinical implication of ICAM-1 polymorphisms in isolated PMR, we examined their potential influence in an unselected series of patients.

Methods. We studied 72 patients with isolated PMR and 129 ethnically matched controls from Lugo, Spain. Patients and controls were genotyped for HLA-DRB1 and ICAM-1 polymorphism at codons 241 and 469 by molecular methods.

Results. The distribution of alleles and genotypes for each ICAM-1 polymorphism did not show significant differences between patients with isolated PMR and controls. There were also no associations between ICAM-1 polymorphisms and relapses of the disease. The latter was primarily associated with carriage of an HLA-DRB1*0401 allele (OR 7.2, p = 0.01), although all relapsed patients with HLA-DRB1*0401 also carried the GG genotype of the ICAM-1 polymorphism at codon 241. The presence of both HLA-DRB1*0401 and the GG241 ICAM-1 genotype gave an OR of 15.2 (p = 0.005) after correction for age and sex.

Conclusion. Although ICAM-1 polymorphisms alone do not appear to be associated with disease severity in isolated PMR, the presence of both HLA-DRB1*0401 and the ICAM-1 codon 241 GG homozygosity was significantly associated with increased risk of relapses in these patients. (J Rheumatol 2002;29:502–4)

Key Indexing Terms:

POLYMYALGIA RHEUMATICA	RELAPSES	VASCULITIS
INTERCELLULAR ADHESION MOLECULE-1	HLA-DRB1	POLYMORPHISM

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are related diseases in the elderly[1,2]. However, PMR may occur alone as an isolated disease. In untreated patients with PMR, high levels of circulating soluble intercellular adhesion molecule-1 (ICAM-1) have been observed[3]. In PMR, ICAM-1 is distributed in the shoulder synovial membranes[4]. Two ICAM-1 coding region biallelic polymorphisms have been identified, Gly (G) or Arg (R) at codon 241 (exon 4) and Lys (K) or Glu (E) at codon 469 (exon 6)[5]. Salvarani, *et al* described a higher frequency of R at codon 241 in Italians with PMR[6]. To further investigate the role of ICAM-1 polymorphisms, we examined a series of unselected patients diagnosed with isolated PMR.

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MATERIALS AND METHODS

Seventy-two patients with isolated PMR and 129 ethnically matched controls from Lugo, northwestern Spain, were studied. Patients were included in this study if they fulfilled the following criteria: (1) severe and bilateral pain associated with morning stiffness (> 30 min) for more than one month in at least 2 of the 3 areas: neck, shoulder, and/or pelvic girdle; (2) erythrocyte sedimentation rate at the time of diagnosis at least 40 mm/h; (3) resolution of the syndrome in < 7 days following treatment with 10–20 mg/day prednisone; (4) exclusion of other diseases that may present with polymyalgia manifestations. Patients with positive rheumatoid factor, clinical signs of GCA, or a positive temporal artery biopsy were excluded. Temporal artery biopsy procedure was performed as described[7,8]. In Lugo the proportion of patients diagnosed with isolated PMR who have developed clinical features of GCA after 2 years followup is lower than 1.5%.

Most patients with isolated PMR received an initial dose of 15 mg prednisone/day. A rate of reduction of 2.5 mg every 2 months or, more commonly, every 3 months was attempted. A relapse of PMR was defined as flare of PMR features, which were again suppressed by resumption of or increase in corticosteroid dose[8].

Molecular analysis of ICAM-1. As reported, amino acid polymorphisms, substitution of R for G at codon 241, and substitution of K for E at codon 469 were examined by polymerase chain reaction restriction fragment length polymorphism[9]. HLA typing was also as described[8,10].

Statistical analysis. Strength of association between PMR and alleles or genotypes of ICAM-1 or between relapses in PMR and ICAM-1 polymorphisms was estimated using odds ratios (OR) and 95% confidence intervals (CI). Chi-square or Fisher exact analyses were used. Logistic regression analyses were used to adjust for age and sex. Evidence for interaction between ICAM-1 and HLA-DRB1 genes, which influenced disease relapses, was also examined.

RESULTS

Patients included in this study had no symptoms or cranial features of GCA during the course of the disease. The mean duration of treatment was 20 months. Sixteen patients had one or more relapses (22.2%). Doses of prednisone at the time of the first relapse were generally lower than 5 mg/day. The speed of tapering in the group of patients with relapses was slightly higher than in the group without relapses (1.1 mg/mo vs 1.0 mg/mo). However, the difference was not statistically significant.

We found no significant differences between patients and controls in the frequency of alleles and genotypes for each ICAM-1 polymorphism (Table 1). Also, we observed no significant differences between patients with and without relapses in the frequency of the alleles and genotypes for each ICAM-1 polymorphism (Table 2).

There was a significantly higher frequency of the HLA-DRB1*0401 genotype in the patients with relapses compared to those without (37.5 vs 10.7%; OR 7.2, 95% CI 1.5–35.5, p = 0.01). All relapsed patients with HLA-DRB1*0401 (37.5%) carried the GG genotype of the ICAM-1 polymorphism at codon 241, while only 7.1% of patients without relapses carried both HLA-DRB1*0401 and the GG genotype (Table 3). Compared with patients with no history of relapses the presence of HLA-DRB1*0401 and the GG241 ICAM-1 genotype increased the OR to 15.2 (95% CI 2.3–99.5, p = 0.005). This was still significant (p = 0.03) after Bonferroni correction for multiple comparisons. Conversely, in the absence of HLA-DRB1*0401 the GG ICAM-1 genotype was decreased in patients with relapses compared to those without relapses (37.5 vs 71.4%; OR 0.21, 95% CI 0.06–0.7, p = 0.014), although significance was lost (p = 0.084) after correction for multiple comparisons. Logistic regression analyses that included the interaction term HLA-DRB1*0401/ICAM-1 GG as well as the individual main effects (HLA-DRB1*0401 and ICAM-1 GG) revealed no evidence of interaction between these factors.

Table 1. Allele and genotype frequencies (%) of ICAM-1 polymorphisms at codons 241 and 469 in Spanish controls and patients with isolated PMR. No significant differences were found.

	Control	PMR
Codon 241	(2N = 258)	(2N = 144)
Alleles		
R	8.1	12.5
G	91.9	87.5
Genotypes	(N = 129)	(N = 72)
RR	1.5	2.8
GG	85.3	77.8
RG	13.2	19.4
Codon 469	(2N = 234)	(2N = 124)
Alleles		
K	52.6	50.0
E	47.4	50.0
Genotypes	(N = 117)	(N = 62)
KK	23.9	19.4
EE	18.8	19.4
KE	57.3	61.3

Table 2. Allele and genotype frequencies (%) of ICAM-1 polymorphisms at codons 241 and 469 in patients with isolated PMR who had relapses.

	Relapse			
	With	Without	OR (95% CI)	p
Codon 241	(n = 16)	(n = 56)		
Alleles				
R	15.6	11.6	1.4 (0.4–4.8)	0.5
G	84.4	88.4	0.7 (0.2–2.5)	0.5
Genotypes				
RR	6.3	1.8	3.7 (0.04–29.2)	0.8
GG	75.0	78.6	0.8 (0.2–3.7)	0.8
RG	18.7	19.6	0.9 (0.2–4.5)	0.9
Codon 469	(n = 14)	(n = 46)		
Alleles				
K	46.4	51.1	0.8 (0.3–2.1)	0.7
E	53.6	48.9	1.2 (0.5–3.1)	0.7
Genotypes				
KK	21.4	19.6	1.1 (0.2–5.8)	0.9
EE	28.6	17.4	1.9 (0.4–9.2)	0.4
KE	50.0	63.0	0.6 (0.2–2.3)	0.4

DISCUSSION

Genetic polymorphisms in endothelial cell adhesion molecules have been implicated in chronic allograft failure[11], susceptibility to polygenic diseases[12,13], and vasculitides[6,14].

In Lugo ICAM-1 polymorphisms at codon 241 or codon 469 were not associated with a higher risk of isolated PMR. These findings are in contrast to those of Salvarani, *et al*, who observed that the R allele at codon 241 was more common in isolated PMR than in controls[6]. These authors also found an association between R241 and a higher risk of relapses. The reason for this is unclear, but could be explained by ethnic differences between the Spanish and Italian populations examined. Differences in HLA-DRB1 predisposition to PMR have been found in these popula-

Table 3. Frequency (%) of ICAM-1 (codon 241) genotypes in patients with and without relapses stratified by HLA-DRB1*0401 status.

	HLA-DRB1*0401 Status					
	Positive			Negative		
ICAM-1 (241) Genotype	RR	GG	RG	RR	GG	RG
No. with relapse (n = 16)	0	6	0	1	6	3
Frequency %	0.0	37.5**	0.0	6.25	37.5*	18.75
No. without relapse (n = 56)	1	4	1	0	40	10
Frequency %	1.8	7.1	1.8	0.0	71.4	17.9

Logistic regression analysis with relapse (+/–) as the dependent variable: * OR 0.21 (95% CI 0.06–0.7), p = 0.014 after correction for age and sex, p_c = 0.084 after Bonferroni correction for multiple comparisons. ** OR 15.2 (95% CI 2.3–99.5), p = 0.005 after correction for age and sex, p_c = 0.03 after Bonferroni correction for multiple comparisons.

tions[6,10]. Our data suggest that ICAM-1 gene polymorphism at codon 241 may play an additive role in occurrence of relapses in HLA-DRB1 genetically predisposed patients. Their influence is likely to be additive rather than synergistic. However, this should be considered a preliminary finding and further studies on larger numbers of patients are needed to confirm this.

The functional consequences of polymorphisms in the ICAM-1 gene are unknown at present, although they occur in regions that could potentially cause alterations in leukocyte binding and/or costimulatory activity of the ICAM-1 molecule[5]. Changes in the function of the ICAM-1 molecule due to such polymorphisms could influence the extent of leukocyte binding to endothelial and/or other cells at sites of inflammation.

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