Journal of Autoimmunity 32 (2009) 64–69

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Familial disease, the *HLA-DRB1* shared epitope and anti-CCP antibodies influence time at appearance of substantial joint damage in rheumatoid arthritis

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ARTICLE INFO

Article history:
Received 29 September 2008
Received in revised form
19 November 2008
Accepted 24 November 2008

Keywords:
Rheumatoid arthritis
Family relations
Radiography
Anti-CCP antibodies
HLA-DRB1
Rheumatoid factor
Extra-articular manifestations
Tumor necrosis factor
Polymorphisms
Genetics

ABSTRACT

Rheumatoid arthritis (RA) progresses more rapidly in some patients than in others and diverse factors influence radiographic progression in a specific population. Thus, we searched for variables that are associated with an early appearance of substantial joint damage in patients with RA by using radiographic assessments. A cohort of 157 consecutively enrolled Colombian RA patients was followed for an average of 3.2 ± 3.1 years. Information on patient demographics and cumulative clinical and laboratory manifestations over the course of the disease was registered, including family history of RA in first-degree relatives, extra-articular manifestations, rheumatoid factor, anti-CCP3 antibodies, *TNF* single nucleotide polymorphism at −308 position, and *HLA-DRB1* status. Radiographs were scored according to the Sharp–van der Heijde method. Survival analyses of the time at appearance of substantial joint damage were performed by using Weibull models. A review of literature about the influence of familial RA on the progression of disease was done. Our results show that family history of RA is consistently associated with joint damage (i.e. erosive and joint narrowing disease). This effect was not found in all the populations reviewed. In addition, we confirm the effect of *HLA-DRB1* shared epitope and anti-CCP seropositivity on erosive disease. Family history of RA is a key risk factor for joint damage and depends on the investigated population because variations in both additive and non-additive genetic factors and the environmental variance are specific to the population. Our results emphasize the usefulness of assessing familial disease, testing anti-CCP antibodies and genotyping *HLA-DRB1* gene in patients with RA because these factors may be used to predict clinical outcomes and guide therapeutic interventions.

1. Introduction

Radiological assessment of rheumatoid arthritis (RA), a chronic, inflammatory systemic disease that affects approximately 0.5% of the Latin American population [1], is usually considered the "gold standard" for diagnosing and evaluating the course of the disease [2]. Radiographic changes, which are generally progressive and considered irreversible, reflect the cumulative history of the disease and correlate with future impairment and disability [3]. Joint damage is objectively assessed by using standardized methods that are based on erosion and/or joint space narrowing (JSN) scores. Moreover, a number of clinical, laboratory and genetic markers have been investigated for their potential value in predicting the radiographic progression of the disease [4]. Previous studies of Colombian patients have indicated some associations of genetic factors with RA disease [5,6]. Lower erosion scores in African Colombian patients than in mestizo Colombian patients have been observed [7], which highlights the fact that both ethnicity and geography are important factors influencing clinical presentation and course of disease [5,7]. The main objective of the current study was to measure the extent to which genetic and immune factors, familial RA, and clinical characteristics of disease

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doi:10.1016/j.jaut.2008.11.004

affect the age at appearance of substantial joint damage in Colombian patients with RA by using Weibull survival analysis [8], which essentially measured the size of the effects of relevant variables on the time to reach a substantial joint damage.

2. Patients and methods

2.1. Patients

This study included 157 consecutive RA patients attending the Clinical Immunology and Rheumatology Unit of the "Clínica Universitaria Bolivariana-Corporación para Investigaciones Biológicas" in Medellin, the Center for Autoimmune Disease Research (CREA) of the School of Medicine at Rosario University, the Rheumatology Unit of the School of Medicine of the "Universidad Nacional de Colombia", and the "Clínica de Artritis y Rehabilitación (CAYRE)" in Bogota, Colombia (Table 1). The patients fulfilled the American College of Rheumatology (ACR) classification criteria [9]. Institutional review boards at each center approved the study design.

2.2. Clinical variables

Data were recorded with a specifically created standard data collection form and included detailed demographic, clinical and laboratory variables as reported elsewhere [5,7]. All clinical and laboratory variables were coded as "present" or "absent" for each patient and registered at least once a year. Depending on disease activity, patients were classified into 3 groups as follows [10]. A patient was considered to have a "very active" RA if he/she had a swollen or tender joint count of more than 5, plus 3 of the following abnormalities: a Westergren erythrosedimentation rate (ESR) higher than 28 mm/h, C-reactive protein higher than 10 mg/dL, a patient's global assessment of disease activity higher than 5, a physician's global assessment of disease activity higher than 5, a visual analog scale for pain higher than 5, or a modified health assessment questionnaire showing a functional class of more than 2. Although these criteria were designed to measure improvement, they were applied to evaluate activity since the main criteria (i.e. number of swollen joints and number of tender joints) are the most reliable indicators of RA activity in clinical practice [10]. Patients were considered in remission if they met the criteria of Pinals et al. [11]. The remaining patients were classified as having "moderately active" RA [10]. The data collection form included information about family history of RA, defined as the presence of the disease in at least one first-degree relative (FDR). Patients were asked at least once a year to provide a full listing and contact information for all FDRs with RA and their participation was requested. FDRs included siblings and parents. The classification of FDRs with RA was made through direct clinical examination and/or medical record review. FDRs affected with RA fulfilled the ACR classification criteria [9]. Smoking status was assessed by a self-reported, validated questionnaire as previously reported [12]. Extra-articular manifestations (EAMs) were recorded and included rheumatoid nodules, lung and heart involvement, Sjögren's syndrome, scleritis and/or episcleritis, vasculitis, Felty's syndrome, Raynaud phenomenon, and cardiovascular disease [5,7].

Table 1
Demographic and clinical characteristics of 157 Colombian patients with RA.

Characteristic	Mean ± SD	Median	25th and 75th percentiles
Age at onset of RA (years)	42 ± 13	41	32 and 51
Disease duration until first visit (years)	5.2 ± 6.5	2.0	1.0 and 8.0
Time from first to last visit (years)	3.2 ± 3.1	2.0	1.0 and 4.0
Erosive score[a]	10.5 ± 16.0	3.1	0.33 and 14
Joint space narrowing score[a]	12.9 ± 14.4	7.8	3.3 and 16.3
Total Sharp–van der Heijde score[a,b]	11.7 ± 14.7	5.5	2.3 and 14.1
Characteristic			***N*** **(%)**
Female gender			132 (84)
Positive smoking status[c]			35 (22)
Family history of RA[b]			11 (7)
Rheumatoid factor[b]			106/145 (73)
Anti-CCP3 antibodies[b]			119/151 (79)
Extra-articular manifestations[b]			71 (45)
Cardiovascular Disease[d]			37/156 (24)
Methotrexate treatment			129/134 (96)
Steroid therapy			115/135 (85)
Any DMARD treatment			88/109 (81)
Tumor necrosis factor alpha inhibitor			40/154 (26)
HLA-DERAA alleles			17 (11)
*HLA-DRB1**0404			26 (17)
*HLA-DRB1**0401/0404			1 (0.6)
HLA-DRB1 QKRAA alleles			3/152 (2)
HLA-DRB1 RRRAA alleles			1/152 (0.7)
HLA-DRB1 QRRAA alleles			71/152 (47)
HLA-DRB1 shared epitope			80 (51)
TNF-308 A allele			40/154 (26)

[a] For each patient, the measures from the patient's different visits were averaged to obtain a representative value for the patient. The table describes the mean, SD, median, and 25th and 75th percentiles of the obtained averages.
[b] See definition in Section 2.
[c] According to a self-reported validated questionnaire, categorizing patients in smokers and nonsmokers [11,12].
[d] Having at least one of the following: coronary heart disease, peripheral vascular disease, arterial hypertension or stroke.

2.3. TNF and HLA-DRB1 genotyping

Genotyping for the tumor necrosis factor alpha (*TNF*) and *HLA-DRB1* was done as previously reported and patients were subsequently categorized according to the presence or absence of the *HLA-DRB1* 'shared epitope' (SE), and DERAA motifs [12]. Genotyping was not performed in FDRs.

2.4. Autoantibodies

The detection of the total rheumatoid factor (RF) and third generation anti-cyclic citrullinated peptide (anti-CCP3) antibodies were measured as previously reported [12].

2.5. Radiographic assessments

Radiographs in a standard posteroanterior view of the hands/wrists and anteroposterior view of the feet were taken at least once a year. Each patient provided at least two radiograph sets separated by a number of months—each set included hands/wrists and/or feet films. The average ± standard deviation (SD) number of radiograph sets per patient was 2.8 ± 1.1. The average ± SD number of hands/wrists radiographs per patient was 2.7 ± 1.1, and of feet radiographs was 2.3 ± 1.0. The average time between the first and last radiograph sets available was 3.2 ± 3.1 years. Films were digitized (VIDAR® SIERRA plus Film Digitizer) and scored by two independent and experienced readers (ARV, ECP) according to the Sharp–van der Heijde (SvdH) method [2]. Three Kodak directView 5 MP monochrome displays (model # DV5MM) were used, and the scores from the two readers were averaged for each radiograph set. The readers were blind to patients' identity, treatment, and chronological sequence of radiograph sets. Each radiograph set yielded 3 scores: erosive, JSN, and total SvdH scores. Each score combined hands/wrists and feet information, and was used to define "substantial joint damage" and build a model as described below (Table 2). Thus, 3 alternative definitions of substantial damage were investigated.

The inter-rater reliability of the SvdH score was assessed separately for right and left hands and feet, and for the first and last radiograph sets available, by using intraclass correlation

Table 2
Factors associated with the age at appearance of substantial joint damage according to 3 alternative definitions of substantial damage.

	β[a]	95% CI[b]	*P*-value[c]	Hazard ratio	95% CI[d]
Substantial erosive damage[e]					
Family history of RA[f]	−0.68	(−1.21, −0.15)	0.01	2.97[g]	(1.3, 6.7)
Number of SE alleles	−0.28	(−0.52, −0.032)	0.03	1.56[h]	(1.06, 2.3)
Positive anti-CCP[i]	−0.43	(−0.83, −0.03)	0.03	1.99[j]	(1.06, 3.7)
Substantial joint space narrowing[k]					
Family history of RA[f]	−1.2	(−2.1, −0.38)	0.005	5.45[l]	(1.7, 17.2)
Number of SE alleles	−0.31	(−0.56, −0.07)	0.01	1.54[m]	(1.1, 2.2)
Female gender[n]	−0.64	(−1.1, −0.13)	0.01	2.42[o]	(1.3, 4.7)
TNF-308 A allele[p]	−0.33	(−0.67, 0.013)	0.06	1.57[q]	(0.99, 2.5)
Total substantial joint damage[r]					
Family history of RA[f]	−0.71	(−1.3, −0.15)	0.01	2.78[g]	(1.3, 6.0)
Number of SE alleles	−0.32	(−0.59, −0.06)	0.02	1.59[h]	(1.09, 2.3)
Positive anti-CCP[i]	−0.39	(−0.78, 0.004)	0.05	1.74[j]	(1.0, 3.0)

95% CI: 95% confidence interval; RA: rheumatoid arthritis; SE: *HLA-DRB1* shared epitope.
The table describes regression coefficients (β) and hazard ratios for variables significantly associated with age at appearance of substantial radiographic joint damage (ASRD) according to 3 Weibull models. The Weibull models are described in footnotes e, k, and r below.

[a] The numbers in this column are the Weibull regression coefficients described in Section 2.6.

[b] 95% CI for β.

[c] Tests the null hypothesis that β is equal to 0 vs. the hypothesis that β is different from 0.

[d] 95% CI for the hazard ratio.

[e] When using an erosive score $\geq$5 as a definition of substantial joint damage, the model was $\log(T) = \alpha - 0.68X_1 - 0.28X_2 - 0.43X_3 + \text{error}$, where X_1 = having a family history of RA, X_2 = number of SE alleles, X_3 = being anti-CCP positive, T = ASRD minus 17 years, $\alpha = 4.3$ [95% CI, (3.9, 4.7)], and the error has an extreme-value distribution with scale 0.62 (0.47, 0.83) and shape 1.6 (1.2, 2.1).

[f] The dichotomous variable was defined as 1 if the patient had a family history of RA, 0 otherwise.

[g] The hazard ratio and its CI are adjusted for the number of SE alleles and anti-CCP seropositivity.

[h] The hazard ratio and its CI are adjusted for family history of RA and anti-CCP seropositivity.

[i] The dichotomous variable was defined as 1 if the patient tested positive for anti-CCP, 0 otherwise.

[j] The hazard ratio and its CI are adjusted for family history of RA and the number of SE alleles.

[k] When using a joint space narrowing score $\geq$5 as a definition of substantial damage, the model was $\log(T) = \alpha - 1.2X_1 - 0.31X_2 - 0.64X_3 - 0.33X_4 + \text{error}$, where X_1 = having a family history of RA, X_2 = number of SE alleles, X_3 = female gender, X_4 = having a *TNF*-308 A allele, T = ASRD minus 17 years, $\alpha = 4.2$ [95% CI, (3.7, 4.7)], and the error has an extreme-value distribution with scale 0.73 (0.55, 0.96) and shape 1.4 (1.0, 1.8).

[l] The hazard ratio and its CI are adjusted for the number of SE alleles, female gender, and having a *TNF*-308 A allele.

[m] The hazard ratio and its CI are adjusted for family history of RA, female gender, and having a *TNF*-308 A allele.

[n] The dichotomous variable was defined as 1 if the patient was female, 0 otherwise.

[o] The hazard ratio and its CI are adjusted for family history of RA, the number of SE alleles, and having a *TNF*-308 A allele.

[p] The dichotomous variable was defined as 1 if the patient had a *TNF*-308 A allele, 0 otherwise.

[q] The hazard ratio and its CI are adjusted for family history of RA, the number of SE alleles, and female gender.

[r] When using a total SvdH score $\geq$5 as a definition of substantial damage, the model was $\log(T) = \alpha - 0.71X_1 - 0.32X_2 - 0.39X_3 + \text{error}$, where X_1 = having a family history of RA, X_2 = number of SE alleles, X_3 = being anti-CCP positive, T = ASRD minus 17 years, $\alpha = 4.1$ [95% CI, (3.7, 4.6)], and the error has an extreme-value distribution with scale 0.70 (0.52, 0.94) and shape 1.4 (1.1, 1.9).

coefficients (ICCs). The observed ICCs ranged from 0.89 to 0.95 for hands and from 0.61 to 0.80 for feet, suggesting a good reliability.

2.6. Statistical analysis

Survival analyses of the age at appearance of substantial radiographic joint damage (ASRD) were performed [8]. In a first analysis, having a substantial joint damage was defined as having an erosive score $\geq$5. This definition was motivated by a validation study with OMERACT 5 experts that suggested that a cutoff value of 5 represents the minimal clinically important difference and the smallest detectable difference [2,13]. Thus, the age at which a patient reached an erosive score equal to 5 was considered as the patient's ASRD. Since each patient provided only a limited number of erosive scores (one for each visit), the exact age at which a patient reached a score equal to 5 was not always known. However, this uncertainty was reduced by "censoring" that age at appropriate observed times [8]. The basic idea underlying the concept of censoring is that, although we may not know the exact age at which a patient reached or will reach a score of 5, we do know an interval of ages at which this occurred or may occur [8]. Such interval can be used by statistical algorithms to estimate the parameters of survival models of ASRD [14].

The second and third analyses of ASRD considered a JSN score $\geq$5 and a total SvdH score $\geq$5 to be the definitions of substantial joint damage respectively [2,13]. Censoring criteria analogous to those applied to the erosive score were also applied to both the JSN and the total SvdH scores.

For each of the 3 above definitions of "substantial joint damage", a Weibull survival model was built [8,14]. In these models, the "survival time" of a particular patient was the time from the moment the patient turned 17 years old to the appearance of a substantial joint damage. Subtracting 17 from ASRD was deemed necessary because the lowest age at onset of rheumatoid arthritis observed in the patient sample was 17 years and, by convention, the Weibull model has a baseline time of 0 [8]. In each analysis, a Weibull model was built that made it possible to estimate the effect size of significant variables on ASRD. The dependent variable of the Weibull models was the natural log of the number of years between the age of 17 and ASRD. Specifically, the form of the models was:

$$\log(T) = \alpha + \sum_i \beta_i X_i + \text{error},$$

where T stands for ASRD minus 17, α is an intercept, the β_is are regression coefficients, the X_is represent significant independent variables, and the error has an extreme-value distribution. Under this model, T has a Weibull distribution [8].

For each of the 3 survival analyses, the independent variables of the Weibull model were selected through a backward selection procedure. The potential independent variables considered were carrying a *TNF*-308 A allele, carrying a single *HLA-DRB1* SE allele, the number of SE alleles (0, 1, or 2 SE alleles in the corresponding *HLA-DRB1* locus), carrying an *HLA-DRB1* DERAA sequence, anti-CCP3 seropositivity, RF seropositivity, a family history of RA, positive smoking status, and female gender.

To assess the clinical importance of significant variables, hazard ratios (HRs) were computed. A hazard ratio measures the effect size of a variable on ASRD [8]. 95% confidence intervals (CIs) for HRs and regression coefficients were computed. *P*-values <0.05 were considered significant. Statistical analyses were performed by using SAS PROC LIFEREG [15]. The adequacy of the Weibull models was assessed through Weibull probability plots. The models fit well.

3. Results

3.1. Factors associated with an erosive disease

When an erosive score $\geq$5 was used as a definition of substantial joint damage, a family history of RA, an increased number of SE alleles, and anti-CCP3 seropositivity were significantly associated with an early ASRD (Table 2). After adjusting for potential

confounders, the hazard of appearance of substantial joint damage in patients with positive anti-CCP3 vs. patients of comparable age with negative anti-CCP3 was 1.99 (Table 2). Thus, at any particular age after 17, the hazard of appearance of substantial damage for a patient with positive anti-CCP3 was 99% higher than that for a patient with negative anti-CCP3. Also, having an additional SE allele was associated with a 56% increase in the hazard of appearance of substantial joint damage (adjusted HR = 1.56, Table 2). A family history of RA increased the hazard of appearance of substantial joint damage by a factor of 3.

The median age at which patients reached substantial damage lowered as the number of SE alleles increased, independently of family history of RA or anti-CCP3 seropositivity status. For total substantial damage (SvdH score $\geq$5) in patients with a family history of RA and positive for anti-CCP a median of 33 ± 5 years was found in those without SE alleles vs. 25 ± 3 years in those with two SE alleles. In patients without a family history of RA and positive for anti-CCP a median of 50 ± 4 years was found in those without SE alleles vs. 34 ± 4 years in those with two SE alleles. Similarly, the median ASRD for positive anti-CCP3 patients was lower than that for negative anti-CCP3 patients.

3.2. Factors associated with JSN

When a JSN score $\geq$5 was used as a definition of substantial joint damage, a family history of RA (HR = 5.45), the number of SE alleles (HR = 1.54) and female gender (HR = 2.42) were significantly associated with an early ASRD (Table 2). Having a *TNF*-308 A allele was borderline significantly associated with early ASRD ($P = 0.06$, HR = 1.57).

3.3. Factors associated with both erosive and joint narrowing disease

When the definition of substantial joint damage was based on the total SvdH score, the survival analysis of ASRD yielded similar results to those based on the erosive score alone (Table 2).

No associations were found between ASRD and EAMs, RF seropositivity or disease activity. During the follow-up period, disease activity decreased from 40% in patients with a "very active" RA at the first visit ($N = 63$) to 9% at the last visit ($N = 14$). We performed a proper control of medication prescription by adjusting variables which may have biased our HR estimates downward due to confounding by indication [16]. In our sample, steroid use, which was registered in 85% of the patients, was significantly associated with an early appearance of substantial joint damage when a total SvdH score $\geq$5 was used as a definition of substantial damage (data not shown). Confounding by indication may produce type II rather than type I errors, which gives us confidence in the significant results obtained [16]. After controlling for RA treatment, the HRs and results found in the three analyses did not substantially change.

4. Discussion

This study examined factors influencing early time to appearance of substantial joint damage in a series of 157 RA patients followed for an average of 3.2 ± 3.1 years (Table 1). Our data revealed important results. First, having a family history of RA and anti-CCP3 seropositivity were significantly associated with an early ASRD and, therefore, with a rapid progression of disease, when erosive and total radiographic scores were used for defining substantial joint damage. Using these definitions, this study also found that the median ASRD decreased as the number of SE alleles increased, reflecting a more rapid damage in patients with two SE alleles in comparison with patients with one SE allele, and in patients with one SE allele in comparison with patients without any SE allele. When the definition was based only on the JSN score, having a family history of RA, having a double-dosage of the SE, and female gender were significantly associated with a more rapid RA progression although the presence of anti-CCP3 antibodies was not.

In the three survival analyses, having a family history of RA had the largest effect size on the time to reach a substantial joint damage. This suggests that this variable is an important predictor of the course of radiographic damage: a patient with a family history of RA had at least a 200% higher hazard of starting to suffer substantial joint damage than a patient of comparable age without a family history. There is a wide range of results on the association between familial RA and radiographic progression. Some studies report a lack of association [17–23] and others a considerable influence of familial RA on damage progression [24–29]. These apparently contradictory results may be explained by differences in the definitions of familial RA and radiographic progression across studies, and in the study designs and statistical methods used (Table 3). The term "familial" has been used arbitrarily in the reports on the genetic epidemiology of autoimmune diseases, which causes difficulties in the interpretation of results [30]. Some reports make a distinction between familial and sporadic disease based solely on the number of siblings affected [24,28,30]. In the current study, we use the term "familial" to describe the aggregation of RA in FDRs. Differences between studies in the effect of

Table 3
Family history of RA and joint damage assessed by radiographic progression (review of literature).

References	Familial cases *n* (%)	Sporadic cases *n*	Familial vs. sporadic sibship size	Cases with an affected first-degree relative (FDR)	Effect on joint damage[a]
[17]	49 (5.7)	804	5.8 vs. 6	49 (parent–offspring pairs)	No
[18]	129 (37)	217	NA	61 (40 affected sibpairs, 15 parent–child pairs, one sibpair with mother affected and six sibtrios)	No
[19]	149 (74)	53	NA	73 (siblings, parents)	No
[20]	36 (20)	142	8.2 vs. 5.5	36 (at least two affected siblings)	No
[21]	194	16	NA	194 (58 multicase families)	No
[22]	174	156	NA	174 (affected sibling-pair families) and 38 RA multiplex families.	No
[23]	223	88	NA	223 (91 multicase families)	No
[24]	62 (9)	628	7.8 vs. 2.3	55 (affected sibpair)	Yes
[25]	31	NA	3.4	15 (two or more siblings affected)	Yes
[26]	240	NA	2	240 (240 same sexed sibships)	Yes
[27]	398	NA	2.9	195 (multicase RA families)	Yes
[28]	565	NA	3	271 (at least two affected siblings)	Yes
[29]	1002	NA	NA	491 (multicase RA families)	Yes
Current study	11 (7)	146	NA	11 (at least one FDR)	Yes

[a] Familial vs. sporadic.

family history of RA on joint damage could also be due to a variable heritability across populations (i.e. the proportion of phenotypic variation in a population that is attributable to genetic variation among individuals) [31]. The contribution of genetic factors to the liability to RA has been estimated by comparing monozygotic and dizygotic twins. In Caucasians, this contribution has been reported to be 50–60% of the total liability [32]. However, the amount of heritability depends on the investigated population because variations in both additive and non-additive genetic factors, and the environmental variance are specific to the population [31].

The three radiographic definitions of substantial joint damage yielded consistent associations between the number of SE alleles and early joint damage in our patients. In fact, in the three survival analyses, the observed effect sizes for an additional SE allele were statistically significant and very similar (Table 2). This suggests a significant and robust effect exerted by the number of SE alleles on ASRD, which is independent of the definition of substantial damage used. These results indicate that the SE is not only a risk factor for RA [6,33] but also a detrimental factor influencing the radiographic progression of RA in our population.

Being positive for anti-CCP3 antibodies was significantly associated with an early ASRD, but only when the erosive and total SvdH scores were used as the basis for the definition of substantial joint damage. The association was not significant when the definition of substantial joint damage was based on the JSN score. Anti-CCP antibodies are particularly useful in the diagnosis of RA because of their high specificity; a number of studies have found an association between anti-CCP positivity and radiographic damage [34,35]. Some studies suggest that SE alleles are associated with an increased production of anti-CCP antibodies, and that the presence of anti-CCP antibodies in early RA is associated with a rapid progression of joint destruction [34,35]. In our patients, the median age at which substantial damage appeared lowered as the number of SE alleles increased regardless of anti-CCP3 seropositivity status. Other authors have found that the radiographic severity of RA is associated with both RF and anti-CCP production, and that SE alleles are more strongly associated with anti-CCP production in RF-negative individuals [36]. Recent studies have pointed out that anti-CCP positive RA and anti-CCP negative RA might have a different pathogenesis [37,38]. Others have found that RF may influence radiographic progression of RA independently of *HLA-DRB1* status [39], a result that was not confirmed in our study.

An association between EAMs and the severity of disease has been reported [40]. Others have found that high RF titers are important predictors of an increasing severity of radiographic damage, and of EAMs (i.e. nodules) which in turn predict radiographic severity at the first film [41]. We did not confirm these results in our study. This may suggest that there are different outcomes in target organs during the course of RA. A similar interpretation can be put on the lack of association between cardiovascular disease and early radiographic damage observed in our study. Finally, no association between disease activity and ASRD was found, indicating that the clinical activity parameters used were not accurate measures to assess joint destruction in our patients.

Two pathological processes may work simultaneously in RA patients' joints. One leads to signs and symptoms of inflammation, and the other to direct joint destruction by synovial cells [42]. This model predicts that in the natural history of progressive joint damage there will be times in which JSN occurs at a rate different from that of the progression of discrete bony erosions [42], and different factors may influence these processes as confirmed by our study.

Although sample size and the inclusion of patients with different disease durations could be considered as shortcomings of this study, the analysis of censored observations via Weibull models allowed us to appropriately estimate the effect size of significant variables on early joint damage [43].

In conclusion, our results emphasize the usefulness of assessing familial autoimmunity, testing anti-CCP antibodies and typing HLA-DRB1 genes in patients with RA, since these factors may be used to predict an early appearance of substantial joint damage and guide therapeutic interventions.

Acknowledgments

We thank all the patients who participated in this study and our colleagues Luis M. Gómez, John Castiblanco, and Mario Quintana for their fruitful contributions. This work was supported by Colciencias, Bogota (1101-04-14156); the Universidad Nacional de Colombia, Bogota (DIB-809275); and the School of Medicine, Universidad del Rosario, Bogota, Colombia. F.J. Diaz and J.C. Salazar were supported by the Faculty of Sciences of the Universidad Nacional de Colombia at Medellin, Colombia.

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