Comparative study of elderly-onset rheumatoid arthritis and young-onset rheumatoid arthritis in a Colombian population: clinical, laboratory and HLA-DRB1 findings

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Abstract

Objectives

Elderly-onset rheumatoid arthritis (EORA) is considered to have different features in relation to young-onset rheumatoid arthritis (YORA). However, results from different evaluated populations worldwide have been inconsistent and in Colombia there are no known descriptions of the differences between these pathologies. The aim of this paper is to compare the clinical, laboratory and immunogenetic features in a Colombian population suffering with EORA and YORA.

Methods

EORA (≥65, n=104) and YORA (<65, n=96) patients were compared regarding clinical, laboratory and HLA-DRB1 alleles features. A control group without rheumatoid arthritis over 65 (n=179) was used to compare the HLA-DRB1 alleles. All patients met the ACR/1987 criteria for rheumatoid arthritis and the clinimetric index was calculated.

Results

*The gender ratio (female/male) was 1.8:1 in EORA. In both groups, the main onset pattern of disease was an insidious polyarticular onset (p=0.35). EORA was characterised by more distal-proximal joint involvement in comparison to YORA (p=0.0007). In EORA, the rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies frequency was close to 50%, lower than in YORA (63%). In both groups, the DAS28 and HAQ-DI score was higher than 6 and 1, respectively. The HLA-DRB1*0403 and *1402 frequency was significantly higher in EORA than in YORA. Also, the shared epitope (p=0.0392), HLA-DRB1*01 (p=0.0068) and *0101 (p=0.0151) were associated with an anti-CCP positivity and the HLA-DRB1*0403 is protective for the anti-CCP presence in EORA (p=0.0201).*

Conclusion

*EORA is characterised by a different clinical presentation and HLA-DRB1 alleles with respect to YORA. HLA-DRB1*0403 and *1402 are significantly more frequent in EORA compared to YORA.*

Key words

rheumatoid arthritis, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, HLA-DRB1 antigen

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Introduction

Elderly-onset rheumatoid arthritis (EORA) is usually defined as the onset of disease after 65 years of age. Other authors define EORA as having an onset after 60 years of age (1). The reported prevalence of EORA is close to 2% (2), representing one-fifth to one-third of cases of rheumatoid arthritis (RA) (3, 4). Historically, EORA has been regarded as a separate clinical entity, differing in demographic, clinical and immunogenic characteristics, with respect to young-onset rheumatoid arthritis (YORA), which begins before 65 years of age. In this sense, EORA is characterised by a less marked predominance in women (5), abrupt onset of symptoms with systemic manifestations, longer duration of morning stiffness, frequent proximal joint involvement (shoulder), and an apparent benign clinical course. Additionally, three forms of EORA clinical presentation have been proposed: the form similar to RA with erosions and rheumatoid factor (RF) positive, which represents 70% of cases, the form similar to polymyalgia rheumatica (25%) with abrupt onset, involvement of proximal joints and RF negative, and, finally, the similar way to remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome (6).

However, these observations come from descriptive studies performed in earlier decades, the 1950s, 1960s and 1970s (7-10), and even today it is still unclear whether RA in adults and elderly represents different diseases or is the same entity with a different expression.

Starting in the 1980s and the 1990s, several comparative studies between EORA and YORA began to appear, where it was found that the clinical behaviour of EORA was not entirely benign as previously thought (11). In this regard, van Schaardenburg *et al*. (12, 13) states that patients with EORA and a positive rheumatoid factor (RF) have high disease activity, radiographic damage and greater functional compromise, similar to or worse than that found in the YORA. These results are corroborated by the first two prospective studies in patients with EORA and YORA (14, 15), which highlights the fact that patients with EORA have a more severe course of disease, high disease activity with higher levels of erythrocyte sedimentation rate (ESR) and a tendency towards greater radiographic damage. However, the study by Ferraccioli *et al*. (14) found no differences in clinical manifestations between EORA and YORA, while the study by van der Heijde *et al*. (15) found that in EORA there is a greater involvement of large and small joints at the beginning of the disease.

With regard to immunological characteristics, the frequency of RF is lower in EORA compared to YORA, with a prevalence varying from 30% to 89% (5). Meanwhile, the reported prevalence of antibodies against citrullinated peptide (anti-CCP) in EORA varies between 65% and 77%, while in YORA it is between 69% and 92% (16, 17).

Regarding the susceptibility of RA, the HLA-DRB1 alleles (DRB1 *0101, *0401, *0404, *0405, *1001 and *1402) encoding the shared epitope (SE) are established as the most important genetic risk factors in the development of the disease (18). In the case of EORA, studies from different countries have found an association with different alleles such as HLA-DRB1 *0101, *04, *0405, *13, *14 and *1502. However, in the Colombian population with EORA there is no known association with HLA-DRB1 alleles.

Due to the heterogeneity of conclusions from studies regarding the behaviour of EORA compared to YORA and ignorance of the characteristics of EORA in the Colombian population, this study was developed to compare the clinical, laboratory and immunogenic characteristics in a Colombian population with EORA (≥65 years) compared to one with YORA (<65 years).

Materials and methods

A cross-sectional study was performed in a group of Colombian patients. A group of cases and two controls were included. Those with elderly onset rheumatoid arthritis (EORA) were considered as a case group, which is defined as the onset of RA symptoms (oedema and joint pain) after 65 years of age. The control group included:

first, young-onset rheumatoid arthritis (YORA) group, defined as having RA between the ages of 18 and 65, and second, subjects over 18 years old without RA from the Outpatient Service of Internal Medicine. All patients gave informed consent. Anyone with another connective tissue disease at baseline or during the course of the disease was excluded.

Each patient in the three groups was assessed by registration forms designed for this study, which were completed and annexed to the file of each patient. Data were taken from a guided interview, rheumatologic medical history, and physical examination. Thus, in this way, the identifying information of patients with YORA and EORA was recorded, including personal identification (name, ID number), sex, current age, age at onset of disease symptoms, abrupt onset (hours) or insidious (days to weeks) of illness, pattern of joint involvement at onset of the disease (polyarticular, oligoarticular), and symptoms associated with the onset of RA. During the physical examination, a count of 28 swollen and tender joints was realised according to the standard method. Pain intensity was evaluated by visual analogue scale. From these findings, the Disease Activity Score 28 (DAS28), a validated instrument, was calculated. A functional status patient was assessed using the Health Assessment Questionnaire-Disease Index (HAQ-DI).

In both groups of patients with RA (EORA and YORA), the following tests were calculated: erythrocyte sedimentation rate (ESR) in mm/h, C-reactive protein (CRP) in mg/dl, 25-hydroxyvitamin D (25[OH] D) levels were tested by electro-chemi-luminescence, and antibodies such as the rheumatoid factor (RF) and second-generation anticyclic citrullinated peptide (CCP) IgG. Through DNA extracted from leukocytes in an anti-coagulated blood sample with EDTA, HLA-DRB1 alleles were analysed in patients with EORA, YORA and in the controls without RA. In this way, 206 alleles were analysed in the EORA group, 178 alleles in the YORA group, and 358 alleles in the control group. Typing of HLA-DRB1 alleles was performed by SSO hybridisation reagents in liquid phase using Gen-Probe (Stamford, CT) and analysed on the Luminex 100 IS system.

Statistical analysis

The different statistical analyses were performed using STATA 10.0 package, (Copyright 1984-2007, College Station, Texas, 77845, USA, 800-STATA-PC, serial number: 87360636346). The Shapiro-Wilks test was used for the distribution of data. The continuous variables with a normal distribution were described with means and standard deviations, variables with a nonparametric distribution with medians, and in both cases the ranges were reported. The Student *t*-test, ANOVA, and nonparametric tests were used for comparison of variables when appropriate. Fisher's exact test or the chi-square test was used to determine the strength of association between variables of interest (shared epitope, HLA-DRB1, disease and positive serology), taking into account the number of cases in the contingency tables developed for analysis of the data. If the expected frequency in any cell is less than 5, then Fisher's exact test was used. The odds ratio (OR) and a 95% confidence interval (95% CI) were calculated as a measure of the epidemiological association. A *p*-value less than 0.05 was considered significant for all data.

Results

A total of 104 patients with EORA, 96 with YORA, and 179 controls without RA were included in this study. The clinical characteristics are presented in Table I. The female:male ratio was 1.8:1 in EORA and 3:1 in YORA. The mean age in EORA was 72.8 years old and in YORA was 46.1. The mean age at onset of illness was 70.4 and 43.3 in EORA and YORA, respectively. The duration of the disease was 2.38 years in EORA and 2.78 years in YORA. 93.6% of patients with YORA and 55.3% of EORA patients consulted a rheumatologist during the first year of onset of symptoms of RA. In both groups, insidious-polyarticular onset was the main pattern of onset disease (p=0.35). In EORA, in comparison to YORA, the first joints affected at the beginning of the disease were the distal (39.8% *vs*. 50%), the distal-proximal "mixed pattern" (35.6% *vs*. 11.5%), and the proximal (24% *vs*. 26%). The frequency of morning stiffness was higher in the YORA group, while extra-articular manifestations occurred in similar proportions in both groups. The smoking status was 16.3% in EORA and 18.7% in YORA. The 28-joint (swollen and tender) count was comparatively higher in YORA than in EORA. The mean of 25 (OH) D levels was 19.23 ng/dl ± 8.65 in EORA and 27.16±12.86 ng/ml in YORA.

Laboratory, disease activity and functionality results

The ESR and CRP levels were higher in EORA with respect to YORA, with only a statistically significant difference

Table I. Clinical characteristics of EORA and YORA.

	EORA n=104	YORA n=96	*p*-value
Female:Male ratio	1.8:1	3:1	0.09
Mean age (years)	72.8 ± 4.9	46.1 ± 12.3	–
Mean age at the onset of symptoms (years)	70.4 ± 4.5	43.3 ± 12	–
Consultation during the 1st year of onset of symptoms	55.3%	93.6%	0.001
Duration of the disease (years)	2.38	2.78	0.0001
Distal joint involvement¶	39.8%	50%	0.02
Distal-proximal joint involvement¶	35.6%	11.5%	0.0007
Proximal joint involvement¶	24%	26%	0.49
Morning stiffness	53%	72%	0.008
Extra-articular manifestations	9.6%	6.2%	0.53
Smoking	16.3%	18.7%	0.655
Swollen joint count-28	15.9 ± 8.1	21.7 ± 7.7	0.001
Tender joint count-28	16.0 ± 8.1	22.5 ± 7.1	0.001

¶At the onset of disease.

Table II. Laboratory results and parameters of disease activity and functionality in EORA and YORA.

	EORA n=104	YORA n=96	*p*-value
ERS (mm/h)	31.9±18	28.5±14	0.18
CRP (mg/dl)	3.2±4.3	1.5±1.9	0.0004
RF positive	49.5%	62.8%	0.08
Anti-CCP positive	54.5%	64.8%	0.19
25(OH) D (ng/ml)	19.23	27.16	<0.001
DAS28	6.0±1.3	6.7±0.9	0.001
HAQ-DI	1.16±0.9	1.15±0.5	0.9

ERS: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor (>16 U); Anti-CCP: anti-cyclic citrullinated peptide antibodies (>20 U); 25(OH) D: 25-hidroxyvitamin D levels; DAS 28: disease activity score 28; HAQ-DI: Health Assessment Questionnaire-Disease Index.

Table III. Frequency of the shared epitope (SE) and HLA-DRB1 alleles in EORA, YORA and control groups.

	EORA 2n=206	YORA 2n=178	Controls 2n=358
SE	32.52%*	25.28%	20.95%
Homozygous SE	9.7%*	5.6%	3.3
Heterozygous SE	22.8%	19.6%	17.6
HLA-DRB1*01	15%	12.9%	10,0
HLA-DRB1*04	20.8%	30.3%δ	24,5
HLA-DRB1*0403	10.10%δ	3.37%	15.97%¶
HLA-DRB1*1402	8.17% δ	3.37%	2.79
HLA-DRB1*1501	11.06%	5.62%	8.66

*p<0.05 significant between EORA and controls; ¶p<0.05 significant between YORA and controls; δp<0.05 significant between EORA and YORA.

for CRP. In EORA, the presence of RF and anti-CCP was lower compared to that observed in YORA, although not statistically significant. Both in YORA and in EORA, the DAS28 score and HAQ-DI were elevated (Table II).

Immunogenetic characteristics

In the three study groups, different HLA-DRB1 alleles were analysed. Table III shows the HLA-DRB1 alleles that were found more frequently in each of the groups.

HLA-DRB1 alleles frequency in EORA and YORA in comparison to the controls

The frequency of alleles that constitute the SE was higher in EORA and RA compared with the controls, but not for YORA (Table IV). The frequency of the HLA-DRB1 alleles was different between patients with EORA, YORA and RA (EORA + YORA) compared with the controls (Table IV). The allele HLA-DRB1 *0101 is almost twice as common in EORA and RA in comparison to the controls, although it was not significant (p=0.0645 and 0.0781, respectively). In comparison to the controls, the presence of HLA-DRB1 *0403 is significantly less frequent in YORA and RA, but it had a non-significant trend in EORA. Therefore, the HLA-DRB1 *0403 is protective in RA, mainly in YORA. Regarding the HLA-DRB1 *1402, it was found to have a frequency three times higher in EORA and two times higher in RA in comparison to the controls. There were no differences in HLA-DRB1 *04 and *10 when comparing EORA with the controls. Similarly, when comparing the frequencies of HLA-DRB1 *01, *04, *14 and *15 between YORA and the controls, no differences were found.

Comparison of HLA-DRB1 between EORA and YORA

The presence of SE was similar in both groups (Table V). In the EORA group, both HLA-DRB1 *0403 and HLA-DRB1 *1402 were significantly more frequent in comparison to the YORA group.

Association of SE and HLA-DRB1 alleles with RF and anti-CCP in EORA, YORA, and RA

In the EORA group, when analysing the association between SE and the presence of antibodies (anti-CCP and RF), there was a statistical significance only with anti-CCP. The presence of DERAA alleles was not associated with negativity of antibodies (Table VI).

In the YORA group, the alleles for the DERAA sequence were associated with a negative anti-CCP (OR 0.35; 95% CI 0.11 to 1.05), however SE was not associated with the presence of any antibodies. In this group, there was no

Table IV. Association of shared epitope (SE) and HLA-DRB1 alleles in EORA, YORA and RA (EORA + YORA) compared to control group.

HLA-DRB1	EORA OR (95% CI)	*p*-value	YORA OR (95% CI)	*p*-value	RA (EORA + YORA) OR (95% CI)	*p*-value
SE	1.81 (1.21–2.72)	0.0023	1.27 (0.81–1.98)	0.2572	1.55 (1.09–2.20)	0.0100
*0101	1.80 (0.90–3.56)	0.0645	–	–	1.64 (0.91–3.02)	0.0781
*0403	0.59 (0.32–1.02)	0.0511	0.18 (0.06–0.43)	<0.0001	0.39 (0.23–0.65)	0.0001
*0404	–	–	2.08 (0.83–5.18)	0.0739	–	–
*1402	3.09 (1.30–7.71)	0.0038	–	–	2.20 (1–5.26)	0.0361

OR: odds ratio.

Table V. Frequency of shared epitope (SE) and HLA-DRB1 alleles in EORA compared to YORA.

	EORA 2n=206	YORA 2n=178	OR (95% CI)	*p*-value
SE	32.52%	25.28%	1.42 (0.89–2.28)	0.1194
HLA-DRB1*0403	10.10%	3.37%	3.21 (1.21–9.95)	0.0098
HLA-DRB1*1402	8.17%	3.37%	2.55 (0.93–8.06)	0.0469
HLA-DRB1*1501	11.06%	5.62%	2.08 (0.92–5.05)	0.0567

OR: Odds ratio.

Table VI. Association of shared epitope (SE) and DERAA sequence with anti-CCP and RF in EORA.

	EORA	OR (95% CI)	*p*-value
SE Anti-CCP + Anti-CCP -	 65.63% 34.38%	1.90 (1–3.73)	0.0392
SE RF + RF -	 53.23% 46.77%	1.21 (0.63–2.32)	0.5370
SE Anti-CCP/RF + Anti-CCP/RF -	 72.88% 27.12%	1.79 (0.87–3.78)	0.0891
DERAA Anti-CCP and RF -	 –	1.36 (0.43–4.19)	0.5459

RF: rheumatoid factor; Anti-CCP: anti-cyclic citrullinated peptide antibodies; OR: odds ratio; DERAA: protector sequence.

Table VII. Association of HLA-DRB1 alleles with the presence of antibodies (RF and anti-CCP) in EORA.

	OR (95% IC)	*p*-value
HLA-DRB1*0101		
Anti-CCP +	4.98 (1.34–27.43)	0.0068
RF +	2.58 (0 .87–8.5)	0.0556
Anti-CCP or RF +	11.10 (1.64–471.0)	0.0044
HLA-DRB1*01		
Anti-CCP +	3.14 (1.13–9.99)	0.0151
HLA-DRB1*0403		
Anti-CCP +	0.31 (0.09–0.94)	0.0201
Anti-CCP and RF +	0.34 (0.08–1.13)	0.0557
HLA-DRB1*1402		
RF +	4.7 (0.85–47.22)	0.051

RF: rheumatoid factor; Anti-CCP: anti-cyclic citrullinated peptide antibodies; OR: odds ratio.

association between the most frequent HLA-DRB1 alleles (*0101, *0403, *0404, *1402 or *1501) with RF, anti-CCP, or both.

Among the alleles that constitute the SE of the EORA group, HLA-DRB1 *01 and *0101 were significantly associated with a positive anti-CCP (Table VII). Similarly, HLA-DRB1 *0101 was significantly associated with positivity of any of the two antibodies. There was a tendency with the association of HLA-DRB1 *1402 with RF positivity. In contrast, HLA-DRB1 *0403 was significantly associated with a negative anti-CCP, conferring a protective factor (Table VII).

When the two patient groups were analysed together (RA: EORA and YORA), an association was found between the presence of SE and anti-CCP positivity (OR 1.88; 95% CI 1.13 to 3.1; *p*=0.0091). The HLA-DRB1 *0101 allele was associated with the presence of both antibodies (OR 3.05; 95% CI 1.03 to 12.26; *p*=0.0325). The HLA-DRB1 *0403 allele is protective for positive serology (OR 0.36; 95% CI 0.11 to 0.96; *p*=0.0277) and this association is maintained when analysing specifically for the presence of anti-CCP (OR 0.30; 95% CI 0.10 to 0.76; *p*=0.0044).

Discussion

In this comparative study of patients with EORA and YORA, there was a more balanced gender involvement in EORA compared to the female predominance over men in YORA. Although the difference between the two groups was not significant, a similar involvement in both men and women alike is a consistently occurring feature seen in EORA and it is consistent with reports of previous studies (10, 12, 15, 19, 20).

In EORA, the average age at the onset of the disease is close to seventy years and half of the patients consulted during the first year of symptom onset. In contrast, in YORA almost all the patients consulted within the first twelve months. It is not known why there is a low frequency of access to a rheumatologist in patients with EORA, but possible causes could be the failure in the recognition of symptoms by the health personnel who refer patients to specialists, confusion of RA symptoms with other diseases (osteoarthritis), and physical limitations in patient mobilisation to medical services.

Regarding the form of onset in RA, both groups are characterised by an insidious-polyarticular onset. This is consistent with the usual presentation in YORA. However, the group with EORA differed from the explosive onset and systemic symptoms reported in other studies of EORA (5). When analysing the joint involvement at the beginning of EORA, the involvement of the proximal-distal joints (big-small joints) was significantly higher compared to YORA, which is similar to what was found by van der Heijde *et al*. (15). Additionally, in EORA there appeared less distal joint involvement in comparison to YORA. This under-

scores the fact that EORA has a specific phenotypic expression within the clinical spectrum of RA, one different from YORA. However, given the peculiarities in the clinical presentation of EORA in this study, it is difficult for these patients to be accommodated in one of the three proposed types of EORA (6).

As regards the disease activity and the functional compromise at the onset of disease, both YORA and EORA have elevated levels of inflammatory activity and moderate functional disability, as evidenced by a DAS28 score higher than 6 and HAQ-DI higher than 1. In addition, both groups present frequently with morning stiffness (significantly higher in YORA). The frequency of anti-CCP and RF was close to 50% in EORA, which is a relatively smaller percentage than that reported by Lopez-Hoyos *et al*. (16) in Spain (65%) and Chen *et al*. (17) in Taiwan (77%). Similarly, the frequency of anti-CCP (65%) found in YORA is comparatively lower than that observed in Spain (92%), but similar to that observed in Taiwan (69%). These two studies, together with this analysis, reflect the variability regarding the frequency of antibodies in different regions of the world, which is probably due to the genetic and environmental factors of each population. In this study, a significant elevation of the systemic markers of inflammation (ESR and CRP) was found, a finding similar to that reported by van der Heijde *et al*. (15) and El-Labban *et al*. (21). As a consequence, the concept of EORA as a benign disease should be reassessed, and it should be considered as a pathology characterised by an aggressive clinical behaviour, as recently stated by several authors in the field (3, 6, 15, 19). From the above, it can also be inferred that EORA must be recognised, evaluated and provided timely treatment, in a similar way to YORA, in order to prevent disease progression and irreversible physical disability.

As regards the immunogenetic analysis in this study, the frequency of the HLA-DRB1 alleles in EORA is different from the ones found in YORA. The allele HLA-DRB1 *0403 (no SE) was found less frequently in patients with RA compared to controls, and appears as a protective factor, especially in the YORA group. Meanwhile, it was found that the HLA-DRB1 *1402 (SE) is associated with significantly EORA, being a susceptibility factor for the disease. Something similar happened with HLA-DRB1 *1501 (no SE), although this did not reach statistical significance. The above is different to that found by other studies in EORA. In Japan, Yukioka *et al*. (22) reported the positive association of EORA with HLA-DRB1 *0101, *0405 and *1502, the latter being significantly more frequent compared to patients with YORA. Already in 1987, Inoue *et al*. (23) also in Japan, had been the first to report a low frequency, although not significant, of HLA-DRB *04 in patients with EORA compared to YORA.

In Spain, Gonzales-Gay *et al*. (24) reported the association of RF positive EORA with HLA DRB1 *01. They also mentioned an increased frequency of HLA DRB1 *13 and *14 in patients with RF negative EORA. In France, Hellier *et al*. (25) found an increased frequency of HLA-DRB1 *0101 and a lower frequency of HLA-DRB1 *04 in EORA in comparison with YORA. In the Caucasian population of the UK, Pease *et al*. (26) reported the association of RF negative EORA with HLA-DRB1 *04 alleles with SE, specifically with the HLA-DRB1 *0401 allele. Conversely, van der Heijde *et al*. (15) in the Netherlands and Terkeltaub *et al*. (27) in the United States showed comparable frequencies of HLA-DRB4 in EORA and YORA.

Considering the above evidence, this study is the first to demonstrate the association of EORA with two HLA-DRB1 alleles not previously described, HLA-DRB1 *0403 and HLA-DRB1 *1402, compared to YORA. Additionally, similarly to what stated by Yukioka *et al*. (22), this study also reports the association of EORA with two alleles that do not belong to SE (*0403 and *1501). In this sense, the Japanese had already shown the association of an allele no SE, HLA-DRB1 *1502, with EORA. To date, the implications of the association of no SE alleles with the physiopathology of EORA is not known, especially considering that the HLA-DRB1 alleles with SE are the ones associated with anti-CCP positive RA, one of the phenotypes of the disease with aggressive behaviour (28, 29). Taking this into account, this study demonstrates for the first time in EORA that SE is a risk factor for the presence of a positive anti-CCP in a population over 65 years of age. For the Japanese, this association is known as "the purest phenotype of EORA," something that has also been demonstrated for YORA. This is important due to the fact that patients with an anti-CCP positive RA constitute a specific phenotype of the disease, about an increased disease activity and radiographic damage, with therapeutic implications and a special prognosis (28, 29). Similarly, this study demonstrates the statistically significant association of HLA-DRB1 *01, as well as *0101, with the presence of a positive anti-CCP in EORA. By contrast, there was no association of SE and HLA-DRB1 alleles with the presence of RF. Interestingly in YORA, there was no association of SE or different HLA-DRB1 with that of antibodies.

An important point in EORA was finding that HLA-DRB1 *0403 allele functions as a protective factor for the presence of a positive anti-CCP. This suggests that patients with HLA-DRB1 *0403 could have a less aggressive clinical course. However, these observations could be confirmed in a prospective study of clinical and radiographic progression.

In analysing the importance of the DERAA sequence, known for its protective nature in the development of RA, in YORA an association was found with a negative anti-CCP. For the EORA group, these associations were not found.

Conclusions

Compared to YORA, EORA is characterised by a lower prevalence in women, insidious-polyarticular onset, and more distal-proximal joint involvement at the onset of disease. Both conditions have high disease activity scores and functional disability. The frequency of RF and anti-CCP is close to 50%. In EORA, the presence of HLA-DRB1 *0403 and *1402 is significantly high-

er with regard to YORA. In patients with EORA, the presence of SE is associated with the presence of anti-CCP, as well as with HLA-DRB1 *01 and *0101. The HLA-DRB1 *0403 allele is a protective factor for RA, especially in YORA, when compared to the healthy controls. In addition, the HLA-DRB1 *0403 allele is a protective factor in the presentation of a positive anti-CCP in EORA, and it is potentially a protective factor against the aggressive behaviour in this subgroup.

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