HLA-Cw6 allele and biologic therapy are protective factors against liver fibrosis in psoriatic arthritis patients

C. Macía-Villa, J.L. Morell-Hita, M. Revenga-Martínez, C. Díaz-Miguel Pérez

Rheumatology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain.

Cristina Macía-Villa, MD, PhD
Jose Luis Morell-Hita, MD
Marcelino Revenga-Martínez, MD, PhD
Consuelo Díaz-Miguel Pérez, MD

Please address correspondence to:
Cristina Macía-Villa
Rheumatology Department, Hospital Universitario Ramón y Cajal, Carretera M-607, Km. 9, 100, 28034 Madrid, Spain.
E-mail: ccmacia@gmail.com

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ORCID iD
C. Macía-Villa: 0000-0002-6822-6730
J.L. Morell-Hita 0000-0003-1776-9142
M. Revenga-Martinez 0000-0002-7350-8214

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ABSTRACT

Objective. *To evaluate the association between liver fibrosis and the HLA-Cw6 allele in psoriatic arthritis (PsA) patients.*

Methods. *A retrospective longitudinal study involving PsA patients with determination of the HLA-Cw6 allele was performed. Liver fibrosis was estimated by using the FIB-4 (fibrosis-4) score. A multivariate logistic model was undertaken to assess the odds ratio (OR), with its 95% confidence interval, of liver fibrosis after adjustment for potential confounding factors.*

Results. *A total of 209 PsA patients were included: 25.3% HLA-Cw6 were positive, 59.8% were receiving biological disease-modifying anti-rheumatic drugs (bDMARDs), 29.6% had arterial hypertension (AHT), 24% dyslipidaemia, and 4.2% acute myocardial infarction (AMI). The HLA-Cw6 allele was more frequent in PsA patients with normal FIB-4 values (p=0.024), as opposed to AHT (p=0.002), AMI (p=0.023) and dyslipidaemia (p=0.030), which were found more frequently in subjects with altered FIB-4 values. The presence HLA-Cw6 and the use of bDMARDs were confirmed as protective factors against liver fibrosis (OR 0.210, 0.062–0.707, p=0.012 and OR 0.397, 0.166–0.949, p=0.038, respectively). Conversely, AHT emerged as a risk factor (OR 2.973, 1.125–7.858, p=0.028).*

Conclusion. *In PsA, the HLA-Cw6 allele and bDMARDs behave as protective factors for liver fibrosis, while AHT is an independent risk factor.*

Introduction

Psoriatic arthritis (PsA) is a systemic inflammatory disease with an important genetic background. The major histocompatibility complex class I alleles of both the HLA (human leukocyte antigen)-B and HLA-C loci and their haplotypes include the greatest genetic information related to PsA heritability and disease expression. One allele in particular, the HLA-Cw6 allele, has taken on a prominent role in recent years. There is a higher prevalence of this allele in PsA patients than in the general population (1), and there are studies indicating possible susceptibility to the development of PsA in HLA-Cw6-positive psoriasis patients (2). However, other authors suggest that HLA-Cw6 is mainly associated with psoriasis and is not associated with PsA (1). Moreover, HLA-Cw6 does not appear to interfere with the PsA phenotype, as it was evenly distributed in a cohort of patients with different clinical patterns (3). Therefore, the association between PsA and HLA-Cw6 has always been debated, making it interesting to explore its relationship with other domains and comorbidities of the disease.

Non-alcoholic fatty liver disease (NAFLD) is not only increased in PsA patients but is also the leading cause of liver disease in these patients. It is one of the consequences of metabolic syndrome and is strongly related to "psoriatic disease" (PsD). NAFLD can range from indolent hepatic steatosis, evolve to non-alcoholic steatohepatitis, even progress to fibrosis and be complicated with cirrhosis. Although the gold standard for the evaluation of these alterations is liver biopsy and imaging techniques are also very useful, some indices have recently appeared, such as the FIB-4 (fibrosis-4) score (4). These non-invasive tests can accurately predict the likelihood of liver fibrosis, reducing the need for biopsies.

The objective of our study was to evaluate the relationship between the HLA-Cw6 allele and the FIB-4 index in patients with PsA for the first time.

Material and methods

We performed a retrospective longitudinal study involving consecutive PsA patients of our clinics older than 18 years, fulfilling the Classification for Psoriatic Arthritis criteria (CASPAR) (first diagnosis 1982, last 2018). All of them had determination of the HLA-Cw6 allele (clinic protocol). The FIB-4 index was calculated to estimate liver fibrosis, both at the onset of PsA and at the last available visit. This index includes age, transaminases and platelets: a score <1.3 points rules out advanced fibrosis (F0-F1), a score >2.67 points implies significant fibrosis (F3-F4), and a score between 1.3 and 2.67 points is an intermediate zone (F2) in which another diagnostic test must be performed.

The latest available FIB-4 score was selected as our main variable, and was categorised as a dichotomous variable into normal (F0-1, non-advanced fibrosis zone) and altered (F2-3-4, intermediate and significant fibrosis zones) for analysis purposes.

Differences between groups were examined using descriptive statistics (mean, SD, median, IQR) based on symmetric or asymmetric distribution, and absolute values and percentages were used for qualitative variables. Patient characteristics at baseline (sex, mean age at PsA onset, psoriasis, acute reactant factors, HLA-Cw6 status, treatment, cardiovascular comorbidities) were collected and evaluated as possible risk factors for liver fibrosis.

A bivariate analysis was carried out using parametric and non-parametric hypothesis contrast tests to determine the association between the main and the secondary variables. Bivariate correlations were analysed using Pearson's coefficient to determine multicollinearity.

A multivariate logistic regression model was plotted to identify the relationship between HLA-Cw6 status and liver fibrosis (based on FIB-4 scores). Odds ratios (OR) were calculated with 95% confidence intervals and adjusted for potential confounding factors. Variables were selected if they modified the crude OR by more than 10%. Statistical significance was assumed at a p-value <0.05. The selection of independent variables in the multivariate model was based on clinical judgement and those with a value of p<0.20 were selected for the bivariate analysis. Multicollinearity between independent variables was also explored using Pearson and Spearman correlations to build the model. All analyses were performed with SPSS software (IBM SPSS statistics version 20.0).

Table I. Clinical features of the patients.

Patients	209
Men (%)	119 (56.9)
Women (%)	90 (43.1)
Mean age at PsA diagnosis (years ± SD)	42.7 ± 14.2
Current age (years ± SD)	56.8 ± 14.4
Disease duration (years ± SD)	13.6 ± 7.7
HLA Cw6 positive (%)	53 (25.3)
Psoriasis (%)	177 (84.7)
Type of PsA	
Axial (%)	23 (11)
Peripheral (%)	96 (46)
Axial and peripheral (%)	90 (43)
CRP mg/l at diagnosis (mean ± IQR)	5.0 (2.5-12.2)
ESR mm/h at diagnosis (mean ± IQR)	16.9 (9-28)
PsA treatment (past and/or current)	
Methotrexate (%)	166 (79.4)
bDMARDs (%)	125 (59.8)
Anti-TNF drugs	101 (80.8)
Cardiovascular comorbidities	
AHT (%)	50/169 (29.6)
Dyslipidaemia (%)	40/167 (24)
Diabetes mellitus (%)	17/168 (10.1)
AMI (%)	7/168 (4.2)

For cardiovascular comorbidities, data available in 169 patients for hypertension (AHT), 167 for dyslipidaemia, 168 for diabetes mellitus, and 168 for acute myocardial infarction (AMI).
PsA: psoriatic arthritis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; bDMARDs: biological disease-modifying anti-rheumatic drugs; TNF: tumour necrosis factor.

Table II. Bivariate descriptive analysis of the characteristics related to current FIB-4 scores.

	Normal current FIB-4 (n=106)	Altered current FIB-4 (n=74)	p-value
Male sex (%)	60.4	39.6	0.627
PsA age onset (years)[1]	37.33±11.71	51.53±12.33	0.630
Positive HLA-Cw6 (%)	18.54	6.74	**0.024**
ESR (mm/h)[2]	16 (9-32)	10 (6-19)	0.362
CRP (mg/l)[2]	5.31 (2.41-12.97)	3.30 (2.11-9.00)	0.348
bDMARDs (%)	64.3	35.7	0.059
Methotrexate (%)	56.8	43.3	0.211
Leflunomide (%)	11.3	10.8	0.915
Psoriasis (%)	58.9	41.1	0.648
AHT (%)	42.2	57.8	**0.002**
Diabetes (%)	6.7	15.8	0.079
AMI (%)	0.7	3.4	**0.023**
Dyslipidaemia (%)	45.9	54.1	**0.030**

FIB-4: fibrosis-4 index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PsA: psoriatic arthritis; bDMARDs: biological disease-modifying anti-rheumatic drugs; AHT: arterial hypertension; AMI: acute myocardial infarction.
[1]Mean±SD [2]Median (IR). p-values <0.05 are shown in bold.

Results

Two hundred and nine patients with PsA were included. Clinical characteristics are attached in Table I.

FIB-4 scores could be calculated for 154/209(73.7%) patients at the onset of PsA, with a mean score of 1.53±9.05 points, of which 58.9% were in the FIB-4 F0-1 zone (non-advanced fibrosis). At the latest available visit, FIB-4 scores could be calculated for 180/209(86.1%) patients, with a mean score of 1.35±0.85 points, of which 86.4% were in the FIB-4 F0-1 zone. The mean platelet count was 259.25±66.89 x10^3/μL at the onset of the disease, and 231.51±63.29 x10^3/μL at the the latest available visit.

Table II shows the bivariate analysis, and Table III shows the multivariate analysis. The HLA-Cw6 allele was found more frequently in PsA patients with normal FIB-4 values (18.54 *vs.* 6.74, p=0.024), as opposed to in those with AHT (42.2 *vs.* 57.8, p=0.002), AMI (16.7 *vs.* 83.3, p=0.023) and dyslipidaemia (45.9 *vs.* 54.1, p=0.030), which were found more frequently in subjects with altered FIB-4 values. Having the HLA-Cw6 allele was confirmed in the multivariate analysis as a protective factor against liver fibrosis (OR 0.210, CI 95% 0.062–0.707, p=0.012) as well as the use of bDMARDs (OR 0.397, CI

Table III. Multivariate model to determine the relationship between HLA-Cw6 status and FIB-4 alteration.

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR *p*-value
Male sex (ref. female)	0.861 (0.472-1.573)	1.553 (0.624-3.864)	0.344
HLA-Cw6 (ref. negative)	0.429 (0.204-0.903)	0.210 (0.062-0.707)	**0.012**
ESR (mm/h)	1.004 (0.987-1.021)	0.993 (0.967-1.019)	0.605
bDMARDs (ref. no)	0.556 (0.301-1.025)	0.397 (0.166-0.949)	**0.038**
Methotrexate (ref. no)	1.676 (0.742-3.787)	1.113 (0.357-3.466)	0.854
AHT (Ref. no)	3.090 (1.493-6.394)	2.973 (1.125-7.858)	**0.028**
Diabetes (ref. no)	2.597 (0.870-7.733)	1.478 (0.395-5.530)	0.561
AMI (ref. no)	8.462 (0.962-74.423)	6.302 (0.495-80.246)	0.156
Dyslipidaemia (ref. no)	2.289 (1.072-4.888)	1.429 (0.541-3.773)	0.471

ESR: erythrocyte sedimentation rate; bDMARDs: biological disease-modifying anti-rheumatic drugs; AHT: arterial hypertension; AMI: acute myocardial infarction; ref: reference.
p-values <0.05 are shown in bold.

95% 0.166–0.949, *p*=0.038). Conversely, AHT emerged as a risk factor (OR 2.973, CI 95% 1.125–7.858, *p*=0.028).

Discussion

In our study, having the HLA-Cw6 allele and receiving bDMARDs behaved as protective factors for liver fibrosis in PsA patients, while AHT was an independent risk factor. The presence of psoriasis was not related to hepatic fibrosis in our PsA cohort.

Recently, the term NAFLD has been replaced by metabolic-associated fatty liver disease (MAFLD) (5), and is the most common cause of chronic liver disease in the western world. The relationship between MAFLD and PsD has been widely described, and this association appears independent of a coexisting metabolic syndrome and the use of hepatotoxic therapies (6). In our study, we chose the fibrosis stage of MAFLD, as it is the most useful marker for predicting future mortality in these patients (7). In addition, we selected the last available FIB-4 score for each patient instead of the PsA-onset FIB-4 score to assess this fibrosis stage with the greatest possible accuracy.

Although the use of MTX was present in almost 80% of the patients, its use did not give rise to differences between the group with normal and altered FIB-4 values, nor did it appear to be a risk factor for fibrosis, similar to other studies (8). In addition, receiving bDMARDs (almost 60% of the patients) was a protective factor against fibrosis. Our hypothesis is that better systemic inflammatory control in PsA patients could lead to better control of MAFLD and therefore prevent patients from reaching the liver fibrosis stage. This thesis is supported by recent studies. CD8 T cells have been shown to be important in the immune-mediated pathogenesis of MAFLD. Additionally, TNF-α promotes insulin resistance and induces transforming growth factor ß and connective growth factor, which have been implicated in the development of MAFLD and, consequently, in contributing to liver fibrosis (9). Moreover, the IL-12 and IL-17/23 axis are associated with MAFLD (10, 11). It is therefore not striking that we found the use of bDMARDs to be a protective factor for liver fibrosis, and Seitz *et al*. showed that anti-TNF-α drugs may exert a protective effect against liver fibrosis in PsA patients who are treated with MTX (8). Targeted treatments seem to protect against the evolution of liver fibrosis in PsA patients.

We found a prevalence of HLA-Cw6 of 25.3% in our series, according to other publications (12). This allele is mainly associated with psoriasis (1), but it is also connected to PsD and higher systemic inflammation levels (13), which opens up an interesting field of research. Atherosclerosis, one of the PsA cardiovascular comorbidities (14), is an immune-mediated inflammatory cardiovascular disease whose incidence is increased in these patients (15), and is associated with HLA-Cw6 and with higher ESR levels (12). However, until now, obesity has not been associated with HLA-Cw6 in PsA patients (13), nor has AHT that was present in almost 30% of our sample similar to others series (6, 9, 12), but knowledge in this field is still scarce.

Our study has some limitations. A retrospective design implies the loss of some data, measuring liver fibrosis by other methods, and the impossibility of obtaining information that could have been useful in the analysis, such as Body Mass Index or other PsA activity data. However, we think that our sample is large and that the data loss in the information we studied is minimal.

Conclusion

In conclusion, in terms of liver fibrosis in PsA patients, we suggest placing special emphasis on the control of AHT within the cardiovascular risk factors and providing a tight-control treatment, as it seems to change the natural progression to MAFLD. Furthermore, requesting the HLA-Cw6 allele status could help us to better stratify risk groups, allowing us to predict patients with a higher risk of liver fibrosis, conditioning their follow-up and possibly their management.

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