Chapter 7

HLA-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging: results from the DESIR cohort of patients with recent onset axial spondyloarthritis

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ABSTRACT

Objectives

To clarify the influence of human leucocyte antigen B27 (HLA-B27) status on the phenotype of early axial spondyloarthritis (SpA).

Methods

708 patients with inflammatory back pain (IBP) defined by Calin or Berlin criteria were recruited; 654 fulfilled at least one of the SpA criteria (modified New York, European Spondyloarthropathy Study Group, Amor or Assessment of SpondyloArthritis international Society classification criteria for axial SpA) and were included in the analyses. Clinical, demographic and imaging parameters were compared between HLA-B27 positive and negative groups. Significant parameters in univariate differences between HLA-B27 positive and negative groups were retested in multivariate models explaining various outcomes.

Results

Patients had a short duration of axial symptoms (mean 1.5 years) and HLA-B27 was present in 61.5%. In multivariate analysis, HLA-B27 positivity was associated with a younger age at onset of IBP (regression coefficient (B)=(−2.60), $p<0.001$), less delay in diagnosis (B=(−1.02), $p=0.01$), lower frequency of psoriasis (OR 0.59, $p=0.01$) and higher frequency of MRI inflammation of the sacroiliac joints (SIJ) (OR 2.13, $p<0.001$), MRI inflammation of the spine (OR 1.59, $p=0.04$) and radiographic sacroiliitis (OR 1.56, $p=0.03$). MRI inflammation of the SIJ was shown to be an intermediate variable between HLA-B27 positivity and radiographic sacroiliitis.

Conclusion

In early axial SpA, HLA-B27 is associated with earlier onset of IBP, less delay in diagnosis, axial inflammation (spine and SIJ), radiographic damage of the SIJ, decreased disease activity and lower frequency of psoriasis. It is not associated with physical function and MRI structural lesions of the SIJ.

INTRODUCTION

Spondyloarthritis (SpA) describes a spectrum of rheumatic diseases where inflammatory back pain (IBP) is a typical feature. The disease is associated with the human leucocyte antigen B27 (HLA-B27) and has other important clinical features such as asymmetrical peripheral arthritis (lower limb predominance), enthesitis, dactylitis, uveitis, psoriasis and inflammatory bowel disease.

Since HLA-B27 was first reported in 1973, its role in the diagnosis, prognosis and management of SpA has been extensively investigated. It is estimated to be present in 75–95% of cases of ankylosing spondylitis (AS) and 42–75%[1–6] of cases of axial non-radiographic/undifferentiated SpA. Its diagnostic importance is reflected by the inclusion of HLA-B27 in the Amor criteria for spondyloarthropathy in 1990[7] and in the Assessment of SpondyloArthritis international Society (ASAS) classification criteria[8,9] for axial SpA in 2009. HLA-B27 is also known to be associated with earlier age of axial SpA onset,[2,10] increased severity and persistence of MRI-demonstrated inflammation at the sacroiliac joints (SIJ) and lumbar spine in early IBP,[11] and anterior uveitis in SpA patients.[10,12]

However, the exact role of HLA-B27 in early axial SpA is still unknown as previous studies focused mainly on its association with AS. The recent shift in focus to earlier diagnosis has enabled more patients to be classified as axial SpA. It is therefore important to explore the role of HLA-B27 in this early disease phase. Our aim was to clarify the influence of HLA-B27 status on the phenotype of early axial SpA. The results may provide important information about its contribution to disease spectrum manifestations in axial SpA.

METHODS

Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) is a prospective longitudinal cohort in France involving 25 rheumatology centres and 708 patients.[13] The aim of DESIR is to study comprehensively the nature and outcome of SpA from early symptom onset. The data presented here comprise a cross-sectional analysis of baseline data of all patients included in DESIR (inclusion period October 2007 to April 2010).

Inclusion and Exclusion

Consecutive patients aged >18 years and <50 years with IBP involving the thoracic, lumbar spine or buttock area for >3 months but <3 years and symptoms suggestive of SpA according to the rheumatologists' assessment (score ≥5 on a Numerical Rating

Scale (NRS) of 0–10 where 0=not suggestive and 10=very suggestive of SpA) were included in the DESIR cohort. Patients had to fulfil the IBP criteria of Calin et al[14] or Berlin.[15] Patients with a definite diagnosis of non-SpA back pain, conditions which might interfere with the validity of the informed consent and/or prevent an optimal compliance (eg, alcoholism, psychiatric disorders) and a history of anti-tumour necrosis factor usage were excluded. Corticosteroid intake was permitted only in doses of <10 mg prednisone per day and had to be stable for at least 4 weeks before recruitment. Details of the protocol and the case record form are accessible on the website.[16] Patients with non-inflammatory chronic back pain were not included in DESIR, although they may represent up to 20–30% of patients with axial SpA.[17]

The sample size was based on the estimated predictive validity of sacroiliac evaluation.[13,16] The last patient was recruited on 29 April 2010 and the database used in our study was locked on 30 June 2010 (intended follow-up of the cohort 10 years). Patients were classified according to different criteria for AS and SpA: modified New York (MNY) criteria,[18] European Spondyloarthropathy Study Group (ESSG) criteria,[19] Amor criteria[7] and ASAS classification criteria for axial SpA.[8,9] Only patients fulfilling at least one of these criteria were included in our analyses.

Study design

In the DESIR cohort, patients are evaluated every 6 months for the first 2 years and annually thereafter. In the present analysis we only used data collected at the first visit. Patients were interviewed for baseline characteristics which included age, ethnicity, date at onset of IBP and peripheral arthritis, nature of IBP, presence of SpA features, relevant family history, medication including use of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs and the number of patient-reported missed work days in the previous year. The duration of axial symptoms was defined as the time difference between the first axial symptom and the initial interview. Delay in diagnosis was defined as the time difference between the onset of any SpA feature and SpA diagnosis by the physician. Physical examination was also performed to determine the Ritchie articular index (53 joints) and swollen joint count (28 joints), spinal mobility as measured by the Bath Ankylosing Spondylitis Metrology Index (BASMI)[20] and chest expansion. Extra-articular features were evaluated in those with relevant complaints.

Intensity of axial, nocturnal and peripheral joint pain was measured on a NRS of 0–10. Patients were asked to complete the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[21] and the Bath Ankylosing Spondylitis Functional Index (BASFI).[22]

Blood tests were performed in the regional rheumatology centres. These included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and HLA-B27 antigen.

The Ankylosing Spondylitis Disease Activity Score (ASDAS),[23] recently validated for assessing disease activity in AS,[24] was calculated using either CRP (ASDAS-CRP) or ESR (ASDAS-ESR). An ASDAS value ≥2.1 represents high disease activity.[25]

All imaging modalities (x-rays and MRIs) were evaluated by the local radiologist or rheumatologist; x-rays of the SIJ were graded according to the following grading scale: 0=normal, 1=doubtful, 2=obvious and 3=fusion, and radiographic sacroiliitis was defined as the presence of grade 2 or grade 3 lesions. Lateral x-rays of the cervical and lumbar spine were used to calculate the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).[26]

T1-weighted fast spin echo and short tau inversion recovery 1–1.5 tesla MRIs of the whole spine and the SIJ were performed to assess inflammatory and structural lesions (missing MRI data in 6.0–6.9% of patients). The MRIs were classified as having definite, doubtful or absent inflammatory (bone oedema) or structural lesions (erosions, sclerosis or bone formation) at the spinal and sacroiliac level, according to ASAS recommendations.[27] Doubtful images were considered as being negative images.

Statistical methods

SPSS Version 17.0 was used for data analysis. Differences between HLA-B27 positive and negative patients were investigated using the χ^2 statistic and independent sample t test for categorical and continuous variables, respectively. Variables noted to have differences in the t tests/χ^2 statistic were used as dependent variables in univariate and multivariate linear/logistic regression analysis. Based on previous literature and knowledge about the disease, other factors in addition to HLA-B27 status known or expected to be associated with the dependent variable under study were also tested in univariate analyses - namely, ethnicity, gender, family history of SpA, current use of NSAIDs, MRI inflammation, duration of IBP, acute phase reactants, clinical disease activity and spinal mobility. Significant ($p<0.1$) independent variables in univariate analyses were retested in multivariate regression models. Interactions between HLA-B27 and gender were tested in each model. Separate regression models were built according to gender if such an interaction existed. Variables with a skewed distribution were transformed using natural logarithms (ln) in linear regression models (ESR and CRP). The results were reported as OR in logistic regression models and regression coefficients (B) and standard coefficients (β) in linear regression models. p Values <0.05 were considered statistically significant in multivariate regression models.

RESULTS

Baseline characteristics

Of the 708 patients included in the DESIR cohort, 654 patients (92.4%) fulfilled at least one of the SpA criteria and were included in the analysis (figure 1). Discordant cases differed in HLA-B27 status, with a subgroup of mainly HLA-B27 negative patients fulfilling ESSG and/or Amor criteria but not ASAS criteria for axial SpA, and a subgroup of mainly HLA-B27 positive patients fulfilling ASAS criteria for axial SpA but not ESSG or Amor (figure 1). The analysed cohort included slightly more women (54%) and HLA-B27

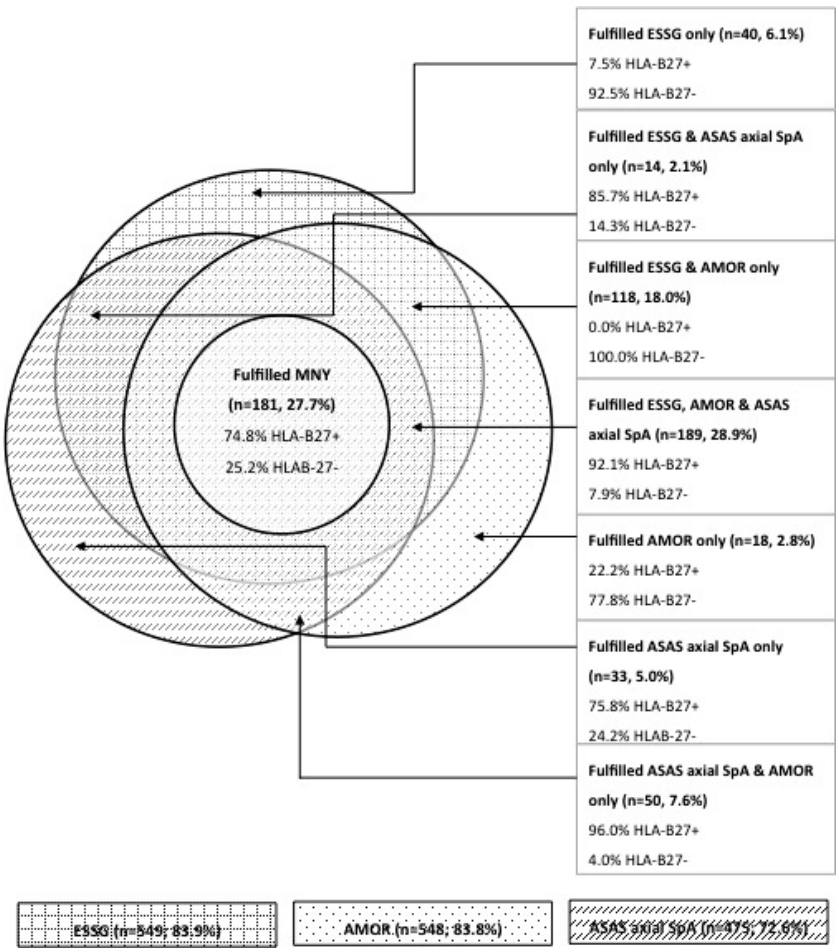

Figure 1. Frequency of HLA-B27 positivity in various subgroups of spondyloarthritis (SpA) classification criteria. AMOR, Amor criteria for spondyloarthropathy; ASAS axial SpA, Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis; ESSG, European Spondyloarthropathy Study Group criteria; MNY, modified New York criteria.

was positive in 61.5% of the patients.

Our cohort was characterised by young age (mean 33.6 years, median 33.0 years) and short duration of axial symptoms (mean 1.5 years, median 1.4 years). Patients had high disease activity (mean BASDAI 4.5, median 4.6), minimal radiographic spinal damage (mean mSASSS 1.1, median 0.0) and moderately affected physical function (mean BASFI 3.1, median 2.6).

Comparisons of baseline characteristics between HLA-B27 positive and negative groups are shown in table 1. The dependent variables selected for regression analysis were: age at onset of IBP, delay in diagnosis, clinical disease activity (ASDAS-CRP and BASDAI), MRI inflammatory lesions of the spine and SIJ, MRI structural lesions of the SIJ, radiographic sacroiliitis, extra articular features and physical function (BASFI).

Regression analysis

A core set of four independent variables were investigated in all univariate analyses: Caucasian race, male gender, HLA-B27 positivity and family history of SpA. Additional independent variables were tested according to the dependent variable under study.

Age at onset of IBP as dependent variable

All the independent variables in the above core set showed a p value of <0.1 in univariate analyses (Caucasian race (B=2.50, p=0.03), male gender (B=(−2.06), p=0.003), HLA-B27 positivity (B=(−2.95), p<0.001) and family history of SpA (B=1.58, p=0.05)) and were therefore retested in multivariate linear regression analysis.

In multivariate analysis, the age at onset of IBP was found to be positively associated with Caucasian race (β=0.12, B=3.54, 95% CI 1.31 to 5.76, p=0.002) and negatively associated with HLA-B27 positivity (β=(−0.15), B=(−2.60), 95% CI −4.02 to −1.19, p<0.001) and male gender (β=(−0.10), B=(−1.77), 95% CI −3.14 to −0.40, p=0.01). The percentage of HLA-B27 positivity in relation to age at onset of IBP is shown in figure 2.

Delay in diagnosis as dependent variable

From the core set of independent variables, only HLA-B27 positivity was significantly associated with delay in diagnosis. This association was negative (β=(−0.11), B=(−1.02), 95% CI −1.75 to −0.28, p=0.01).

Table 1. Comparison of baseline characteristics between HLA-B27 positive and negative patients

	HLA-B27 positive	HLA-B27 negative	p Value
Male gender	206 (51.2%)	92 (37.4%)	0.001
Mean age (years)	32.5±8.4	35.6±8.7	<0.001
Mean age at onset of IBP (years)	31.0±8.5	34.0±8.8	<0.001
Mean duration of axial symptoms (years)	1.5±1.0	1.5±0.8	0.64
Mean delay in diagnosis (years)	2.7±4.2	3.7±5.1	0.01
Caucasian race	368 (91.5%)	212 (86.5%)	0.04
Family history of ankylosing spondylitis	120 (30.2%)	48 (19.7%)	0.003
Presence of peripheral arthritis	216 (53.9%)	165 (67.3%)	0.001
Mean age at onset of peripheral arthritis (years)	31.5±9.6	32.8±8.7	0.02
Presence of enthesitis	186 (46.3%)	158 (64.2%)	<0.001
Using NSAIDs	299 (74.4%)	147 (59.8%)	<0.001
Ever used NSAIDs	386 (96.0%)	217 (88.2%)	<0.001
Using steroids	54 (13.4%)	29 (11.8%)	0.54
Using DMARDs	36 (9.0%)	23 (9.3%)	0.87
Ever used DMARDs	54 (13.5%)	36 (14.6%)	0.68
Using analgesics	249 (61.9%)	164 (66.7%)	0.23
Mean CRP (mg/l)	8.1±14.0	7.6±14.0	0.67
Percentage of patients with elevated CRP	28.6	30.6	0.59
Mean ESR (mm/h)	14.5±16.3	14.0±16.0	0.72
Percentage of patients with elevated ESR	22.0	17.6	0.19
Percentage of patients with elevated CRP or ESR	34.1	37.4	0.40
Dactylitis	54 (13.4%)	38 (15.4%)	0.48
Presence of any extra-articular features	98 (24.4%)	82 (33.3%)	0.01
Psoriasis	57 (14.2%)	52 (21.1%)	0.02
Crohn's disease	7 (1.7%)	11 (4.5%)	0.04
Ulcerative colitis	5 (1.2%)	9 (3.7%)	0.04
Palmoplantar pustulosis	5 (1.2%)	3 (1.2%)	0.98
History of uveitis	38 (9.5%)	18 (7.3%)	0.35
BASDAI	4.2±2.1	4.9±1.8	<0.001
BASDAI ≥4	213 (53.4%)	178 (73.3%)	<0.001
ASDAS-CRP	2.4±1.1	2.7±1.0	0.07
ASDAS-CRP >2.1	233 (60.5%)	159 (68.2%)	0.053
ASDAS-ESR	2.4±1.0	2.7±0.9	0.04
ASDAS-ESR >2.1	226 (59.0%)	159 (70.4%)	0.01
BASFI	2.8±2.2	3.5±2.3	<0.001
BASFI ≥4	120 (30.2%)	99 (41.4%)	0.004
Intensity of axial pain (NRS)	4.6±2.8	5.5±2.5	<0.001
Intensity of nocturnal axial pain (NRS)	4.3±3.1	5.1±2.8	<0.001
Intensity of peripheral joints pain (NRS)	3.0±2.8	3.8±2.7	<0.001
Physician global assessment	4.2±2.2	4.6±2.1	0.01
Tender joint count (53 joint count)	3.4±6.6	6.2±10.8	<0.001
Swollen joint count (28 joint count)	0.1±0.7 8.5	0.2±1.0 7.3	0.28
Percentage of patients with swollen joint(s)	8.5	7.3	0.55
Number of missing work days due to spondyloarthritis	26.6±55.3	46.7±87.9	0.003
BASMI	2.2±0.9	2.4±0.9	0.03
Chest expansion (cm)	5.7±2.0	5.5±2.3	0.33
MRI inflammatory lesions of the SIJ	168 (44.1%)	57 (24.9%)	<0.001
MRI inflammatory lesions of the spine	98 (25.9%)	38 (16.8%)	0.01
MRI structural lesions of the SIJ	119 (31.2%)	49 (21.4%)	0.01
MRI structural lesions of the spine	38 (10.1%)	16 (7.2%)	0.23
Definite radiographic changes in SIJ	131 (32.8%)	49 (19.4%)	0.001
mSASSS	1.2±3.0	0.9±2.9	0.34
mSASSS >0	105 (26.9%)	51 (22.1%)	0.18

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; IBP, inflammatory back pain; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, Numerical Rating Scale; SIJ, sacroiliac joints.

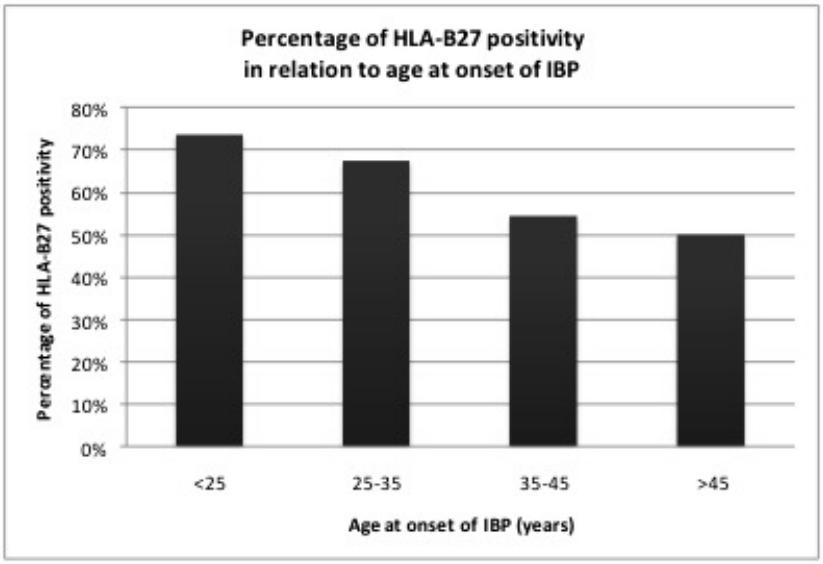

Figure 2. Percentage of HLA-B27 positivity in relation to age at onset of inflammatory back pain (IBP). Spondyloarthritis (SpA) was defined as patients fulfilling at least one of the following criteria: modified New York criteria, European Spondyloarthropathy Study Group criteria, Amor criteria or Assessment of SpondyloArthritis international Society classification criteria for axial SpA.

ASDAS-CRP and BASDAI as dependent variables

In addition to the core set of four independent variables, the following variables were also investigated in univariate regressions: MRI inflammatory lesions of SIJ, MRI inflammatory lesions of the spine and current use of NSAIDs. CRP and ESR were also tested in models with BASDAI as dependent variable.

Significant variables in the ASDAS-CRP univariate linear regression analysis were Caucasian race (B=(−0.57), p<0.001), HLA-B27 positivity (B=(−0.20), p=0.02) and MRI spinal inflammation (B=0.21, p=0.04). For BASDAI analysis, significant variables were Caucasian race (B=(−1.07), p<0.001), male gender (B=(−0.63), p<0.001), HLA-B27 positivity (B=(−0.75), p<0.001), CRP (B=0.25, p<0.001), ESR (B=0.46, p<0.001) and MRI inflammatory lesions of SIJ (B=(−0.60), p<0.001). The results of multivariate linear regression models are shown in table 2. ASDAS-CRP and BASDAI were found to be negatively associated with HLA-B27 positivity.

Imaging outcomes

Independent variables investigated in univariate regressions for all imaging outcomes included the core set of four independent variables and age at onset of IBP, duration of IBP, CRP and current use of NSAIDs.

Table 2. Multivariate linear regression analysis of factors associated with ASDAS-CRP and BASDAI

	ASDAS-CRP			BASDAI		
	Standard coefficient	**Regression coefficient (95% CI)**	**p Value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p Value**
HLA-B27 positivity	−0.11	−0.23 (−0.40 to −0.05)	0.01	−0.13	−0.53 (−0.86 to −0.21)	<0.001
Caucasian race	−0.16	−0.56 (−0.83 to −0.28)	<0.001	−0.17	−0.91 (−1.45 to −0.38)	0.001
Male gender	NS	NS	NS	−0.09	−0.34 (−0.68 to −0.00)	0.048
CRP	NI	NI	NI	0.11	0.18 (0.03 to 0.33)	0.02
ESR	NI	NI	NI	0.13	0.31 (0.10 to 0.52)	0.01
MRI spinal inflammation	0.10	0.24 (0.04 to 0.44)	0.02	NS	NS	NS
MRI SIJ inflammation	NS	NS	NS	−0.16	−0.66 (−1.00 to −0.32)	<0.001

ASDAS, Ankylosing Spondylitis Disease Activity Score (CRP-based); BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; NI, not included in multivariate analysis; NS, not significant in multivariate analysis; SIJ, sacroiliac joints.

Table 3. Multivariate logistic regression analysis of factors associated with MRI inflammatory lesions and radiographic sacroiliitis

	MRI inflammatory lesions (SIJ or spine)		MRI inflammatory lesions of the SIJ		MRI inflammatory lesions of the spine		Radiographic sacroiliitis	
	OR (95% CI)	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
HLA-B27 positivity	2.08 (1.44 to 3.01)	<0.001	2.13 (1.44 to 3.15)	<0.001	1.59 (1.02 to 2.46)	0.04	1.56 (1.04 to 2.33)	0.03
Caucasian race	NS	NS	0.49 (0.27 to 0.86)	0.01	NS	NS	NS	NS
Male gender	1.80 (1.27 to 2.56)	0.001	1.85 (1.28 to 2.66)	0.001	2.07 (1.37 to 3.12)	0.001	1.56 (1.07 to 2.28)	0.02
Age at onset of IBP	0.98 (0.96 to 1.00)	0.045	0.97 (0.95 to 0.99)	0.01	NS	NS	0.97 (0.95 to 0.99)	0.04
Family history of SpA	NS	NS	NS	NS	NS	NS	NS	NS
CRP	1.02 (1.00 to 1.03)	0.01	1.01 (1.00 to 1.03)	0.047	1.02 (1.00 to 1.03)	0.01	1.02 (1.01 to 1.03)	0.03

CRP, C-reactive protein; HLA-B27, human leucocyte antigen B27; IBP, inflammatory back pain; NS, not significant in multivariate analysis; SIJ, sacroiliac joints; SpA, spondyloarthritis.

MRI inflammatory lesions as dependent variable

Significant variables associated with MRI inflammatory lesions in the univariate models were as follows:

1. SIJ: Caucasian race (OR 0.59, p=0.05), male gender (OR 2.37, p<0.001), HLA-B27 positivity (OR 2.38, p<0.001), age at onset of IBP (OR 0.96, p<0.001) and CRP (OR 1.02, p=0.002).
2. Spine: male gender (OR 2.47, p<0.001), HLA-B27 positivity (OR 1.73, p=0.01), family history of SpA (OR 1.68, p=0.03) and CRP (OR 1.02, p=0.03).
3. SIJ or spine: male gender (OR 2.32, p<0.001), HLA-B27 positivity (OR 2.33, p<0.001), age at onset of IBP (OR 0.97, p=0.001) and CRP (OR 1.02, p=0.001).

Table 3 shows the multivariate logistic regression models for MRI inflammatory lesions of the SIJ and/or the spine: male gender and HLA-B27 positivity were positively associated with MRI inflammatory lesions of the SIJ and/or the spine. An interaction between male gender and HLA-B27 positivity was found in the regression model for SIJ: more men had MRI SIJ inflammatory lesions (47.5% of men; 27.9% of women), and a stronger association was observed between HLA-B27 positivity and MRI inflammatory lesions of the SIJ in the men (OR 2.80, 95% CI 1.56 to 5.05, p=0.001). This association was lost in the women.

MRI structural lesions of the SIJ and radiographic sacroiliitis as dependent variables

Significant variables associated with MRI structural lesions of the SIJ in univariate analysis were HLA-B27 positivity (OR 1.67, p=0.01), age at onset of IBP (OR 0.97, p=0.002) and CRP (OR 1.01, p=0.04). For radiographic sacroiliitis, associated variables were male gender (OR 1.96, p<0.001), HLA-B27 positivity (OR 1.91, p=0.001), age at onset of IBP (OR 0.96, p<0.001) and CRP (OR 1.02, p<0.001). In multivariate analysis, HLA-B27 positivity was found to be positively associated with radiographic sacroiliitis (table 3) while the association with MRI structural lesions of the SIJ was lost.

When included as one of the regressors in the multivariate models, MRI inflammation of the SIJ was found to be associated with MRI inflammation of the spine (OR 3.87, 95% CI 2.52 to 5.94, p<0.001) and radiographic sacroiliitis (OR 9.75, 95% CI 6.26 to 15.18, p<0.001). The independent associations with HLA-B27 were lost in these models.

Extra-articular features as dependent variables (uveitis, psoriasis, Crohn's disease, ulcerative colitis and palmoplantar pustulosis)

Independent variables investigated in univariate regressions included the core set of four independent variables and age at onset of IBP, duration of IBP, CRP, ESR and current use of NSAIDs. In univariate regression, Crohn's disease, ulcerative colitis and psoriasis were negatively associated with HLA-B27 (OR 0.38, p=0.048; OR 0.33, p=0.05; and OR 0.62, p=0.02, respectively). However, in multivariate analyses, only psoriasis was found to be associated negatively with HLA-B27 (OR 0.59, 95% CI 0.39 to 0.90, p=0.01).

BASFI as dependent variable

Independent variables investigated in univariate regressions included the core set of four independent variables and MRI inflammatory lesions of the SIJ, MRI inflammatory lesions of the spine, current use of NSAID, ASDAS-CRP and BASMI. Significant variables associated with BASFI in the univariate models included Caucasian race (B=(−0.68), p<0.001), male gender (B=(−0.57), p=0.002), HLA-B27 positivity (B=(−0.66), p<0.001), MRI inflammatory lesions of SIJ (B=(−0.39), p=0.04), MRI inflammatory lesions of the spine (B=0.46, p=0.04), ASDASCRP (B=1.30, p<0.001) and BASMI (B=0.85, p<0.001). In multivariate analysis, BASFI was not associated with HLA-B27 positivity (β=(−0.05), B=(−0.25), 95% CI −0.56 to 0.05, p=0.11).

DISCUSSION

The analyses of the large DESIR cohort resulted in important new insights into the phenotypic associations in patients with early axial SpA. HLA-B27 was independently associated with earlier age at onset of IBP, less delay in diagnosis, MRI spinal and SIJ inflammation, radiographic sacroiliitis and lower frequency of psoriasis. In addition, MRI SIJ inflammation was associated with MRI spinal inflammation and with radiographic damage of the SIJ.

The effects of HLA-B27 status on age at disease onset have been reported in previous studies but not in patients with such a short duration of symptoms. Feldtkeller et al[10] reported an earlier age at disease onset in HLA-B27 positive patients with AS. Recently, the German Spondyloarthritis Inception Cohort also reported such an association in patients with expert-diagnosed axial SpA (radiographic and non-radiographic) with mean symptom duration of 5.2 years.[2] We report the presence of such an association even in the very early stage of the disease, further supporting the concept of axial SpA as a continuous spectrum.

The regression models for MRI lesions and radiographic sacroiliitis yielded new and relevant findings. Our models showed that HLA-B27 positivity was independently associated with MRI inflammation of the SIJ and the spine, while MRI inflammation of the SIJ was independently associated with radiographic sacroiliitis. Interestingly, when MRI inflammation of the SIJ was removed from the models, HLA-B27 positivity was also found to be associated with MRI spinal inflammation and radiographic sacroiliitis. HLA-B27 therefore seems to be contributing to SIJ inflammation which may lead to subsequent structural damage, inflammation being an intermediate variable between HLA-B27 and SIJ structural damage. The association between radiographic sacroiliitis and HLA-B27 positivity also suggests that the HLA-B27 group may have more rapid progression of new bone formation, a phenomenon where inflammation may play an intermediate role. These findings are consistent with previous findings of HLA-B27 association with radiographic sacroiliitis as well as with the severity and persistence of MRI-demonstrated inflammatory changes in the SIJ and lumbar spine in early IBP.[11]

The association between MRI SIJ and spinal inflammation is expected as inflammation at both sites shares similar mechanisms. The association between MRI SIJ inflammation and structural damage is also consistent with a recent follow-up study showing that MRI SIJ activity is related to the diagnosis of AS (according to MNY criteria) at follow-up.[28] Our model for radiographic sacroiliitis also echoes previous findings showing that MRI sacroiliitis in HLA-B27 positive patients with IBP has high specificity for development of MNY-defined AS.[29]

Apart from HLA-B27 positivity, we found male gender to be independently associated with MRI inflammation. Although in previous studies male gender had been associated with more severe spinal radiographic damage,[30] we did not find a similar association, possibly due to the early disease phase of our cohort, with very low mSASSS values. Further follow-up of the DESIR cohort may reveal this association.

The analyses of extra-articular features showed a negative association between HLA-B27 positivity and psoriasis. This is probably due to the selection bias of HLA-B27 negative patients (by the Amor criteria) because they require more extra-articular features in order to be classified as having SpA.

Finally, the negative association between HLA-B27 positivity and clinical disease activity (ASDAS-CRP and BASDAI) was a rather unexpected finding. This could be explained by increased use of NSAIDs in HLA-B27 positive patients during the survey (table 1). Furthermore, a decreased delay in diagnosis was also found in the HLA-B27 positive group. We therefore hypothesise that HLA-B27 positive patients may have lower disease activity because they were diagnosed earlier and were more adequately treated than HLA-B27 negative patients. These findings highlight the importance of early diagnosis and treatment.

It is noteworthy that ASDAS-CRP was positively associated with MRI inflammation of the spine while BASDAI was negatively associated with MRI inflammation of the SIJ. These results support the validity of ASDAS-CRP as a measurement instrument for clinical disease activity in early axial SpA and suggest that ASDAS-CRP performs better than BASDAI.

Our study has several limitations. First, there is no international consensus about the assessment of chronic MRI lesions which limits their interpretation. Second, images were not anonymised, which may have biased some of the imaging results. However, the technique used to acquire the images was standardized and centres were selected based on the experience of investigators in conducting multicentre controlled trials, longitudinal epidemiological studies and had to fulfil predefined quality standards. The use of such quality standards is likely to have reduced the potential of bias and increased the quality of the imaging evaluation. A third limitation of our study relates to the potential exclusion of affected joints using the Richie articular index and 28-joint count instead of a more extensive joint count (eg, 66/68 joint count).

The DESIR cohort enabled us to study the HLA-B27 phenotype in a very large (n=654) and unique population of patients with early axial SpA and IBP duration of <3 years. In the early disease stage of axial SpA, we have shown an association between HLA-B27 and earlier age of IBP onset, less delay in diagnosis. We have also shown that HLA-B27 and male gender are associated with axial inflammation and that HLA-B27 is associated with skeletal damage of the SIJ. Moreover, inflammation seems to act as an intermediate variable between HLA-B27 and radiographic sacroiliitis. These findings may have prognostic importance and HLA-B27 status, gender and inflammation should all be investigated as potential prognostic factors contributing to structural damage in SpA.

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