





SHORT REPORT

Clinical profile and treatment utilisation based on HLA-B*27 status in axial spondyloarthritis: results from ASAS-PerSpA study

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ABSTRACT

Objective We aimed to characterize differences of clinical features, extra-musculoskeletal manifestations and treatment utilizations based on the patients' HLA-B*27 status in a global axSpA cohort and identify predictors of HLA-B*27 negativity in these patients.

Methodology In post-hoc analysis of the ASAS-PerSpA study, patients fulfilling the 2009 ASAS classification criteria for axSpA and typed for HLA-B*27 were included. The patient characteristics were compared between the HLA-B*27(+) and HLA-B*27(-) subgroups. Multivariable logistic regression was conducted to identify predictors of HLA-B*27 negativity.

Results Of 2910 patients with axSpA from 24 countries, 2269 were tested for HLA-B*27 [1753 HLA-B*27(+) and 516 HLA-B*27(-)]. The proportion of males was higher in the HLA-B*27 (+) compared to the HLA-B*27 (-) subgroup (72.1 vs 54.3%). Patient population with HLA-B*27 (+) more often had positive family history for axSpA (29.8 vs 15.3%), and younger age at diagnosis, 31.6 years (SD 10.9) vs 37.7 years (SD 12.1). HLA-B*27 (-) patients had significantly higher peripheral arthritis (47.5 vs 42.1%, $p < 0.05$), psoriasis (19.4 vs 10.2), enthesitis (56.6 vs 49.8%) and IBD (12.8 vs 3.4) ($p < 0.001$). The exposure to csDMARDs in HLA-B*27 (-) patients was higher (61.2 vs 55.0%, $p < 0.05$). On multivariable analysis, HLA-B*27 (-) status was positively associated with enthesitis, psoriasis and IBD with an OR 1.27 (1.02-1.57), 1.84 (1.36-2.48) and 4.84 (3.23-7.30) respectively, and inversely associated with uveitis, OR 0.37 (0.27-0.50).

Conclusion HLA-B*27 (-) axSpA patients had a longer delay in diagnosis, more frequently had peripheral arthritis, enthesitis, IBD, psoriasis, and were more often treated with csDMARDs compared to HLA-B*27 (+) subgroup.

Spondyloarthritis (SpA) is a heterogeneous group of rheumatic diseases causing inflammation of sacroiliac joints, spine, peripheral joints and/or entheses, with frequent extra-musculoskeletal manifestations (EMM), such as uveitis, psoriasis and inflammatory bowel disease (IBD).¹ The disease is further characterised into radiographic and

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Prevalence of HLA-B*27 gene varies worldwide among patients with axial spondyloarthritis (axSpA) with variable effects on disease phenotype.
- ⇒ HLA-B*27 (-) axSpA patients are often diagnosed late due to unrecognised signs and symptoms.

WHAT THIS STUDY ADDS

- ⇒ This cross-sectional study of a large international cohort of patients with axSpA demonstrates that HLA-B*27 (-) group had more frequent peripheral arthritis, enthesitis, psoriasis and inflammatory bowel disease and were more often treated with conventional synthetic disease-modifying antirheumatic drugs compared to HLA-B*27 (+).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Earlier recognition of axSpA in HLA-B*27 (-) patients may improve disease outcomes.
- ⇒ Longitudinal studies assessing the effect of HLA-B*27 genotype on the evolution of disease phenotypic characteristics in axSpA, its impact on therapeutic selection and response may be warranted.

non-radiographic axial spondyloarthritis (axSpA) based on the presence of sacroiliitis on imaging.² The human leucocyte antigen B*27 (HLA-B*27) is an established genetic marker and is strongly associated with axSpA.^{3,4} However, the frequency of this gene varies across the world and in various racial-ethnic backgrounds, and so does the strength of this association with the various subtypes of SpA.³⁻⁵ The prevalence of HLA B*27 gene in axSpA population of African American, Arab, Turkish and Latin American descent is 50%–71%, which is lower than patients of northern European heritage.⁵⁻⁷ Additionally, the HLA-B*27 prevalence is also lower in female population of axSpA, which manifests

as a distinct non-radiographic phenotype with greater peripheral involvement compared with men.⁸

The disease pathogenesis in HLA-B*27 negative patients is poorly understood, with unrecognised signs and symptoms, and delay in diagnosis and treatment. Few regional studies have assessed the effect of HLA-B*27 status on the clinical presentation of axSpA, but at present, there are no world-wide studies. To better evaluate the association of HLA-B*27 with disease phenotypes, we evaluated the clinical profile of the peripheral involvement in spondyloarthritis (ASAS-perSpA) cohort that comprises a large, systematically collected data by rheumatologists from 24 participating countries from Asia, Europe, Middle-East/North Africa, Latin America and North America. It provides a robust database of axSpA patients for comparison of clinical features based on HLA-B*27 status across all these countries.⁹

MATERIALS AND METHODOLOGY

Study design

The details of patient recruitment and data collection are found in the original PerSpA study.¹⁰ We performed a post hoc analysis of the original data set that included patients with axial (axSpA), peripheral SpA (pSpA), psoriatic arthritis (PsA), juvenile SpA, SpA associated with IBD and reactive arthritis based on the participating rheumatologists' diagnoses. For this ancillary analysis, we identified and included all patients who had been diagnosed with axSpA fulfilling the ASAS classification criteria and were typed for HLA-B*27. We compared patient demographics that included age, gender, race/ethnicity; clinical characteristics comprising family history of SpA, age at symptom onset, age at diagnosis, past or current peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis and IBD. We also analysed treatment utilisation with use of non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologics (bDMARDs) based on HLA-B*27 status. Additionally, we compared the gender-based differences in the HLA-B*27 negative population.

Statistical analysis

Descriptive data were expressed as the mean and SD for quantitative variables and as absolute and relative frequencies for qualitative variables. We performed the Kolmogorov-Smirnov normality test before any comparison of quantitative variables between the groups. Comparisons of quantitative variables between HLA-B*27 (+) and HLA-B*27 (-) patients were made using Student's t-test as a parametric test and the Mann-Whitney U test as a non-parametric test. A multivariable logistic regression (using the backward stepwise procedure) was conducted to evaluate factors independently associated with HLA-B*27 (-) status, using variables with a p value <0.15 in the univariate analysis. Variables with a p value <0.15 in the final multivariate model were tested as confounding factors and interactions. The hypothesis

test was two-tailed, and a p value <0.05 was considered significant. Purposeful selection of variables for a multivariate analysis to identify predictors of HLA-B*27 negativity was done using univariate analysis first. All data were processed and analysed using R Software.

RESULTS

Baseline characteristics of included cohort are summarised in [table 1](#). Among the 2269 patients with axSpA that fulfilled the ASAS classification criteria, 1753 (77.3%) were HLA-B27 (+). The mean age of these HLA-B*27 (+) patients was 40.6 years (SD 12.8) vs 43.4 years (SD 12.6) among the HLA-B*27 (-) patients (p<0.001). Proportion of men was higher in the HLA-B*27 (+) compared with the HLA-B*27 (-) subgroup (72.1 vs 54.3%). Patient population with HLA-B27 (+) more often had a family history for axSpA (29.8 vs 15.3%, p<0.001), younger age at symptom onset (p<0.001) and younger age at diagnosis (p<0.001) with a mean age of 31.6 (SD 10.9) versus 37.7 years (SD 12.1) in the HLA-B*27 (-) group. In patients with axSpA, frequency of peripheral arthritis was higher in HLA-B*27 (-) patient population (47.5 vs 42.1%, p<0.05), along with enthesitis (56.6% vs 49.8%, p<0.001). For the EMM, HLA-B*27 (-) group more often had concomitant IBD (12.8 vs 3.4%, p<0.001) and psoriasis (19.4% vs 10.2%, p<0.001).

The axSpA diagnosis was more common in HLA B*27 (+) group vs HLA-B27 (-) group (87.9% vs 70.9%, p<0.001) as shown in [table 2](#). Pooled peripheral manifestations (peripheral arthritis, dactylitis and enthesitis) were more common in HLA B*27 (-) group, (71.5% vs 65.0% p<0.001).

Regarding gender-based differences in the HLA-B*27 (-) group, the prevalence of peripheral arthritis was higher in women (57.8%) compared with men (42.1%); (online supplemental table S1). There were no significant differences in enthesitis, dactylitis, uveitis, psoriasis, IBD and NSAID, csDMARDs or bDMARD use between the two genders in this subgroup analysis.

With regards to treatment, both the groups were comparable in terms of past or current use of NSAIDs and bDMARDs. The exposure to csDMARDs in HLA-B*27 (-) patients was higher compared with HLA-B*27 (+) group (61.2 vs 55.0%, p<0.05). On multivariable analysis, the past or current presence of enthesitis, psoriasis and IBD was positively associated with HLA-B*27 (-) status, with an OR 1.27 (1.02 to 1.57), 1.84 (1.36 to 2.48) and 4.84 (3.23 to 7.30), respectively. The details of analysis are summarised in [table 3](#).

DISCUSSION

The study investigated the differences in clinical profile and treatment utilisation using a multinational axSpA population with an available HLA-B*27 status from ASAS-PerSpA cross-sectional cohort. The geographical proportion of the original cohort, which included 4465 patients, was from Europe and North America (37.2%), Middle

Table 1 Baseline demographics, clinical characteristics and treatment utilisation based on HLA-B*27 status

	Total N=2269	HLA-B*27 + N=1753	HLA-B*27 – N=516	P value
Age	41.3 (12.8)	40.6 (12.8)	43.4 (12.6)	<0.001
Gender (male)	1554 (68.0%)	1264 (72.1%)	280 (54.3%)	<0.001
University studies	1056/2267 (46.6%)	837/1751 (47.8%)	219 (42.4%)	0.032
Family history of axSpA	601 (26.5%)	522 (29.8%)	79 (15.3%)	<0.001
Age of symptoms onset	26.8 (10.0)	25.9 (9.4)	30.0 (11.1)	<0.001
Age of diagnosis	33.0 (11.5)	31.6 (10.9)	37.7 (12.1)	<0.001
BMI	25.9 (5.1)	25.7 (4.9)	26.5 (5.6)	0.001
Past or current peripheral arthritis	981/2266 (43.3%)	736/1750 (42.1%)	245 (47.5%)	0.029
Past or current enthesitis	1165/2268 (51.4%)	873/1752 (49.8%)	292 (56.6%)	0.007
Past or current dactylitis	205 (9.0%)	153 (8.7%)	52 (10.1%)	0.347
Past or current uveitis	520 (22.9%)	461 (26.3%)	59 (11.4%)	<0.001
Past or current psoriasis	279/2268 (12.3%)	179/1752 (10.2%)	100 (19.4%)	<0.001
Past or current IBD	125 (5.5%)	59 (3.4%)	66 (12.8%)	<0.001
NSAIDs ever	1606 (70.8%)	1240 (70.7%)	366 (70.9%)	0.932
csDMARDs ever	1281 (56.5%)	965 (55.0%)	316 (61.2%)	0.013
bDMARDs ever	1377 (60.7%)	1070 (61.0%)	307 (59.5%)	0.529

axSpA, axial spondyloarthritis; bDMARDs, biological disease-modifying anti-rheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; JuvSpA, juvenile spondyloarthritis; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis; REA, reactive arthritis.

East and North Africa (30.2%), Asia (22.4%) and Latin America (10.2%).⁹ Our analysis revealed a 77.3% prevalence of HLA-B*27 positivity in the axSpA cohort. There was an earlier age of diagnosis of axSpA in HLA-B*27 (+) patients with a mean age of 31.6 years compared with 37.7 years in HLA-B*27 (-) group. The study also showed a higher frequency of HLA-B*27 (72.0%) in the male population of axSpA with greater familial aggregation and prevalence of uveitis. On the contrary, HLA-B*27 (-) group had a greater BMI and prevalence of enthesitis, psoriasis and IBD than HLA-B*27 (+) patients. The

peripheral manifestations were more common in HLA-B*27 (-) group.

The prevalence of HLA-B*27 in our post hoc analysis of PerSpA cohort, with this diverse population, was not different from previous systematic review of studies from various geographic locations.^{10,11} Although, some studies have reported variable male gender proportion, 88.2% in the Korean study¹² and 58.6% from French cohort,³ most of recent and old studies consistently reported higher male gender prevalence in HLA-B*27 (+) groups similar to this study. There exists a lack of understanding

Table 2 Axial and Peripheral involvement based on HLA-B*27 status with details of subtypes of SpA captured

	Total N=2269	HLA-B*27+ N=1753	HLA-B*27– N=516	P value
Axial involvement	2211 (97.4%)	1707 (97.4%)	504 (97.7%)	0.706
Any peripheral manifestation	1507 (66.4%)	1138 (65.0%)	369 (71.5%)	0.006
	1907 (84.0%)	1541 (87.9%)	366 (70.9%)	<0.001
▶ Axial SpA	149 (6.6%)	111 (6.3%)	38 (7.4%)	
▶ pSpA	124 (5.5%)	56 (3.2%)	68 (13.2%)	
▶ PsA	43 (1.9%)	16 (0.9%)	27 (5.2%)	
▶ ReA+IBD	46 (2.0%)	29 (1.7%)	17 (3.3%)	
▶ JuvSpA+others				

axSpA, Axial spondyloarthritis; bDMARDs, biological disease-modifying anti-rheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; JuvSpA, juvenile spondyloarthritis; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis; REA, reactive arthritis.

Table 3 Independent associations of various clinical characteristics with HLA-B*27 (–) status in axial spondyloarthritis

	OR (95% CI)	P value
Age	0.96 (0.94 to 0.97)	<0.001
Gender (male)	0.50 (0.40 to 0.62)	<0.001
Family history of axSpA	0.44 (0.33 to 0.58)	<0.001
Age of diagnosis	1.08 (1.06 to 1.10)	<0.001
BMI	1.03 (1.00 to 1.05)	0.020
Past or current enthesitis	1.27 (1.02 to 1.57)	0.033
Past or current uveitis	0.37 (0.27 to 0.50)	<0.001
Past or current psoriasis	1.84 (1.36 to 2.48)	<0.001
Past or current IBD	4.84 (3.23 to 7.30)	<0.001

Multivariate analysis using variables with $p < 0.15$. axSpA, axial spondyloarthritis; BMI, body mass index; IBD, inflammatory bowel disease.

of these gender-based disparities for the expression of HLA-B*27.

We noted a difference of 6 years in the mean age at diagnosis of axSpA between the HLA-B*27 (+) and HLA-B*27 (–) groups similar to previously reported mean difference of 5–8.5 years based on studies from DESIR (Devenir des Spondylarthropathies Indifférenciées Récentes),³ GESPIC (The German Spondyloarthritis Inception cohort),¹³ REGISPONSER (Registro Español de Espondiloartritis de la Sociedad Española de Reumatología)¹⁴ cohorts in Europe and other countries in Asia.^{12 15} The multivariate analysis showed that older age was independently associated with HLA-B*27 (–) status, similar to previous studies...^{3 4 14 16} This difference, may in, part be influenced by the utility of HLA-B*27 test in the clinical setting, leading to earlier diagnosis when positive along with more frequent radiographic involvement in this group.¹⁷ HLA-B*27 (+) patients have significantly greater familial aggregation and higher rates of uveitis, which correlates with data from previous studies.^{3 4 14 16} Interestingly, 15% of HLA-B*27 (–) patients in perSpA cohort had a family history of axSpA, which is slightly higher when compared with European and Asian cohorts (11%–12%).^{3 4 14 16} Moreover, a similar analysis of pSpA population from the ASAS-perSpA cohort reported that 66.7% HLA B*27 (–) patients had familial disease,¹⁸ sigene varies worldwide among patients with axial spondylizing variable genetic factors contributing to pathogenesis in the subsets of SpA with a predominant role of HLA-B*27 in axSpA.

Our observation of higher prevalence of enthesitis in HLA-B*27 (–) patients is similar to studies from DESIR and REGISPONSER cohorts.^{3 14} However, a higher prevalence of ankle involvement and heel enthesitis was reported among HLA-B*27 (+) Brazilian cohort with axSpA.¹⁹ One plausible explanation is the inclusion of Juvenile SpA population in the cohort. In addition, few studies from parts of Asia reported higher prevalence of peri-articular involvement in HLA-B*27(+) cohorts, whereas recent study by Zhang

et al from China¹⁶ found no significant difference between both groups, similar to results from some older studies from various regions in Asia and Europe.^{4 12 15} A study in Korean population revealed higher frequency of hip joint involvement in HLA-B*27 (+) patients compared with HLA-B*27 (–).¹³ Interestingly, the study on pSpA subgroup from ASAS-perSpA cohort did not find an independent association of enthesitis with HLA-B*27 status, which is in contrast to our findings of axSpA patients.¹⁸ We also observed higher prevalence of psoriasis and IBD in HLA-B*27 (–) patients, which is in line with previous studies investigating the relationship of HLA-B*27 with these EMM in axSpA.^{3 4 14 16} In terms of gender-based differences in HLA-B27 (–) group, women had higher frequency of peripheral arthritis compared with men but no significant difference in enthesitis, which is in contrast to a recent study that revealed higher prevalence of both in females.⁸

We analysed the treatment of axSpA patients based on HLA-B*27 status, which only differed in terms of higher use of csDMARDs in HLA-B*27(–) patients. It is plausible that the higher rate of peripheral arthritis in HLA-B27* (–) in this axSpA cohort led to such an observation, [table 2](#). The use of NSAIDs and bDMARDs was similar in both the groups. We did not look for predictors of response, but previous studies have shown C reactive protein may be useful for guiding treatment decisions in axSpA.²⁰

We analysed a large, heterogeneous, multicentre cohort of axSpA patient, which provides a reliable and global view of inter-relationships between HLA-B*27 status and axSpA phenotypes. We do note some limitations. The cross-sectional design comes with an inherent limitation of reporting associations. Moreover, the evaluation of clinical manifestations with inclusion of past occurrences as performed in this analysis can lead to the patient's recall bias. Moreover, imaging data were not available to ascertain the differences between the two groups. Although the relative representation of patient population from North and South America was lower compared with other regions, this study adds to the body of existing evidence of HLA-B*27 influencing disease phenotype. Future longitudinal studies showing evolution of axSpA in the two groups may validate and improve our existing knowledge for EMM recurrence, prognosis and management.

Conclusion

Patients with axSpA who were HLA-B*27 (–) had longer delays in axSpA diagnosis, higher frequency of peripheral arthritis and more frequently developed psoriasis and IBD. Use of csDMARDs was also more prevalent in this group. Increased awareness of this clinical phenotype of axSpA among healthcare providers is needed for early diagnosis and timely treatment of these patients to improve outcomes.

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