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THE ROLE OF HLA B27 IN THE TREATMENT RESPONSE, FUNCTIONAL LIMITATION AND DISEASE ACTIVITY IN ANKYLOSING SPONDYLITIS PATIENTS

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ABSTRACT

Objective: To assess the HLA B 27 impact on the treatment, disease activity and functional limitation of Ankylosing Spondylitis (AS) patients. **Materials & Methods:** 69 patients of both genders were enrolled in our study according to the ASAS criteria of Ankylosing Spondylitis. Demographic, clinical, disease activity (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), were compared regarding HLA-B27 status at baseline and after three months. They are investigating the role of HLA B27 in response to the treatment, functional impairment and clinical activity of the AS patients. **Result:** Data from 69 patients 52 male (73.2 %) were analyzed ,58 (81.7%) HLA B27 positive. HLA B27 positive group presented a statistically higher BASFAI score compared with a negative group at baseline. While there is no difference between both groups regarding the response to the treatment after three months nor the BASDAI and ASDAS scores. We also find the HLA B27 has not related to the age at the diagnosis. **Conclusion:** We found that the most crucial role of HLA B27 in AS patient is the prediction of more functional impairment to whom antigen is positive. while we did not find any evidence about a strong relationship between the antigen and the response of the patients to the treatment nor the activity of the disease.

KEYWORDS: Ankylosing Spondylitis, HLA B27, BASDAI, BASFAI, ASDAS.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory immune-mediated arthritis belongs to the so-called group of axial spondyloarthritis (SPA).[1] This group of SPA characterized by their strong association with HLA B27 antigen and involvement of the axial skeleton. AS is the primary disease in this group and defined clinically by inflammatory back pain but also it can affect other sites like enthesitis, peripheral arthritis, dactylitis, and extra-articular manifestations as psoriasis, uveitis, inflammatory bowel disease(IBD).Considerably, the onset of the disease occurs in patients between the third and the fourth decade of life, and if not treated effectively it can lead to disability in about third of the patients.[2–6] HLA B27, from its discovery in 1973,[7] represents the central genetic factor related to disease etiopathogenesis. However, about 10-20% of defined AS patients were HLA B27 negative[8] HLA B27 antigen positivity becomes one of the two central arms for the Diagnosis of AS in the new classification criteria for axSPA settled by The Assessment of the Spondyloarthritis.

International Association (ASAS)[9] which depend on finding of sacroiliitis on imaging with one additional SPA feature (imaging arm) or HLA B 27(human leucocyte antigen B27) positivity with additional two SPA features(clinical arm) in chronic low back pain patients less than 45 years old at onset of symptoms.[10]

Despite ongoing research, The pathogenesis of AS is not fully understood and the exact way by which HLA B27 affect the disease is not clear[1] beside patients with AS vary in their clinical features and response to treatment.[11] Previous studies suggest a relationship between HLA B27 and a younger age of onset, family history, and axial manifestations and less prevalence of Inflammatory Bowel Disease (IBD) and psoriasis.[12,13] Nevertheless, few studies are estimating the role of HLA B27 in defined AS patients[14,15] We aimed in this study

to assess the HLA B 27 impact on the treatment, disease activity and functional limitation of Ankylosing Spondylitis (AS) patients.

SUBJECTS AND METHODS

The study involved 69 patients with ankylosing spondylitis who visited the outpatients of rheumatology, Tongji Medical College, HUST, Wuhan, China, during the period from July/2018 to january/2019, according to the following criteria:

Inclusion criteria

Patients were selected depending on the new ASAS criteria for the diagnosis of AS:

-chronic back pain in 3 or more months and age 45 or less at the beginning of the disease Plus

- Sacroiliitis on imaging plus one or more SPA features

OR

- HLA B 27 positivity plus two or more SPA features

SPA features include

- Inflammatory back pain
- Peripheral arthritis
- Enthesitis
- Dactylitis
- Family history of SPA
- Good response to NSAIDs
- Uveitis
- Psoriasis
- IBD(ulcerative colitis or Crohn's disease)
- HLA b27
- Elevated CRP

Exclusion criteria

- Patients did not fulfill the ASAS inclusion criteria.
- Patients with metabolic diseases.
- Patients with other rheumatic diseases.
- Patients with genetic bone or joint diseases.
- Patients with blood diseases.

Data Collection

We included 69 AS patients who fulfill the ASAS criteria. The patients were classified into two groups according to the HLA B27 to a positive group and a negative one. Only 24 patients had recorded, ASDAS ESR, ASDAS CRP, BASDAI and BASFAI scores at baseline and after three months. Measuring the treatment response regarding the HLA B27 applied by comparing the scores of the patients at baseline and after three months of the treatment in both groups. The response of the patient to the treatment was measured through following up of this score while taking the medication.

All 69 patients were investigated to find the relation between HLA B27 and the following

- The functional impairment of the patients comparing the BASFAI score in both groups at baseline.
- The disease activity of the patients comparing the ASDAS score in both groups at baseline.
- The proportion of patients requiring biological drugs to achieve remission.
- The proportion of the patients requiring additional treatment together with the biological agents.
- The relation between HLA B27 positivity with the sex and the age of the patients.
- All Patients included in this study were subjected to full history taking, general and local examination

Statistical analysis

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). The normality of the data was assessed using the Shapiro-Wilk Test. Numerical data were described as mean ±SD if normally distributed, or median and interquartile range [IQR] if not normally distributed. Frequency tables with percentages were used for categorical variables. Independent Student t-test was used to compare parametric quantitative variables; while Mann-Whitney tests were used to compare non-parametric quantitative variables. Chi-square test was used to analyze categorical variables. A p-value < 0.05 is considered statistically significant.

RESULTS

The characteristics of the patients

A total of 69 patients were enrolled in our study with 58 (81.7) patients being HLA B27 positive and 11 (15.5) being HLA B27 negative. The mean ±SD of the age (29.8 ±9.1). Males represent 52 (73.2) with no difference in both groups regarding the presence of HLA B27 (79.3% of males in the HLA B 27 positive group vs. 54.5 % in the HLA b27 negative group); nonsignificant. From those 69 patients, 53 patient is using biological treatment (74.6%). The baseline characteristics of the enrolled patients were summarized in **(table 1)**.

Table 1: Baseline characteristics of the patients.

Variables	Patients (N =69)
Age, mean ±SD	29.8 ±9.1
Male, No. (%)	52 (73.2)
HLA-B27, No. (%)	
Positive	58 (81.7)
Negative	11 (15.5)
Baseline BSADAI, median (IQR)	1.9 (1 -3.56)
Baseline BASFI, median (IQR)	1.35 (0.27 – 2.8)
Baseline ASDAS-CRP, median (IQR)	2.53 (1.75 – 3.6)
Baseline ASDAS-ESR, median (IQR)	2.47(1.71 – 3.71)
CRP, median (IQR)	7.99 (1.2 – 18.7)
Biological treatment, No. (%) 1. Etanercept 2. Others Non-biological treatment, No. (%)	 27 (38.02) 26 (36.6) 15 (21.2)

Baseline data of the patients according to the HLA B27

Regarding the classification of the baseline data of the patients according to the presence of HLA B27 gene, we found no relation between the presence of the HLA B27 gene and the sex (p=0.09) nor the age of the patients (p=0.42). Moreover, concerning the treatment regimen, 51 patients were using biological drugs (43 patient in HLA B27 positive group and 8 patient in the negative group). While 18 patients were using nonbiological drugs (15 in the positive group and 3 in the negative group) **(table 2)**.

Table 2: Baseline characteristics of the patients according to HLA B27.

Variables	HLA-B27, No. (%)		P-value
	Positive (N =58)	Negative (N =11)	
Age, mean ±SD	30.2 ±9.4	28 ±7.7	0.42
Gender Male Female	 46 (79.3) 12 (20.7)	 6 (54.5) 5 (45.5)	0.09
Male, No. (%)	46 (79.3)	6 (54.4)	0.123
Treatment, No. (%)			
1. Biological	43 (74.1)	8 (72.7)	0.99
2. Non-biological	15 (25.9)	3 (17.3)	

The association of HLA B27 and the response of the patients to the treatment

From 69 patients 24 were subjected to BASFAI, BASDAI, ASDAS ESR, ASDAS CRP, CRP, ESR scores at the baseline (0 months) and after three months of receiving the treatment. The relation between the presence of HLA B27 gene and high BASFAI score at the baseline was significant (p<0.04) indicating that there is increasing of the functional impairment in AS patients with the presence of HLA B27. While all the disease activity indices showed an insignificant relation to the presence of the gene BASDAI score(p=0.41), ASDAS CRP (p=.056) and ASDAS ESR (p=0.21).

Also, the recorded scores after three months showed insignificant results regarding the presence of HLA B27 gene and the disease activity, functional activity and acute phase reactant indices. As the BASDAI, BASFAI scores the ASDAS CRP and ASDAS ESR scores after three months of the treatment showed insignificant result regarding the presence of HLA b27 gene (p=0.86), (p=0.103), (p=0.482) and (p=0.921)**(table 3).**

Table 3: Show The association of HLA B27 and the response of the patients to the treatment.

Variables, median (IQR)	HLA-B27, No. (%)		P-value [a]
	Positive (N =58)	Negative (N =11)	
Baseline BSADAI	1.94 (1 – 3.9)	1.6 (0 – 1.6)	0.414
Baseline BASFI	1.5 (0.4 – 2.8)	0.1 (0 -0.1)	0.048
Baseline ASDAS-CRP	2.53 (1.9 – 4.3)	1.47 (1.25 - 1.47)	0.056
Baseline ASDAS-ESR	2.48 (1.79 – 3.9)	1.53 (1.39 - 1.53)	0.21
Baseline CRP	9.48 (2.1 -23.7)	0.63 (0.4 – 0.63)	0.11

Baseline ESR	19 (8.5 -36.5)	11 (3 -11)	0.316
BSADAI at 3 months	0.8 (0.8 – 1.32)	0. (0 -1.6)	0.86
BASFI at 3 months	0.075 (0 - 0.3)	0 (0 -0)	0.103
ASDAS-CRP at 3 months	0.79 (0.39 -1.3)	0.27 (0.23 – 0.27)	0.482
ASDAS-ESR at 3 months	0.85 (0.46 -1.6)	1.01 (0.29 – 1.01)	0.921
CRP at 3 months	1.025 (0.49 -3.12)	0.5 (0.14 – 0.5)	0.119
ESR at 3 months	3.5 (1 – 12)	5 (1 -5)	0.98

[a] Mann-Whitney test

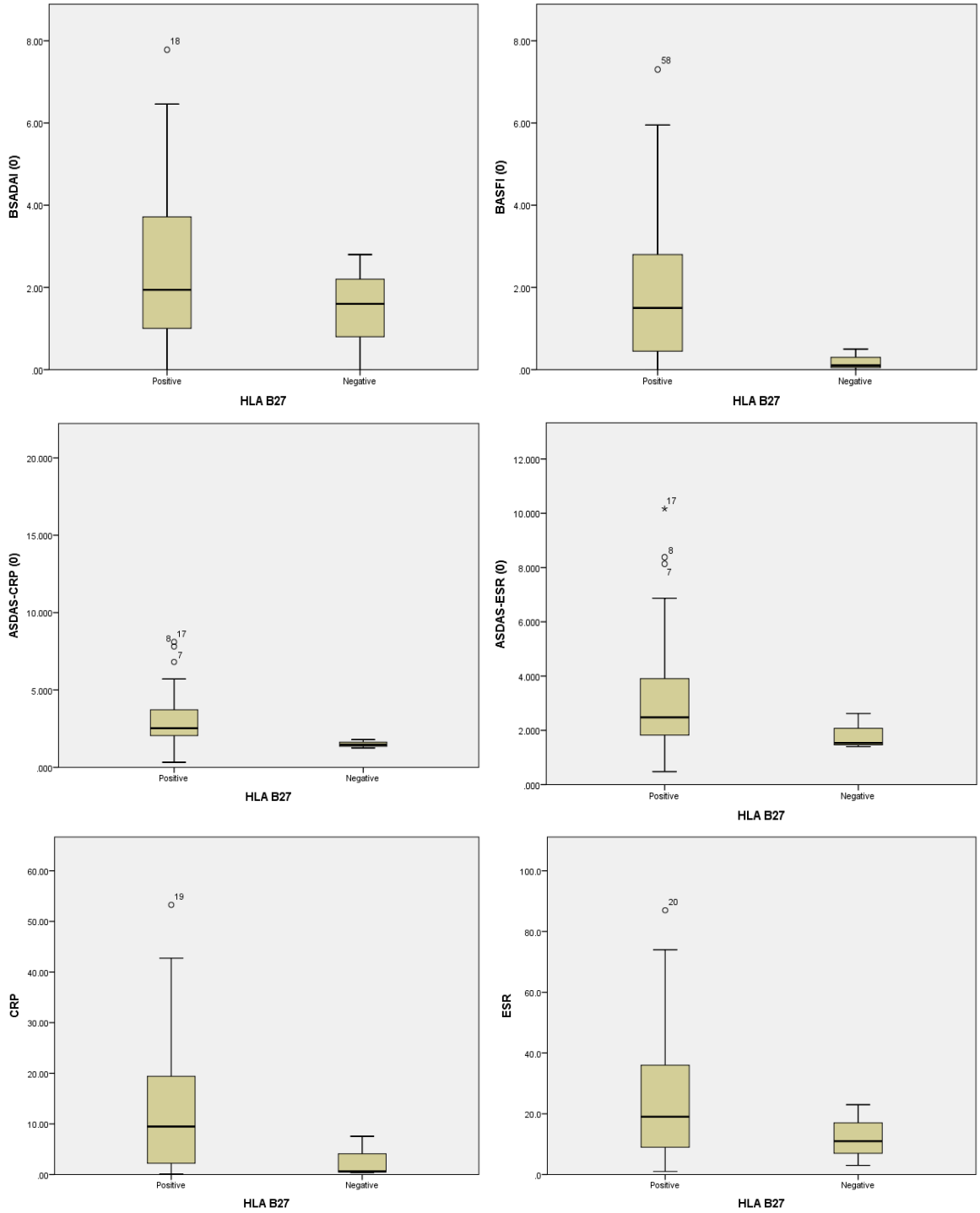

Figure 1: Relation between HLA B 27 and BASDAI, BASFAI, ASDAS CRP, ASDAS ESR, CRP, ESR at baseline.

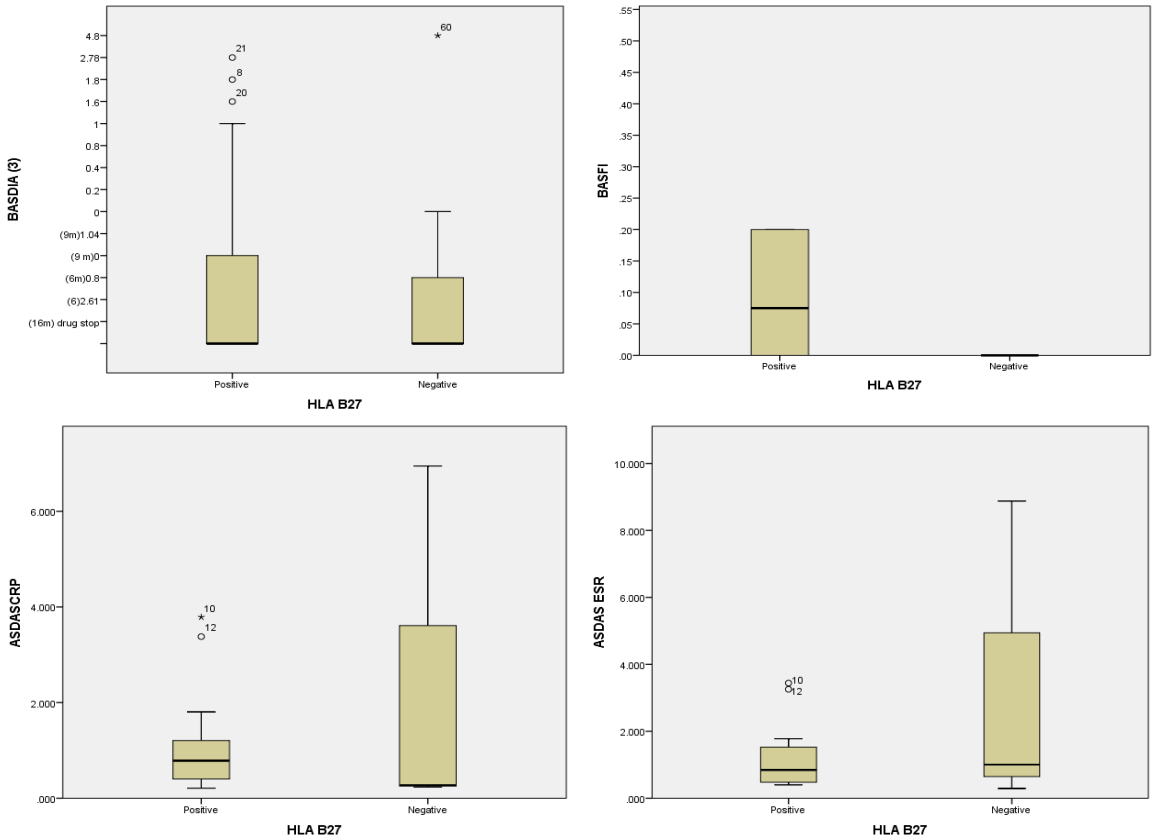

Figure 2: Relation between HLA B27 and BASDAI, BASFAI, ASDAS CRP, ASDAS ESR after three months.

3.4 Score change for 3 months

The rate of the change in all functional and disease activity indices showed an insignificant relationship with the presence of the HLA B27 antigen. BSADAI (p=0.08), BASFAI (p=0.12), ASDAS CRP (p=0.17) and ASDAS ESR(p=.08).**(table 4).**

Table 4: the relation between HLA B-27 and the change in response of the patient to the treatment.

Variables, median (IQR)	HLA-B27, No. (%)		P-value [a]
	Positive (N =58)	Negative (N =11)	
Change in BSADAI	-1.78 (-4.5 - -0.3)	0 (-1.6 -0)	0.08
Change in BASFI	-1.4 (-2.6 – -0.2)	-0.1 (-0.5 - -0.1)	0.12
Change in ASDAS-CRP	-1.83 (-4.3 – 0.4)	-0.98 (-1.3 – 0.98)	0.17
Change in ASDAS-ESR	-1.79 (-4.1 – 0.6)	-0.39 (-1.3 – 0.39)	0.08
Change in CRP	-3.72 (-14.8 - 0)	-0.49 (-6.9 - -0.49)	0.51
Change in ESR	-10.5 (-34.3 - -1.8)	-6 (-11 - -6)	0.51

[a] Mann-Whitney

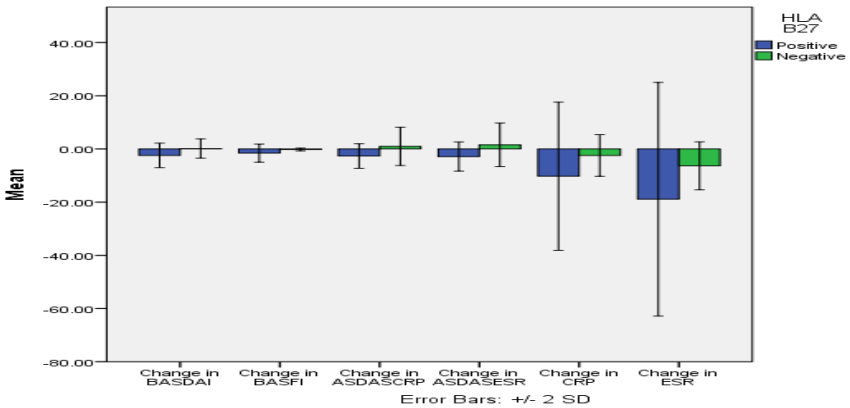

Figure 3: the association between HLA B-27 and the change in response of the patient to the treatment.

Treatment regimen according to HLA B27

We found that the presence or the absence of the HLA B 27 did not affect the decision of the treatment regimen because That is because the relation between AS patients using biological treatment and the presence of the gene was insignificant (p=0.826). Moreover, also, the relation of patients using additional treatment together with the biological drugs was insignificant between both groups(p=0.56). **(table 6).**

Table 5: Show the association between HLA B27 and treatment regimen.

Variables, No (%)	HLA-B27, No. (%)		P-value
	Positive (N =58)	Negative (N =11)	
Biological treatment			
• **Yes**	43 (74.1)	8 (72.7)	0.826
• **No**	15 (25.9)	3 (27.3)	
Additional treatment			
• **Yes**	9 (15.5)	2 (18.2)	0.56
• **No**	49 (84.5)	9 (81.8)	

DISCUSSIONS

As adequate treatment of AS patients are essential as early as possible to achieve remission and prevent disability of the patients, it is essential to detect the role of essential factors interfere with the treatment response to achieve the most favorable effect. Based on the vital role of the HLA B27 gene in the etiology and pathogenesis of AS, we decided to disclose its role in the patient's treatment, the effect on disease activity and functional limitation. As we thought it might play a role in the response of the patients to the treatment or selection of the treatment strategy depending on the gene positive or negative results. The prevalence of HLA B27 in our study represent 81.7 which is comparable with that shown in previous studies of AS patients [16] We observed the male to female ratio 3:1 which is agreed with **Arévalo et al** whatever the HLA B27 state is .[16] However, it is entirely different from the previously reported gender ratio in nrAxSpA patients where there is not a male predominance.[12,13] Our results also are not agreed with those showed by **Yang et al**. who reported a clear male predominance for the presence of HLA B27 gene in AS patients.However both ours and his study was on Asians, but this difference may be due to small sample size.[14]

Our study using BASDAI, BASFAI, ASDAS CRP, and ASDAS ESR scores as indicators of the clinical response of the patients to the treatment in both groups of positive HLA B27 and negative ones. We were expecting that the presence of this antigen will have a role in the treatment response. However, we did not find a statistical difference in both groups regarding these scores after three months of treatment. The finding from this study suggests that the presence or absence of HLA B27 did not affect the response of the AS patients to the treatment. This finding agreed with previous studies who failed to find a decisive role of HLA B27 as a predictor of the disease remission.[17] While more recent studies like **Baraliakos et al**.[18] and **Rudwaleit et al.**[19] reported a strong association between younger age, higher C-reactive protein (CRP) levels, HLA-B27 positivity, and previous exposure to anti-TNF as markers of disease remission, the results from these studies open a field for more studies investigating the role of HLA B27 in the treatment outcome. Moreover, for us, it was like an incentive for reconsideration of the Role played by this antigen in affecting AS patients. The difference between our study and those may be due to our relatively small sample size and few numbers of HLA B27 negative patients in this study.

The estimation of the patient functional impairment detected by BASFAI score showed a significant relation with HLA B27. As the absence of the antigen is associated with less BASFAI score. Our results are supported by other studies as **Freeston et a**l. who reported that HLA-B27(+) patients with AS have longer disease duration significantly and present worse (BASFI), (BASDAI), and (ASQoL) compared with HLA-B27(−) AS[20] Furthermore, **Vargas-Alarcón et al**. found that the Bath indices for disease activity and functioning were higher in HLA-B27(+) patients.[21] While this finding is inconsistent with that reported by **Kim et al.** who did not found a significant relationship between the BASFAI score and the HLA B27 in AS patients**.**[22]

Our result did not find a significant difference between both groups regarding the baseline BASDAI, ASDAS CRP and ASDAS ESR this is comparable to the results suggested by **Ziade et al**. who reported in significant relation between the HAL B 27 gene and ASDAS, CRP, BASDAI.[23] While there are other studies found a strong association between the antigen and the activity indices including BASDAI and ASDAS like **Popescu et al**. and **Freeston et a**l.They reported higher activity indices in HLA B27 positive group more than the negative group. [20][24] The difference between our results and those may be due to few numbers of negative HLA B27 patients.

The treatment strategy, we thought that the presence or the absence of HLA B27 gene might have a role in the selection of the treatment strategy. However, unexpectedly we did not found a significant role of this gene with specific treatment for achieving remission as to use the biological or non-biological drug and even shifting from one biological to another or addition of

non-biological drugs to the biological regimen. The small number of patients using non-biological treatment may result in difficulty to have a conclusion regarding the decision of its usage or not. We found that the number of AS patients who switched from one biological treatment to another were few only ten, so they did not have a statistical power to have a conclusion. However, with this patient, we did not find a difference between the HLA B 27 group and the HLA B27 negative ones regarding the shifting from one drug to another. This is in line with **Shimabukuro et al**. who also reported an insignificant role of HLA B27 gene in switching biological treatment. [25] Our study showed some limitations. The study sample is relatively low, The few numbers of patients with negative HLA B2, finally we could not calculate the three months scores for all the patients due to their irregular attendance at the outpatient clinic.

CONCLUSION

We concluded from this study that the HLA B27 gene has no role in the treatment response of AS patients while its presence has predictive role of increasing the functional limitation in AS patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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