Smoking as associated factor for spondyloarthritis related uveitis: results from a single centre cross-sectional study

Costa E[1], Almeida D[1], Cerqueira M[1], Costa JR[1], Ribeiro AR[1], Sousa-Neves J[1]

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ABSTRACT

Ocular involvement in spondyloarthritis (SpA) is a frequent extra-articular manifestation and contributes to the burden of disease. Factors associated with spondyloarthritis-related uveitis (SpA-U) are poorly defined in literature. The influence of smoking status on the occurrence of uveitis in SpA is controversial.

To clarify the factors associated with SpA-U, we performed an observational cross-sectional study in a Tertiary Rheumatology Centre. Factors independently associated with uveitis were determined by logistic regression models.

The study included 164 patients fulfilling the ASAS criteria for axial SpA with follow-up visit between January and June 2019. Smoking was independently associated with uveitis (OR=2.54; 95%CI [1.01-6.42]; p=0.03).

Our study emphasizes the importance of smoking cessation in SpA which may have a positive effect in different disease features like uveitis and overall prognosis.

Keywords: Association study; Uveitis; Axial spondyloartrhitis; Smoking.

INTRODUCTION

Although spondyloarthritis (SpA) is primarily a musculoskeletal condition, ocular involvement is an important clinical feature that may have an impact on the overall prognosis. Acute anterior uveitis (AAU) is classically described as the most frequent extra-articular manifestation of SpA and in some cases the first clinical presentation[1, 2]. The prevalence of AAU varies according to the subtype of SpA[3]. In a systematic literature review, the mean prevalence of AAU in SpA patients was 32.7%[4]. Some variables have been reported as predictors of spondyloarthritis-related uveitis (SpA-U). Positive associations between HLA-B27 positivity, axial SpA, male sex, disease duration and uveitis were found in some studies[4,5,6,7]. One study reported enthesitis and dactylitis independently associated to uveitis in an axial SpA cohort[8]. More recently, some cross-sectional and cohort studies have described lower odds of spondyloarthritis-related uveitis (SpA-U) in smokers[7,9]; another study revealed higher odds for uveitis in ex-smokers than current smokers[10]. These findings contradict the higher AAU risk of smokers in the general population[11].

Despite the available studies, data is scarce and so predictors of SpA-U are poorly defined in literature and the influence of smoking status remains controversial.

To clarify the factors associated with SpA-U, we performed an observational cross-sectional study in a Tertiary Rheumatology Centre.

METHODS

Patients fulfilling the ASAS criteria for axial SpA with a follow-up visit between January and June 2019 in our Rheumatology Centre were selected to clinical charts review.

Patients whit psoriatic arthritis and enteropathic spondyloarthritis were excluded so the sample would be more homogeneous.

Data was collected regarding the following variables: age in years (continuous); gender (dichotomic); history of uveitis confirmed by ophthalmologist observation (dichotomic); recurrence of uveitis (dichotomic); smoking status (dichotomic: ever smoker, which in-

1. Serviço de Reumatologia, Hospital de Braga

cludes current and past smokers, and non-smoker); HLA-B27 (dichotomic); disease duration in years after diagnosis (continuous); disease duration dichotomisation (dichotomic: ≤10 years and >10 years); disease (dichotomic: ankylosing spondylitis and non-radiographic axial spondyloarthritis); disease distribution (dichotomic: exclusively axial or axial and peripheral); history of enthesitis (dichotomic); presence of syndesmophytes (dichotomic); use of biologic disease-modifying anti-rheumatic drugs (bDMARD) (dichotomic); use of classical disease-modifying anti-rheumatic drugs (cDMARD) (dichotomic); use of non-steroidal anti-inflammatory drugs (NSAID) (dichotomic).

In case of missing data, we opted to exclude the concerned patient from given analysis to avoid the need of statistical correction method.

Descriptive statistics were used to show the population characteristics through absolute (N) and relative (%) measures. Normality was tested for continuous variables and the results were displayed as means and standard deviations (SD) or medians and interquartile range (IQR) as applicable.

One binary logistic regression model was generated for each variable in univariate analysis applying insert algorithm. Then, all statistically significant variables were included in multivariate analysis through the maximum likelihood algorithm to find independent associations. Multivariate model was also performed including all variables in order to eliminate potential interactions and to minimise confounding. The dependent variable in the models was history of uveitis. P value <.05 was defined as statistically significant.

Statistical analysis was performed with Statistical Package for the Social Sciences version 26.0 (SPSS 26).

RESULTS

The study included 164 patients (62.8% men) with median age of 44.0 years (IQR 37 to 54) and a median disease duration of 14.6 years (IQR 9.28 to 20.32). Population characteristics are shown in Table I-A and I-B. SpA diagnosis was ankylosing spondylitis in 70.7% cases and the remaining were non-radiographic axial SpA. HLA-B27 was positive in 84.1%; 31.1% of patients were ever smokers and 21% had both axial and peripheral joint involvement. Twenty four percent of patients had at least one AAU episode and recurrence of uveitis occurred in 70%.

In univariate logistic regression model, ever smoking (OR=2.26; 95%CI [1.08-4.28]; p<0.05) and the presence of syndesmophytes (OR=2.13; 95%CI [1.01-4.48]; p<0.05) showed a statistically significant association with uveitis (Table II). We did not find association between history of uveitis and gender, age, disease duration, disease involvement, HLA-B27 positivity, treatment and history of enthesitis.

TABLE I-A. CHARACTERISTICS OF STUDY POPULATION

	(N=164)
Gender, n (%)	
Male	103 (62.8)
Age, median (IQR), years	44.0 (37-54)
Disease, n (%)	
Ankylosing spondylitis	116 (70.7)
Non-radiographic axial SpA	48 (29.3)
Disease distribution, n (%)	
Exclusively axial	130 (79.3)
Axial and peripheral	34 (20.7)
Disease duration, median (IQR), years	14.6 (9.3-20.3)
Treatment, n (%)	
bDMARD	50 (30.5)
cDMARD	30 (18.3)
NSAID	129 (78.6)
History of uveitis, n (%)	
Yes	40 (24.4)
No	124 (75.6)
Recurrent uveitis, n (%)	
Yes	28 (70.0)
No	12 (30.0)
HLA-B27, n (%)	
Positive	138 (84.1)
Negative	26 (15.9)
Smoking Status, n (%)	
Ever smoker	51 (31.1)
Non-smoker	113 (68.9)
Enthesitis, n (%)	
Yes	44 (26.8)
No	120 (73.2)
Syndesmophytes, n (%)	
Yes	49 (29.9)
No	115 (70.1)

bDMARD- Biologic disease-modifying anti-rheumatic drug; cDMARD - Classic disease-modifying anti-rheumatic drug; IQR - Inter Quartile Range; NSAID - Non-steroidal anti-inflammatory drug; SpA - Spondyloarthritis

TABLE I-B. TREATMENT SUBGROUPS CHARACTERIZATION

					(N=164)
NSAID					
Yes	cDMARD	Yes	bDMARD	Yes	4
				No	24
		No	bDMARD	Yes	11
				No	90
No	cDMARD	Yes	bDMARD	Yes	2
				No	0
		No	bDMARD	Yes	33
				No	0

bDMARD- Biologic disease-modifying anti-rheumatic drug; cDMARD - Classic disease-modifying anti-rheumatic drug; NSAID - Non-steroidal anti-inflammatory drug.

In multivariate logistic regression model, presented in Table III, only ever smoking was independently associated with uveitis (OR=2.54; 95%CI [1.01-6.42]; p<0.05). Two models were performed. First model included only the variables with statistical significance demonstrated in univariate analysis to assess independent association. Second model included all the study variables in order to guarantee independent association. In the two models, ever smoker SpA patients showed larger odds of uveitis.

Although not statistically significant, a trend to association was found between smoking and recurrence of AAU (OR=2.24; 95%ICI [0.97-5.14], p=0.058).

DISCUSSION

Contrary to few studies showing a possible protective effect of smoking in SpA-U, and in line with new data from a prospective study of Zhao *et al*[12], we report a statistically significant independent association between smoking and uveitis in patients with axial SpA. This is consistent with an increased risk of uveitis observed among smokers in the general population; the known inflammatory properties of cigarette smoking may be a plausible explanation[11].

In this study, we also found a non-independent association between syndesmophytes and uveitis. However, this possible association might have been found because of bias of other variables like disease duration. In study sample, median disease duration was relatively high (median of 14.6 years). This could lead to more radiographic progression and more time to the occurrence of SpA-U. Another possible explanation for loss of statistical significance of syndesmophytes variable in the multivariate model could be the interaction with the variable smoking status onceit is recognised that smoking increases radiographic progression in axial SpA[13]. Other factors cannot be ruled out since this is a retrospective study.

In our sample, we did not find association between uveitis and gender, age, disease duration, disease involvement, HLA-B27 positivity, treatment and history of enthesitis as previously reported in other studies. Some clarifications could justify these results: smaller sample size than other studies and different inclusion and exclusion criteria. Of note, the majority of studies regarding SpA-U included psoriatic arthritis and enteropathic spondyloarthritis; those patients are more likely to have a negative HLA-B27 and display a wider variability of clinical picture leading to more heterogeneous samples that could justify the positive associations found.

Although not statistically significant, we also report a trend to association between smoking and recurrence of AAU which is consistent with the worse overall prognosis of SpA in smokers. In fact, smoking appears to contribute to multiple outcomes in SpA. One of them is the impaired response to tumor necrosis factor inhibitors (iTNF)[14,15]. However, this was refuted in other studies[16,17]. A recent well-designed study involving a prospective cohort[18] concludes that iTNF response did not differ according to baseline smoking status and attributes conflicting previous results to methodologic differences.

Regarding treatments, we did not find association between use of DMARD's and SpA-U; on one hand, it would be expectable to find a positive association between use of bDMARD or cDMARD and uveitis since the occurrence of uveitis is a possible indication to start such treatments, especially if recurrent; on the other hand, starting a DMARD's may lower the risk of SpA-U.

In this study, no distinction has been made between current or past smokers and no data were collected regarding smoking pack years. In clinical patient's chart review, smoking cessation was not registered. Those are some of identified potential bias of this study.

Since this is a retrospective study, we recognise the contribution of confounding in our results. Despite that, statistical analysis and data collection methodology was planned to minimise the effect of study design in results. We also recognise the difficulty to include

TABLE II. ASSOCIATION OF FACTORS WITH UVEITIS IN UNIVARIATE ANALYSIS

	N	OR (95%CI)	P value
Smoking status	164		
Non-smoker		(reference)	-
Ever smoker		2.26 (1.08-4.28)	0.03*
Syndesmophytes	164		
No		(reference)	-
Yes		2.13 (1.01-4.48)	0.04*
History of enthesitis	164		
No		(reference)	-
Yes		1.69 (0.78-3.64)	0.18
HLA-B27	164		
Negative		(reference)	-
Positive		1.72 (0.55-5.37)	0.35
Gender	164		
Female		(reference)	-
Male		1.13 (0.54-2.39)	0.74
Disease distribution	164		
Axial and peripheral		(reference)	-
Axial		0.87 (0.37-2.06)	0.75
cDMARD	164		
No		(reference)	-
Yes		1.73 (0.73-4.10)	0.21
bDMARD	164		
No		(reference)	-
Yes		1.32 (0.62-2.81)	0.48
NSAID	164		
No		(reference)	-
Yes		0.96 (0.29-3.18)	0.95
Age	164	1.01 (0.97-1.03)	0.58
Disease duration	164	1.02 (0.99-1.04)	0.36
≤10 years		(reference)	-
>10 years		1.38 (0.61-3.09)	0.44

bDMARD- Biologic disease-modifying anti-rheumatic drug; cDMARD - Classic disease-modifying anti-rheumatic drug; NSAID - Non-steroidal anti-inflammatory drug. * Statistical significance.

TABLE III. ASSOCIATION OF FACTORS WITH UVEITIS IN MULTIVARIATE ANALYSIS.

	Significative variables#			All variables		
	N	OR (95%CI)	P value	N	OR (95%CI)	P value
Smoking status	164			164		
Non-smoker		(reference)	-		(reference)	-
Ever smoker		2.54 (1.01-6.42)	0.03*		2.31 (1.10-4.87)	0.03*

Multivariate logistic regression model with variables that showed statistical significance in univariate model.
* Statistical significance.

representative disease samples.

Uveitis is an important contribute to disease burden in axial spondyloarthritis. Our study emphasizes the importance of smoking cessation in SpA which may have a positive effect in different disease features and overall prognosis.

Besides these results, we highlight the need for more studies to be performed, ideally prospective, in order to draw definite conclusions.

CORRESPONDENCE TO
Emanuel Davide Ferreira da Costa
Hospital de Braga, Sete Fontes – São Victor
4710-243 Braga
E-mail: emanueldavidecosta@gmail.com

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