Early factors associated with the initiation of treatment with biologics in patients with Axial Spondyloarthritis – results from a single centre retrospective cohort study

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ABSTRACT

Background: Axial Spondyloarthritis (axSpA) refers to a group of rheumatic diseases that mainly affect the axial skeleton. Treatment with Biological Disease Modifying Anti-Rheumatic Drug (bDMARDs) is indicated when low disease activity is not achieved with Non-Steroid Anti-inflammatory Drugs. Certain clinical and socio-demographic features may be predictive of future need for treatment with bDMARDs in a patient with axSpA.

Objectives: To study a population of patients with axSpA and determine whether the presence of certain factors at diagnosis is associated with a later need for biological treatment.

Methods: A single centre retrospective cohort study was conducted comprising 150 patients with axSpA that attended the Rheumatology Outpatient Clinic from January to December 2019. Logistic Multivariate Regression was performed to understand which factors independently contributed to the use of bDMARDs.

Results: Fifty-two patients (34,7%) were under biological treatment. In comparison to the group that was not under treatment with bDMARDs, these were significantly more likely to be *hard-workers* (57,8% *vs* 29,7%; p = 0.003), to have had elevated C-Reactive Protein at the time of diagnosis (81,6% *vs* 48,9%; p < 0.001), to have had a grade of sacroiliitis at diagnosis greater than 2 (67,4% *vs* 29,5%; p < 0.001) and to have history of enthesitis, (32,7% *vs* 13,3%; p = 0.006). In multivariate regression analysis, only the *hard-worker* type (OR = 3.09, CI: 1.14 – 8.37; p = 0.027) and the highest grade of sacroiliitis (OR = 4.41, CI: 1.69 - 11.50; p = 0.002) were found to be independently associated with the use of bDMARDs.

Conclusion: In this study, the performance of work associated with greater biomechanical stress and the presence of greater structural damage at diagnosis were shown to be associated with the use of bDMARDs. The authors highlight the importance of recognizing these factors that seem to relate to more aggressive disease, with higher use of bDMARDs, thus suggesting a need for a tighter control management strategy in these patients.

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BACKGROUND

In Axial Spondyloarthritis (axSpA), chronic inflammation of the vertebral and sacroiliac joints leads to the remodelling of these structures, due to bone destruction and inappropriate new bone formation. Eventually, it results in spine deformation which in turn implicates skeletal and postural changes that, along with the significant pain associated with this process, may end up greatly affecting the patient's quality of life (QL) and function[1,2].

Pathogenesis is still poorly understood, but strong associations between the development of axSpA and genetic factors have been documented, especially the HLA-B27 gene. Further, factors related to gut microbiome and biomechanical stress also seem to be contributors to axSpA[3].

More data are available for the prevalence of ankylosing spondylitis than for axSpA as a whole[4]. Even so, some studies have reported that the global prevalence of axSpA is between 0,32% and 1,4%[3, 5-7].

Besides being relatively prevalent, it is a disease that carries a significant burden and has a major negative impact on the patient's QL[2]. It is recognized that, without treatment, patients may experience incapacitating levels of pain, limitations in physical functioning, including the ability to perform activities of daily living and poor sleep quality, which in turn brings out high levels of fatigue during daytime[2, 8]. Further, the physical limitations of axSpA can also affect employment,

leisure activities, mood and interpersonal relationships[2, 9]. On top of that, spinal deformation and aberrant posture can result in significant body image disturbances, which may be linked to increased rates of anxiety and depression[2, 10].

Considering all the possible nefarious outcomes of axSpA, it is crucial to properly diagnose and promptly treat the condition. First-line pharmacological treatment usually relies on Non-Steroid Anti-inflammatory Drugs (NSAIDs), which have been proven to improve both pain and spine mobility when compared to placebo and should be used in a treat-to-target manner. The target is to achieve remission[11-13]. Disease activity can be measured through the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or the Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP), which help monitoring inflammatory disease activity and perceiving if remission has been achieved[11, 13, 14].

In spite of being very effective, some patients do not achieve remission or may not tolerate the adverse effects of NSAIDs. In this case, the use of biological Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) is strongly recommended[11].

In fact, bDMARDs have been extremely effective in the setting of axSpA. Approximately 60% of patients have an adequate and usually sustained response to these agents, often with partial or full remission of symptoms and QL improvement[1,2,15,16].

Factors associated with the initiation of bDMARDs have not been extensively studied. The authors performed a literature revision and found two interesting studies in which the respective authors were successful in identifying several factors present in an early stage of the disease of patients that further in time ended up being started on biological therapy[17, 18].

It is the authors' opinion that it would be pertinent to focus efforts on studying the presence of certain clinical factors in early encounters with the patient and their possible relationship with subsequent bDMARDs initiation. Thus, this would probably help physicians to plan treatment for these patients ahead and promptly optimize the management of axSpA in regards to the use of biologics.

The purpose of this investigation is to study a population of patients with axSpA and investigate what characteristics the patients presented in early encounters in greater frequency, in order to identify which may have a higher association with initiation of biological treatment.

METHODS

STUDY DESIGN AND SAMPLE

A retrospective cohort study regarding patients fulfilling the ASAS criteria for axial SpA with a follow-up visit between January and December 2019 in our Rheumatology Centre was performed. Every patients' clinical file was revised and filtering was performed based on previously determined inclusion and exclusion criteria.

The study included patients aged 18 or older diagnosed with non-radiographic axial Spondyloarthritis or Ankylosing Spondylitis.

We excluded patients diagnosed with any form of spondyloarthritis other than axial: exclusively peripheral spondyloarthritis, spondyloarthritis associated with inflammatory bowel disease, reactive spondyloarthritis, psoriatic spondyloarthritis and undifferentiated spondyloarthritis; patients who previously received a bDMARD but were not under a bDMARD at the time of data extraction and patients whose file was missing over 50% data.

STUDY VARIABLES

The investigators met and debated which factors would make up the most pertinent variables to include in this study. They hypothesized factors of clinical importance, based on the clinical experience as well as on bibliographic research on the matter, performed prior to the meeting by each of the authors. Moreover, when selecting the variables, the investigators also took into account the probability of them being registered in the clinical files and to be accurate[19].

Data was collected regarding the following variables: Treatment with bDMARD (dichotomic, at time of data extraction); gender (dichotomic); state of employment at diagnosis (dichotomic); worker type at diagnosis (dichotomic: *hard worker* or *non-hard worker*); smoking status at diagnosis (dichotomic: smoker, which includes current and past smokers, and non-smoker); age of onset of symptoms (continuous, in years); age at diagnosis (continuous, in years); diagnostic delay (time, in years, between onset of symptoms and definite diagnosis); HLA-B27 (dichotomic); level of C-Reactive Protein (CRP) at diagnosis (dichotomic: normal or elevated, according to laboratory's reference range $<$ or $\geq$ 5mg/L respectively); grade of sacroiliitis at diagnosis (dichotomic: $\leq$2 or $>$2, according to the New York radiological grading criteria for axSpA[20]); history of anterior uveitis prior to diagnosis (dichotomic, con-

firmed by ophthalmologist observation); suggestive history of dactylitis prior to diagnosis (dichotomic); suggestive history of enthesitis prior to diagnosis (dichotomic).

To guarantee that extracted data refers to early disease stages, the authors determined to only consider information registered in clinical patient file until second appointment, except for the variable of interest (treatment with bDMARD) which extracted data refers to last appointment.

The objective of studying a variable such as worker type was to compare outcomes between people who performed heavy labor with those who did not. For that end, the authors decided to use the nomenclature "*hard worker*" and "*non-hard worker*", in order to describe the type of work carried out by each patient throughout the majority of their working years until diagnosis. *Hard worker* was defined as an individual who performs activities that are demanding on the body, involving long hours standing up, dealing with heavy loads, being exposed to the elements. This includes examples like industrial workers, construction workers, military related professions, farmers, etc. *Non-hard worker* was defined as an individual who performs desk, managerial or administrative work, most times inside an office or an appropriate station, using a computer or a pen; almost never performs physically demanding activities when laboring. This includes examples like corporate jobs, teachers, drivers, cashiers, information technology related jobs, etc.

As a marker of inflammation, the authors preferred CRP over Erythrocyte Sedimentation Rate (ESR), because CRP is more frequently used to monitor inflammatory activity in Spondyloarthritis in clinical practice and correlates better with future structural damage; furthermore, CRP changes minimally with age, whereas ESR rises with age and is generally higher in females.[21,22] Eligible results of CRP level could be either the one previously obtained by an analytical study carried out upon suspicion of axSpA or the level obtained in the first analytical study carried out after diagnosing axSpA. These were then classified as "normal" or "elevated" according to the responsible laboratory's reference ranges.

STATISTICAL ANALYSIS

Statistical analysis was carried out using the International Business Machine Statistical Package for the Social Sciences® (SPSS®), version 26.

Numerical variables were tested for normal distribution considering the visual interpretation of the histogram and the QQ' graph, as well as the results from the Shapiro-Wilk test for normality[23]. Because these variables did not respect normal distribution, both parametric and non-parametric tests were performed. Since the results for both tests were accordant, only the parametric test's results were reported[24]. Thus, for descriptive analysis of numerical variables, mean (M) and standard deviation (SD) were reported. For inferential analysis, these were tested using the independent samples t-test (t) and the equal variances assumption was assessed using Levene's test[25]. Cohen's D (d) was the measure used for evaluating the effect size and values of 0,2, 0,5 and 0,8 stood for small, medium and large effect sizes, respectively[26].

Regarding categorical variables, for descriptive analysis, absolute and relative frequencies were calculated using crossed tables. Inferential analysis consisted in running Chi-Square tests (χ^2) and using the Pearson's Chi-Square significance value or the equal value of the Fisher's Exact test when the assumption of less than 20% cells having an expected count less than 5 was not fulfilled[27]. As a measure of effect size, because all the categorical variables were dichotomic, the value of Phi (Φ) was used and values of 0,1, 0,3 and 0,5 were considered small, medium and large effect sizes, respectively[26].

Lastly, a multivariate logistic regression analysis was conducted to determine which of the variables were independently associated with the use of bDMARDs. In order to obtain the most reliable model possible, not all variables were taken into analysis[28]. Variable inclusion was based on both their statistical significance and also on plausibility, whether supported from clinical practice or literature reports. The model obtained was evaluated for its goodness of fit using the Hosmer–Lemeshow test and its respective chi-square and significance values were reported. The model's Nagelkerke R-square and the percentage of cases correctly predicted were also reported[29]. The variables were tested for multicollinearity and excluded from analysis by listwise method.

ETHICAL CONCERNS

This study received approval from the Ethics Committee for Health of Hospital de Braga of the Hospital where the study was conducted and was performed accordingly with good clinical practice and Helsinki declaration[30].

RESULTS

We identified 168 patients diagnosed with axSpA; 18 patients were excluded (5 exclusively axial psoriatic arthritis, 4 axial spondyloarthritis associated with inflammatory bowel disease, 2 patients previously treated with bDMARDs, stopped for surgery and had not restarted due to sustained remission and 7 patients whose files were missing over 50% data needed).

Among the 150 patients included in this study, 52 (34,7%) were under biological treatment and 96 (64%) were male; 126 (84%) were employed at diagnosis and regarding the type of work performed by each individual, 53 (35,3%) were classified as *"hard workers"*. Additionally, 49 (32,7%) individuals had history of smoking. Finally, 122 (81,3%) individuals were HLA-B27 positive.

A comparative analysis between patients on treatment with bDMARDs and patients not on treatment with bDMARDs, is summarized in Tables I and II.

Regarding sociodemographic factors, individuals who had started bDMARDs were more likely to be classified as a *hard worker*, whereas no statistically significant differences were found in regards to gender, employment and smoking status.

Scoping clinical variables, table III, individuals on bDMARDs had a higher likelihood of having had elevated CRP at the time of diagnosis. Similarly, they were more likely as well to have had a grade of sacroiliitis at diagnosis higher than 2. In addition, they were also more likely to have had a previously positive history of enthesitis. In turn, no statistically significant differences were found in reference to age at onset, age at diagnosis, diagnostic delay, HLA-B27, history of anterior uveitis and history of dactylitis.

The model of multivariate logistic regression obtained, presented in table IV, had a good fit, χ^2 (7) = 4,802, p = 0.684 (Nagelkerke R-square = 0.356; percentage of correctly predicted cases = 80.0%). It indicated statistically significance for the variables grade of sacroiliitis at diagnosis, and worker type. More specifically, *hard workers* had a chance of being on treatment with bDMARDs 3,09 times higher as opposed to those who did not perform hard work and individuals with a grade of sacroiliitis at diagnosis higher than 2 had a chance 4,41 times higher of using bDMARDs when compared to those with a sacroiliitis grade of 2 or lower. Although not statistically significant, a trend to association was found between elevated CRP and use of bDMARDs in multivariate logistic regression model.

DISCUSSION

Our study was performed to investigate a range of factors present at the time of diagnosis that could be associated with the future need for treatment with bDMARDs. As previously mentioned, these drugs have had a significant impact on the outcomes of axSpA controlling symptoms and inhibiting radiographic pro-

TABLE I. DISTRIBUTION OF THE SOCIODEMOGRAPHIC VARIABLES, ACCORDING TO THE TREATMENT WITH bDMARD

	Treatment with bDMARD				
	Yes % (N)	No % (N)	p	Φ	χ^2
Gender			0,213	0,10[9]	χ^2 (1) = 1,768
Female	28,8 (15)	39,8 (39)			
Male	71,2 (37)	60,2 (59)			
Employment			0,099	0,153	χ^2 (1) = 3,215
Unemployed	2,2 (1)	11,0 (10)			
Employed	97,8 (45)	89,0 (81)			
Worker type			0,003	0,271	χ^2 (1) = 10,002
Non-hard	42,2 (19)	70,3 (64)			
Hard	57,8 (26)	29,7 (27)			
Smoking status			0,071	0,150	χ^2 (1) = 3,363
Non-smoker	57,7 (30)	72,4 (71)			
Smoker	42,3 (22)	27,6 (27)			

% - Relative frequency; N – Absolute frequency; p – p-value; Φ – value of Phi (Effect size); χ2 – Chi-square test value

TABLE II. DISTRIBUTION OF THE NUMERICAL CLINICAL VARIABLES, ACCORDING TO TREATMENT WITH bDMARD

	Treatment with bDMARD				
	Yes (N)	No (N)	p	d	t
Age at Onset			0,849	0,003	t (147) = -0,190
M	28,87	28,58			
SD	8,977	8,706			
Age at Diagnosis			0,885	0,002	t (148) = -0,145
M	35,75	35,46			
SD	12,003	11,547			
Diagnostic Delay			0,948	0,001	t (147) = -0,065
M	6,88	6,79			
SD	8,031	8,088			

p – p-value; d – Cohen's D (Effect size); t – t-student test value; M – Mean; SD – Standard Deviation

TABLE III. DISTRIBUTION OF THE CATEGORICAL CLINICAL VARIABLES, ACCORDING TO TREATMENT WITH bDMARD

	Treatment with bDMARD				
	Yes % (N)	No % (N)	p	Φ	χ^2
HLA-B27			0,126	0,133	χ2 (1) = 2,664
Negative	11,5 (6)	22,4 (22)			
Positive	88,5 (46)	77,6 (76)			
CRP[a]			<0,001	0,320	χ2 (1) = 14,226
Normal	18,4 (9)	51,1 (46			
Elevated	81,6 (40)	48,9 (44)			
Grade of Sacroiliitis[a]			<0,001	0,361	χ2 (1) = 17,031
≤2	32,6 (14)	70,5 (62)			
>2	67,4 (29)	29,5 (26)			
History of Anterior Uveitis			1,000	0,006	χ2 (1) = 0,005
No	75,0 (39)	74,5 (73)			
Yes	25,0 (13)	25,5 (25)			
History of Dactilitis			1,000	0,021	χ2 (1) = 0,065
No	96,2 (50)	96,9 (95)			
Yes	3,8 (2)	3,1 (3)			
History of Enthesitis			0,006	0,231	χ2 (1) = 8,014
No	67,3 (35)	86,7 (85)			
Yes	32,7 (17)	13,3 (13)			

[a]At the time of diagnosis; % - Relative frequency; N – Absolute frequency; p – p-value; Φ – value of Phi (Effect size); χ2 – Chi-square test value

gression. Moreover, some studies have attested that these drugs are even more effective when taken in an earlier stage of the disease[31-33]. So, taking into consideration factors that can be established in an early stage of the disease and may influence outcome is a matter of great importance.

This study was successful in identifying two factors that were independently associated with the use of bDMARDs: the grade of sacroiliitis at diagnosis and the type of work performed by the patient.

Sacroiliitis is graded by applying the New York radiological criteria usually to a radiograph or a computed tomography scan, but there is a high interobserver variability in the application of these criteria[34].

TABLE IV. RESULTS FROM THE MULTIVARIATE LOGISTIC REGRESSION OF VARIABLES ASSOCIATED WITH INITIATION OF bDMARDS

	OR	95% CI	p
Worker type			
Non-hard	–	(reference)	–
Hard	3.09	1.14 – 8.37	0.027
HLA-B27			
Negative	–	(reference)	–
Positive	3.17	0.85 – 11.77	0.085
CRP[a]			
Normal	–	(reference)	–
Elevated	2.73	0.97 – 7.69	0.058
Grade of Sacroiliitis[a]			
≤2	–	(reference)	–
>2	4.41	1.69 – 11.50	0.002
History of Enthesitis			
No	–	(reference)	–
Yes	1.35	0.44 – 4.15	0.602

[a]At the time of diagnosis; S.E. – Standard Error; OR – Odds Ratio; 95% CI – 95% Confidence Interval; p – p-value

For that reason, the authors felt that categorizing this variable into 5 groups correspondent to each grade would not be highly reliable and decided to group them into only two categories (grade of 2 or less and grade higher than 2). The results obtained indicated that the group with the highest grades of sacroiliitis at diagnosis had a higher chance of starting biological treatment. This finding may be justified by the fact that the grade of sacroiliitis is known as a direct indicator of an aggressive disease that progresses with radiographic damage, which implicates a higher chance of persistently active disease and loss of function, which in turn are associated with need for initiation of biologics[35, 36].

Furthermore, results also reported that individuals who performed *hard work* were more likely to be under bDMARDs than those who did not. In fact, biomechanical stress has been correlated with axSpA pathogenesis and so, in accordance to Ramiro *et al*, 2015, it is plausible that individuals who perform heavy, manual work and are therefore subject to a great deal of mechanical stress on their vertebrae on a daily basis, are not only more susceptible to incidence of the disease, but also more likely to have a worse prognosis.[3, 37]

Elevated levels of CRP at diagnosis were associated with the use of bDMARDs in chi square test. However, only a trend to association was found in logistic regression analysis; the *p* level of significance was not met. Being a marker of inflammation, it would make sense that individuals with greater inflammation at diagnosis would later require biological treatment. In addition to this hypothesis, many studies have also suggested that patients with radiographic axSpA who have an increased CRP have the highest likelihood of treatment success, which further supports that CRP might be a factor of interest in this context[38]. Still, the fact that in our study the chi-square test was significant allows for the assumption that the level of CRP at diagnosis should be taken into consideration, granting that it is considered in association with the presence of other factors and not in isolation. Moreover, we emphasize the need of future studies to be performed, including greater samples, in order to better understand the relationship of this factor with the interested outcome.

Regarding HLA-B27 positivity, despite no differences having been described between the individuals who use bDMARDs and those who do not, it was decided to integrate this factor into the logistic regression analysis as the presence of this gene has been associated with more severe disease and poorer prognosis[39, 40].

Also, the authors raised the question if variables such as age at onset and diagnostic delay would be associated with future treatment with biologics but, in this sample, this was not verified. Theoretically, when an immune mediated disease, as is the case of axSpA, manifests itself at an earlier age, it is likely to progress and cause higher damage over time. Similarly, greater diagnostic delay reflects a greater time of active disease without proper treatment with a potential for higher damage and poorer prognosis. In spite of this, it is the authors' opinion that these parameters should be included in future studies to better understand these plausible associations.

Initially, the authors had also intended to include other variables, namely anthropometric data: weight and body mass index (BMI). As previously mentioned, biomechanical stress has been correlated with axSpA pathogenesis and so the investigators hypothesized that higher weight and BMI reflecting higher mechanical stress on the vertebrae could be associated with worse prognosis and future need for the use of bDMARDs[3]. In fact, Mass *et al*, 2016 attested to the theory that obesity in axSpA is associated with poor prognosis[41]. However, in this study this was not analysed as the majority of clinical files lacked records of patient's anthropometric data. Nonetheless, we stand by the idea

that these variables are worthy of attention and should be included in future studies on the matter.

Disease activity scores, namely BASDAI or ASDAS-CRP, are applicable criteria for monitoring disease activity and selecting patients to initiate bDMARD therapy[42, 43]. Given this applicability, the authors had also planned to study these parameters, at the time of diagnosis, in order to investigate a possible association with later starting a bDMARD. Patients who present with higher disease activity at diagnosis may be associated with a more refractory disease and poorer prognosis, as was in fact described by van Lunteren *et al*, 2018, and for that reason may also more often undergo biological therapy in the future[44]. However, as opposed to tightly controlled clinical trials, the time to fill out the questionnaire's surveys included in those assessment tools during regular follow-up appointments is often scarce and certain patients with lower levels of literacy have difficulty in comprehending the questions; therefore, data regarding these parameters were often missing and these variables were not included. Nonetheless, these activity scores should be the object of investigation in relatable future studies as well.

In other sense, axSpA can present with different phenotypes that show high variability, with patients presenting a more persistently active course of disease and others with a more benign course with periods of lower back pain intercalated with periods of asymptomatic disease. Alongside with non-pharmacological therapies, NSAIDs are the recommended first-line treatment in axSpA[11]. An as-needed regimen is usually the treatment choice in regards to patients with periods of asymptomatic disease, whereas continuous treatment for patients with persistently active disease is preferred according to the ASAS/EULAR recommendations[11, 45]. Baseline treatment with NSAIDs was not included as a study variable due to the previously described high heterogeneity of NSAIDs regimens among patients. Due to the dynamic nature of NSAIDs treatment strategy, changing through time, baseline treatment may not reflect the following course of treatment with this therapy. Taking all this into account, the authors chose not to include this variable in the study.

Summing up, there may be early factors, that could predict the future need to initiate bDMARDs in axSpA, beyond the disease activity scores and predictors of good response to biological therapy[38, 42, 43, 46, 47].

Finally, the authors are aware of the study limitations that should be stated. The major one, was missing data and data not entirely complete or accurate. We also recognise the contribution of confounding in our results which is common in all retrospective studies. Despite that, statistical analysis and data collection methodology was planned to minimise the effect of study design in results. Besides that, this study included a relatively small sample size.

CONCLUSION

In this study, the performance of work associated with greater biomechanical stress and the presence of greater structural damage at diagnosis were shown to be associated with the use of bDMARDs. The authors highlight the importance of recognizing these factors that seem to relate to more aggressive disease, with higher use of bDMARDs, thus suggesting a need for a tighter control management strategy in these patients. In addition, we highlight the need for more studies to be performed, ideally prospective, in order to draw definite conclusions and search for other factors that could predict bDMARD need in treatment of axSpA.

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