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ORIGINAL ARTICLE

Difficult-to-treat axial spondyloarthritis patients

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ABSTRACT

Objectives: This study aimed to formulate D2T (difficult to treat) criteria for axial spondyloarthritis (AxSpA) patients and identify the prevalence of D2T patients and their characteristics.

Patients and methods: The cross-sectional study was conducted with 166 AxSpA patients (93 males, 73 females; mean age: 47.1±12.9 years; range, 19 to 78 years) between February 2023 and March 2023. The criteria were based on patients treated according to the European Alliance of Associations for Rheumatology (EULAR) recommendations for AxSpA. Entry criteria were treatment failure to ≥2 biological/targeted synthetic disease-modifying antirheumatic drugs with two different mechanisms of action or ≥3 biological/targeted synthetic disease-modifying antirheumatic drugs. Potential preliminary factors for D2T criteria were analyzed, and the characteristics of the subjects matching D2T criteria were compared with those of others.

Results: One hundred forty-two ankylosing spondylitis patients and 24 nonradiographic AxSpA patients were included in the study. The rate of fulfilling the D2T criteria was 22.9% (n=38) among AxsPA patients treated with biological agents. The potential D2T criteria were met by 23.2% of ankylosing spondylitis and 20.8% of nonradiographic AxSpA patients. Baseline characteristics, such as sex, age, diagnosis age, occupation, and education, of D2T patients were not statistically different from other patients. The prevalence of fibromyalgia was higher in D2T patients ($p<0.001$). Disease activity indices and acute phase response indicators were higher and quality of life was worse in D2T patients.

Conclusion: There was a considerable amount of AxSpA patients fulfilling the D2T criteria despite new and effective treatment agents.

Keywords: Axial spondyloarthropathy, biological agents, difficult-to-treat, disease activity, drug-switching.

Axial spondyloarthritis (AxSpA) is an inflammatory disease of the spine characterized by chronic low back pain. AxSpA-associated chronic inflammatory pain, fatigue, morning stiffness, and disability negatively affect the quality of life.[1]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line pharmacological treatment in managing AxSpA. They exert their effects by decreasing the production of prostaglandin E2, which is responsible for inflammation and new bone formation.[2] They establish disease control in 50% of the patients,[3] although there is conflicting data on radiologic progression in those treated with NSAIDs.[4,5] The main treatment modality in case of NSAID intolerance or partial response to NSAIDs is biological agents.[1]

Tumor necrosis factor-alpha inhibitors (TNFi) and interleukin (IL)-17 inhibitors are biological agents approved by the Food and Drug Administration and European Medicines Agency for the treatment of AxSpA. Data on the effectiveness of JAK (Janus kinase) inhibitors in the treatment of ankylosing spondylitis (AS) have been increasing.[6] Despite considerable developments achieved in the field of the treatment of AxSpA during the last two decades, treatment failure is still an issue for the majority of patients. Treatment response rates with TNFi agents were 60 to 75% in the studies in which Assessment of SpondyloArthritis International

Society (ASAS) 20 response criteria were considered.[1]

Although the patients with AxSpA for less than two years achieved better treatment response rates, low socioeconomic status, obesity, and mental health problems were found to be related to worse TNFi response rates in the 2020 Britain registries.[7] In the registries of Nordic countries, the ratio of the patients treated with ≥3, ≥4, and ≥5 biological agents were 8%, 3%, and 1%, respectively. Multiple biological drug switching was found to be related to the female sex, short disease duration, number of comorbidities, and the presence of psoriasis.[8]

The concept of D2T (difficult to treat) was defined by the European Alliance of Associations for Rheumatology (EULAR) task force as the persistence of signs of activity with failure of at least two biological/targeted synthetic disease-modifying antirheumatic drugs (DMARDs) of two different mechanisms of action.[9] D2T rheumatoid arthritis (RA) criteria were recently described to investigate the demographic, clinical, and laboratory characteristics of the subjects with multiple biological agent unresponsiveness and determine subgroups by performing cluster analysis.[9,10] Healthcare costs for diagnosis and treatment are known to be higher in these subgroups compared to patients with true refractory RA.[10]

In recent years, the treat-to-target approach has gained acceptance for AxSpA.[11] Some parameters, such as disease activity scores, radiologic progression, and functionality, are considered in clinical decision-making, while an exact description has not been suggested.[8] Despite the wide range of treatment options available for AxSpA patients, a significant number of AxSpA patients experience treatment failure. In addition to the financial burden it imposes on healthcare systems, treatment failure is closely associated with chronic pain, structural progression, and decreased quality of life.[12,13]

This study aimed to determine potential D2T criteria by using a defined criteria set, detect the prevalence of patients meeting D2T criteria, and identify risk factors and disease burden in patients with AxSpA receiving biological/targeted synthetic DMARDs.

PATIENTS AND METHODS

In this cross-sectional study, 166 consecutive patients (93 males, 73 females; mean age: 47.1±12.9 years; range, 19 to 78 years) who presented to the Akdeniz University Faculty of Medicine Department of Internal Medicine, Division of Rheumatology between February 2023 and March 2023 were evaluated. Those aged >18 years with at least 12 months history of AxSpA according to the ASAS classification criteria[14] or AS according to the New York Criteria[15] who had been receiving biologic treatment for at least 12 months were enrolled.

A detailed medical history and physical examination were performed for all patients. Data on demographic characteristics, age at the time of diagnosis, disease duration, smoking, alcohol use, marital status, the number of children, educational status, body mass index, the presence of active uveitis and the history of uveitis, the current biological agent and its mode of delivery, comorbidities, the presence of active arthritis and enthesitis, and laboratory parameters, such as HLA (human leukocyte antigen)-B27 positivity, C-reactive protein (CRP), and erythrocyte sedimentation rate, were recorded. Patients with psoriasis, inflammatory bowel disease, or a history of uveitis were grouped as subjects with extramusculoskeletal manifestations. The presence of fibromyalgia was evaluated according to the 2010 American College of Rheumatology (ACR) fibromyalgia criteria.[16]

History of NSAID or conventional synthetic DMARD treatment, previous biological/targeted synthetic DMARD use, the reasons for drug switching, and the period between the diagnosis and biologic treatment initiation (years) were recorded. Reasons for biological drug switching/discontinuation were retrospectively investigated. Switching was accepted if a new biological/targeted synthetic DMARD was initiated after discontinuation of the biological/targeted synthetic DMARD. If the same biological/targeted synthetic DMARD was restarted after a period of discontinuation (<90 days) or there was a change from an original molecule to a biosimilar agent, it was not considered switching. Only those who underwent drug switching due to treatment failure were included in the study.

The analysis did not include switching with biological/targeted synthetic DMARDs due to side effects and patient or physician preference.

Disease activity was determined by using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[17] Additionally, Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, and ASDAS-Sedimentation activity parameters were also evaluated. The Bath Ankylosing Spondylitis Functional Index (BASFI) and Health Assessment Questionnaire (HAQ) disability index were utilized as physical functionality tests.

Potential D2T AxSpA criteria were described (Table 1). These criteria were developed considering the articular and extraarticular involvement, disease activity scores, and biologic therapy histories of AxSpA patients. There is a proposal criterion for D2T AxSpA (extrapolated definition from D2T RA criteria) in the literature.[18] Characteristics of patients with AxSpA fulfilling D2T criteria were compared to those without D2T criteria.

In patients in whom magnetic resonance imaging was performed, the presence of bone marrow edema adjacent to the sacroiliac joint in two different areas in at least two different series was considered positive. Radiological progression of spinal changes was defined as a two-point increase in the modified Stoke Ankylosing Spondylitis Spinal Score on X-rays taken at least two years apart.

Statistical analysis

The sample size was determined using G*Power version 3.1.7 software (Heinrich-Heine Universität Düsseldorf, Düsseldorf Germany). Considering the rate of biological DMARD-resistant patients with different mechanisms of action (12-15%), with a 5% type 1 error and 95% confidence interval, the sample size was calculated as 162 to 195 patients.

Statistical analysis was performed using the IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to present the general characteristics of the study population. Data were defined as total numbers and percentiles. Parametric data were calculated as mean ± standard deviation (SD), while numeric variables were expressed as median value (interquartile range) and categorical variables as numbers (%). The chi-square test or Fisher exact test was used to compare the categorical data of the groups, and Student's t-test was used to compare numeric (continuous) variables. The Mann-Whitney U test

Table 1. Definition of D2T AxSpA criteria

	Entry criterion	
1	In the patients treated according to EULAR recommendations, treatment failure to ≥2 b/tsDMARDs with two different mechanisms of action or ≥3 b/tsDMARDs.	
2	Signs suggesting active or progressive disease, at least one of the following:	
	a)	Moderate or high disease activity in at least 1 composite index, BASDAI >4, ASDAS-CRP >1.3,
	b)	Signs (including acute phase reactants and imaging) and/or symptoms (articular or other) indicating active disease,
		• CRP >5.0 mg/L and/or ESR >25 mm/h,
		• The presence of active bone marrow edema on sacroiliac and lumber MRI,
	c)	Regular or frequent use of NSAIDs due to pain or stiffness,*
	d)	The presence of uveitis attacks despite treatment,
	e)	Well-controlled disease according to the above criteria, but the presence of AxSpA symptoms leading to low quality of life (eg. enthesitis and dactylitis)
3		Management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient

* Patients with regular NSAID use for more than half a week were enrolled; D2T: Difficult-to-treat; AxSpA: Axial spondyloarthropathy; EULAR: European Alliance of Associations for Rheumatology; b/tsDMARD: Biological/targeted synthetic Disease-modifying Antirheumatic Drug; BASDAI: Bath ankylosing spondylitis disease activity index; ASDAS: Ankylosing spondylitis disease activity score; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MRI: Magnetic resonance imaging; NSAIDs: Nonsteroidal anti-inflammatory drugs.

was used for the comparison of nonnormally distributed parametric values. A *p*-value <0.05 was considered statistically significant.

RESULTS

The study included 142 AS and 24 nonradiographic AxSpA (nr-AxSpa) patients. The flowchart of patient selection is shown in Figure 1. There were 38 (22.9%) patients fulfilling potential D2T criteria. The characteristics of the patients are presented in Table 2. When comparing D2T (n=38) and non-D2T (n=128) patients, there was no statistically significant for sex, mean age, age at the time of diagnosis, body mass index, HLA-B27 positivity, alcohol use, smoking status, marital status, and educational level (Table 2).

Clinical signs, disease activity scores, medications, and comorbidities are presented in Table 3. The frequency of active peripheral arthritis (p=0.010) and fibromyalgia (p<0.001) were significantly higher in D2T patients. There was no significant difference between the groups in the presence of uveitis (current and previous), inflammatory bowel disease, extramusculoskeletal manifestations, and the number of comorbidities.

Compared to the non-D2T group, treatment with multiple biologics was significantly more common in the D2T group (p<0.001). The most commonly used agent was adalimumab. While secukinumab and certolizumab pegol were similar in both groups as the first choice, the frequency of use increased in the second and later preferences in the D2T group. Of non-D2T patients, 71.9% were not using any concomitant agents, whereas 60.5% of D2T AxSpA patients were using NSAIDs (Table 3).

As expected, at the time of inclusion in the study (cross-sectional), all disease activity scores, such as BASDAI, BASFI, ASDAS-CRP, ASDAS-Sedimentation, and HAQ score were significantly higher in the D2T group than in the non-D2T group (p<0.001 for all). Furthermore, CRP and erythrocyte sedimentation rate levels were statistically significantly higher in D2T patients.

DISCUSSION

The current study evaluated patients with AxSpA in terms of D2T. Some proposals are available for D2T criteria in patients with AxSpA.[18] Potential D2T criteria for AxSpA

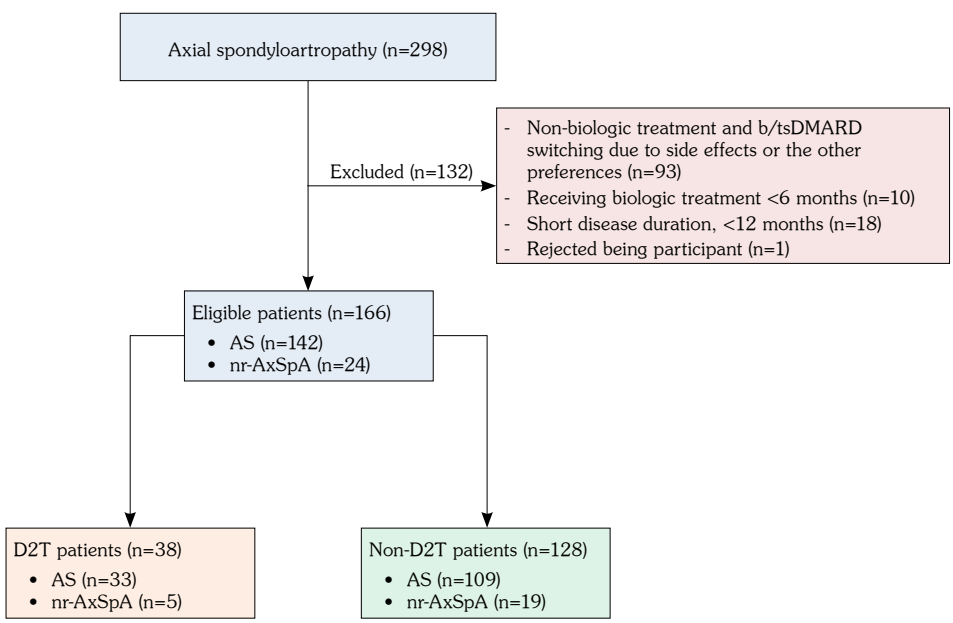

Figure 1. Flow diagram of the patient selection.

b/tsDMARD: Biological/targeted synthetic disease-modifying antirheumatic drugs; AS: Ankylosing spondylitis; nr-AxSpA: Non-radiographic axial spondyloarthritis; D2T: Difficult-to-treat.

Table 2. Baseline characteristics of the study groups

	All patients (n=166)			D2T (n=38)			Non-D2T (n=128)		
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD
Age (year)			47.1±12.9			47.7±11.9			46.9±13.7
Age at diagnosis (year)			34.4±12.1			34.1±11.3			34.5±12.3
Disease duration (year)			12.7±7.5			13.6±7.2			12.4±7.1
Body mass index (kg/m^2)			27.8±4.6			28.7±4.7			27.6±4.5
Sex									
Female	73	44.0		19	50.0		54	42.2	
AS	142	85.5		33	86.8		109	85.2	
nr-AxSpA	24	14.5		5	13.2		19	14.8	
HLA B-27 positivity*	76	60.0		12	52.2		64	61.5	
Marital status									
Single	20	12.0		4	10.5		16	12.5	
Married	133	80.1		31	81.6		102	79.7	
Divorced/Widow	13	7.9		3	7.9		10	7.8	
Number of children									
0	25	17.6		4	10.5		21	16.4	
1-2	78	54.9		18	47.4		60	46.9	
≥3	39	27.5		11	28.9		28	21.9	
Occupation									
Housewife	30	18.1		8	21.1		22	17.2	
Unemployed	7	4.2		2	5.3		5	3.9	
Manual worker	66	39.8		16	42.1		50	39.1	
Government worker	31	18.7		6	15.8		25	19.5	
Retired	30	18.1		5	13.2		25	19.5	
No data	2	1.2		1	2.6		1	0.7	
Education&									
Primary and secondary school	53	41.4		14	36.8		39	30.5	
High school and university	75	58.6		17	44.7		58	45.3	
Smoking									
Current	51	30.7		14	36.8		37	28.9	
Past	35	21.1		6	15.8		29	22.7	
Never	80	48.2		18	47.4		62	48.4	
Alcohol use									
Regular	9	5.7		2	5.3		7	5.5	
Social drinker	26	16.5		8	21.1		18	14.1	
Never	123	77.8		28	73.3		95	74.2	
Fibromyalgia	18	10.8		10	26.3		8‡	6.3	
Number of comorbidities									
0	75	45.2		16	42.1		59	46.1	
1	45	27.1		8	21.0		37	28.9	
≥2	46	27.1		14	36.8		32	25.0	
Concomitant use of drugs									
None	106	63.9		14	36.8		92‡	71.9	
NSAIDs	53	31.9		23	60.5		30‡	23.4	
Methotrexate	5	3.0		-	-		5	3.9	
Sulphasalazine	5	3.0		2	5.3		3	2.3	

SD: Standard deviation; D2T: Difficult-to-treat; AS: Ankylosing spondylitis; nr-AxSpA: Non-radiographic axial spondyloarthritis; HLA-B27: Human leukocyte antigen B27; NSAIDs: Nonsteroidal anti-inflammatory drugs; * The number of patients with available HLA-B results is 125; & Data from 128 patients; ‡ p <0.001.

have been revealed by considering D2T RA criteria sets established by EULAR,[9] D2T criteria set for PsA,[19] and activity parameters for AxSpA. D2T AxSpA criteria were adopted from the EULAR D2T RA criteria.[9] This criteria set is based on treatment failure to multiple biological agents. Despite treatment according to EULAR recommendations, moderate and higher disease activity, elevated acute phase reactants, radiographic findings, regular NSAID use, and

Table 3. Disease activity signs, scores, medications, and comorbidities in the study groups

	D2T (n=38)					Non-D2T (n=128)				
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max
Current peripheral arthritis	6	15.8				4†	3.1			
Current enthesitis	6	15.8				8	6.3			
Current uveitis	3	7.9				6	4.7			
Uveitis, (ever)	12	31.6				32	25.0			
Extra-musculoskeletal manifestations, (ever)	18	47.4				44	34.3			
Inflammatory bowel disease (ever)	5	13.2				12	9.4			
Bone marrow edema on sacroiliac joints (MRI)	7	18.4				3‡	2.3			
Radiographic progression (Spinal X-ray)	5	13.1				11	8.9			
b/tsDMARDs (currently)										
Adalimumab	11	28.9				38‡	29.7			
Infliximab	2	5.3				26	20.3			
Etanercept	4	10.5				25	19.5			
Secukinumab	4	10.5				15	11.7			
Golimumab	1	2.6				19	14.8			
Certolizumab pegol	16	42.1				4	3.1			
	1st	≥2nd	Total			1st	≥2nd	Total		
	n	%	n	%		n	%	n	%	
b/tsDMARDs (overall)										
Adalimumab	11	21	33	86.8		34	14	48‡	37.5	
Infliximab	7	13	20	52.6		36	8	44	34.3	
Etanercept	8	18	26	68.4		28	10	38	29.7	
Secukinumab	6	13	19	50.0		8	9	17	13.3	
Golimumab	3	7	10	26.3		18	4	22	17.2	
Certolizumab pegol	3	21	24	63.2		4	3	7	5.7	
Number of b/tsDMARDs										
One	-	-				84‡	65.6			
Two	6	15.8				40	31.2			
≥ Three	32	84.2				4	3.1			
Time from diagnosis to 1st biologic agent (year)				3.0	0-27				3.0	0-25
Duration of exposition to b/tsDMARDs, (month)				102	8-168				72	10-226
Inflammation, disease activity, and quality of life indices (Cross-Sectional)										
CRP (mg/L)			9.52±11.7					3.97±5.44‡		
ESR (mm/h)			16.0±15.7					10.8±9.6†		
BASDAI				5.5	0.6-8.6				2.7‡	0-9.6
BASFI				4.7	0.25-9.6				1.4‡	0-9.5
ASDAS-CRP				3.1	1.2-4.6				1.8‡	0.6-4.1
ASDAS-ESR				3.0	3.2-4.8				1.8‡	0.5-4.9
HAQ				0.75	0-2.38				0.25‡	0-1.88

SD: Standard deviation; D2T: Difficult-to-treat; MRI: Magnetic resonance imaging; b/tsDMARD: Biological/targeted synthetic disease-modifying antirheumatic drugs; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; ASDAS: Ankylosing spondylitis disease activity score; HAQ: Health assessment questionnaire; NSAIDs: Nonsteroidal anti-inflammatory drugs; * Patients with regular NSAID use for more than half a week were enrolled; † $p<0.05$; ‡ $p<0.001$.

the presence of extra-articular involvement were considered indicators of active and progressive disease.

The subjects with AxSpA receiving biological/targeted synthetic DMARDs were cross-sectionally evaluated, and previous treatments were retrospectively investigated. Factors that may be associated with biological/targeted synthetic DMARD failure, such as sociodemographic characteristics, clinical features, and laboratory findings, were evaluated. In AxSpA patients, 22.9% were found to have D2T disease. Furthermore, the rate of D2T patients was not different between AS and nr-AxSpA patients. The presence of active peripheral arthritis, fibromyalgia, use of

NSAIDs, high-level acute phase reactants, higher disease activity scores, and lower quality of life were statistically significant parameters in D2T patients.

In a multicenter retrospective French study, the subjects with D2T AxSpA were evaluated, and the ratio of the patients unresponsive to biological agents with two different mechanisms of action was 28%.[20] They reported that the D2T cohort was found to have higher pretreatment BASDAI scores and more frequent peripheral joint involvement, similar to the present study. Differently, uveitis was more common in D2T groups, and they had a shorter disease duration than the non-D2T group. The results of the five-year longitudinal study revealed that most of the AxSpA patients stayed in the same cluster (axial or peripheral predominant involvement).[21] Therefore, it can be speculated that patients with currently active peripheral arthritis or with peripheral involvement at the time of diagnosis are similar and associated with high disease burden.

The results of this study did not reveal a difference among sexes for D2T in AxSpA. However, growing data indicates that disease burden differs among female and male subjects with AxSpA. Whether this difference is related to inflammatory reasons is not clear. Although radiologic progression is less prominent in females, disease activity scores are higher, and life quality scores are worse.[22,23] Tournadre et al.[23] demonstrated a positive correlation between high BASDAI and ASDAS-CRP scores and the female sex in patients with AxSpA. Similar findings were found in another study showing higher BASDAI and BASFI scores in female patients with nr-AxSpA compared to male patients.[24] Di Giuseppe et al.[8] reviewed the records of Nordic countries and found that treatment with ≥3 biologic agents was significantly more common in female patients compared to male patients. Compared to males, female patients with AxSpA have lower IL-17 levels, while enthesitis and dactylitis are also more common in female patients.[25] The presence of peripheral arthritis and enthesitis negatively affects disease burden.[26-28] Neuropathic pain and fibromyalgia syndromes are also more common in female patients.[29,30]

Fibromyalgia is a disease that predominantly affects females. Referred pain, fatigue, pain on tender points, sleep and mood disorders, and irritable bowel syndrome are frequently observed in patients with fibromyalgia. AxSpA and fibromyalgia overlap is quite common, and various studies report that the prevalence of fibromyalgia is about 10.8 to 38.4% among patients with AxSpA.[31] Studies are showing that the presence of fibromyalgia syndrome or fibromyalgianess and neuropathic pain affects disease activity scores and may lead to unnecessary biological drug switching.[30,32] It was termed fibromyalgianess by Wolfe,[33] who demonstrated that the degree of fibromyalgia predicts pain and disability in all rheumatic diseases.[32] Moreover, slow progression of the disease and concomitant fibromyalgia, observed particularly in female subjects with nr-AxSpA, result in delayed diagnosis.[31,34] However, it is still unknown whether the presence of fibromyalgia and the female sex are independent factors or if they are related to each other. The 2022 ASAS/EULAR recommendations strongly suggest the evaluation of the presence of comorbidities, including fibromyalgia, and the accuracy of the diagnosis in case of treatment unresponsiveness.[35] It was determined that the frequency of fibromyalgia was higher in the D2T group in this study. Fibromyalgia can be a confounding disease to identifying potential D2T criteria by raising disease activity indices and reducing quality of life. Possibly, it should be considered an exclusion criterion for D2T AxSpA.

There is evidence that HLA-B27 positivity is a good indicator of TNFi responsiveness in AxSpA,[36-38] while some studies indicate the opposite.[39,40] In the study by Fröchlich et al.,[41] about 1,000 patients with AxSpA were evaluated, and HLA-B27 positivity was found to be related to earlier disease onset, longer disease duration, and the male sex. Drug discontinuation was more common among female patients, and drug retention was less commonly encountered in patients with HLA-B27 negativity. Our analysis showed that HLA-B27 is not an indicator for D2T AxSpA.

In patients who underwent magnetic resonance imaging, bone marrow edema was detected more frequently in the D2T group.

It is an expected finding since it is one of the disease activity findings. However, no difference was detected between the two groups regarding the radiological progression of spinal changes. This may be due to factors affecting radiological progression, such as sex and HLA-B27, not being effective in terms of D2T.

The present study has some limitations. First, the D2T criteria suggested for AxSpA are researchers' predictions; they are not validated or meta-analysis-based parameters. Second, previous biological/targeted synthetic DMARD treatments were retrospectively investigated, and the information about the duration of biological agent use, disease activity scores at the time of diagnosis, and switching biological agents was obtained retrospectively. The parameters of D2T AxSpA were cross-sectionally evaluated. In addition, biological/targeted synthetic DMARD options were limited to TNFi and IL-17 inhibitors; the cohort had no subjects receiving JAK inhibitors since they have not been approved for AxSpA in Türkiye. The small number of patients and the absence of patients using targeted synthetic DMARDs are the most important limitations of this study.

In conclusion, 22.9% of AxSpA patients met the D2T criteria according to the potential D2T criteria recommended in this study. The presence of active peripheral arthritis, NSAID use, high disease activity scores, high levels of acute phase reactants, and worse life quality scores are prominent characteristics of D2T AxSpA patients. Fibromyalgia should be investigated as a confounding factor for D2T criteria or a distinguishing feature of D2T AxSpA patients. Further studies are required to confirm our findings and identify the parameters to diagnose D2T AxSpA patients.

Ethics Committee Approval: The study protocol was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (date: 08.02.2023, no: KAEK-97). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Have designed the study: V.Y., T.S.Ö.; Have collected the data: T.S.Ö., M.N., M.D., M.F.Ş., A.Y.Ö.; Data analyses and interpretation have been performed: V.Y., T.S.Ö.; Literature review is done: T.S.Ö., F.E.; Have written the first draft of the manuscript, and all authors commented on the last version of the manuscript: V.Y., T.S.Ö.; Critical review of the manuscript is performed: M.E.T. All authors have read and approved the final and revised manuscript.

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