Applying the ASAS definition of difficult-to-manage and treatment-refractory axial spondyloarthritis: an exploratory single centre cross-sectional study

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Dear Editor,

The Assessment of SpondyloArthritis International Society (ASAS) has recently proposed a consensus-based expert definition for difficult-to-manage (D2M) axial spondyloarthritis (axSpA) and treatment-refractory (TR) axSpA[1].

Our aim is to determine the proportion of D2M and TR axSpA according to the ASAS definition and describe the characteristics of these patients.

We conducted an observational cross-sectional single-centre study that included all adult patients with axSpA, meeting the ASAS classification criteria, exposed to biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs). Patients included had at least one visit registered after 2017 (when different mechanisms of action (MoA) became available for prescription). The demographic and clinical data were retrieved from medical records. The baseline was defined as the start date of the first b/tsDMARD. D2M axSpA was defined according to the ASAS criteria[1] as 1) treatment according to the ASAS-European alliance of associations for rheumatology (EULAR) recommendations and failure of ≥2 b/tsDMARDs with different MoA, 2) insufficient control of signs/symptoms of axSpA (axial spondyloarthritis disease activity score (ASDAS)≥2.1 or C-reactive protein (CRP)>5.0mg/L or active inflammation on magnetic resonance imaging (MRI) or rapid radiographic spinal progression) and 3) the signs/symptoms are perceived as problematic by the patient/physician (patient global assessment or physician global assessment ≥4/10)[2]. Regarding point 2), the component “other axSpA symptoms that are attributable to axSpA and cause a reduction in quality of life despite otherwise well-controlled disease” from the original ASAS definition was not included due to limited data.[1] TR axSpA was a subset of D2M axSpA in which 1) the use of ≥2 b/tsDMARDs was due to treatment failure, 2) with high or very high disease activity (ASDAS≥2.1) plus evidence of inflammatory activity (CRP>5.0mg/L or MRI showing active inflammation) and 3) other causes of signs and symptoms excluded[1]. The fulfilment of the ASAS definition was assessed in the last registered visit.

The proportion of D2M and TR axSpA was estimated. The patients’ demographics and clinical characteristics are presented as absolute frequencies and percentages for categorical variables and as mean ± standard deviation or as medians and interquartile ranges for continuous variables. There was no imputation of missing values. An exploratory analysis was performed to compare D2M and non-D2M axSpA. Fisher’s exact test was used for categorical variables, and Student’s t-test or Mann-Whitney U test for continuous variables. Multivariate analysis was not conducted due to the small sample size. Data were analysed using IBM® SPSS® Statistics version 27.0. Statistical significance was considered with a *p-value* < 0.05.

We included 207 patients, of whom 2.9% (n=6) met the criteria for D2M axSpA and 1.4% (n=3) for TR axSpA. Among axSpA patients, 52 (25.1%) had prior treatment with ≥2 b/tsDMARDs, but only 12 (5.8%) had different MoA. Additionally, 42.8% (n=86) and 38.3% (n=77) fulfilled the second and third criterion for D2M axSpA, respectively, but only 13.2% (n=26) met the second criterion for TR axSpA (Figure I).

Patients' characteristics are described in Table I. D2M axSpA was associated with a younger age at symptom onset and diagnosis. No further statistically significant differences were identified.

All D2M axSpA patients were HLA-B27 positive, and the majority had radiographic axSpA (83.3%). A minority had peripheral disease (33.3%) or extra-musculoskeletal manifestations (16.7%).

All TR axSpA patients (n=3) were HLA-B27 positive, two with radiographic axSpA and one with peripheral disease.

Applying the ASAS definition, we found a low proportion of D2M and TR axSpA. Previous studies using different definitions reported higher prevalences[3–7]. However, according to the ASAS definition, Smits et al. identified a similar proportion of TR axSpA of 1.7%, although with a higher proportion of D2M axSpA (9.7% vs 2.9% in our study)[8]. The requirement for prior use of ≥2 b/tsDMARDs with different MoA likely limited the classification of patients as D2M or TR, probably reflecting differences in treatment access. This is among the first studies to apply the ASAS definition and the first in the Portuguese cohort. Limitations are related to the observational design, particularly the missing data, and the small sample size. The restriction to patients previously exposed to b/tsDMARDs, may have overestimated the prevalence of TR and D2M axSpA. Larger nationwide studies are needed to better characterise patients with D2M and TR axSpA.

Tables and Figures

Table I – Clinical and demographic characteristics of patients with axSpA and TR axSpA and comparison of patients with D2M/non-D2M axSpA.

	axSpA n=207	Non-D2M axSpA, n=201	D2M axSpA, *n*=6	*p* value*	TR axSpA, *n*=3
Male sex, *n* (%)	121 (58.5)	117 (58.2)	4 (66.7)	1.000	2 (66.7)
Caucasian, *n* (%)	193 (93.2)	187 (96.9)	6 (100)	NA	3 (100)
Age, *years*	51.0 ± 13.2	51.2 ± 13.1	46.4 ± 15.2	0.386	48.8
Age at symptom onset, *years*	26.7 (17.0)	27.1 (16.9)	20.2 (14.1)	**0.018**	23.6 (17.8-26.3)
Age at diagnosis, *years*	31.7 (18.1)	32.0 (18.3)	25.2 (9.8)	**0.012**	25.6 (24.8-28.3)
Family history of axSpA, *n* (%)	21 (10.1)	20 (10)	1 (16.7)	0.478	0
Peripheral disease†, *n* (%)	55 (26.6)	53 (26.4)	2 (33.3)	0.657	1 (33.3)
Radiographic axSpA, *n* (%)	175 (84.5)	170 (84.6)	5 (83.3)	1.000	2 (66.7)
HLA-B27 positivity, *n* (%)	159 (83.7)	153 (83.2)	6 (100)	NA	3 (100)
Extra-musculoskeletal manifestations (cumulative), *n* (%)	77 (37.2)	76 (37.8)	1 (16.7)	0.415	0
Psoriasis, *n* (%)	14 (6.8)	14 (7.0)	0	NA	0
Uveitis, *n* (%)	63 (30.4)	63 (31.3)	0	NA	0
IBD§, *n* (%)	15 (7.2)	14 (7.0)	1 (16.7)	0.367	0
Comorbidities					
Previous or current smoking, *n* (%)	95 (48)	92 (47.9)	3 (50)	1.000	2 (66.7)
BMI (kg/m^2), *n (%)*					
Normal weight (<25 *kg/m^2*)	75 (36.2)	73 (40.6)	2 (33.3)		1 (33.3)
Overweight (≥25 and <30 *kg/m^2*)	78 (37.7)	75 (41.7)	3 (50)	0.916	2 (66.7)
Obese (≥30 *kg/m^2*)	33 (15.9)	32 (17.8)	1 (16.7)		0
Cardiovascular disease and/or risk factors‡, *n* (%)	81 (39.1)	78 (38.8)	3 (50)	0.681	2 (66.7)
Osteoarthritis, *n* (%)	33 (15.9)	31 (15.4)	2 (33.3)	0.245	1 (33.3)
Depression, *n* (%)	49 (23.7)	47 (23.4)	2 (33.3)	0.629	0
Anxiety, *n* (%)	7 (3.4)	6 (3.0)	1 (16.7)	0.189	0
Fibromyalgia, *n* (%)	14 (6.8)	14 (7.0)	0	NA	0
Disease activity at baseline (start date of first b/tsDMARDs), median (IQR or min-max)					
ESR, *mm/1st hour*	32 (42)	32.0 (43)	37 (26-39)	0.956	-
CRP, *mg/L*	8.2 (17.9)	8 (17.9)	11 (9.4-24)	0.327	-
PtGA, *0-10*	6.1 (3.0)	6.0 (4.0)	5.8 (3.0-5.9)	0.266	-
PhGA, *0-10*	4.7 (1.9)	4.6 (2.0)	4.6 (4.2-4.9)	1.000	-
Back pain VAS, *0-10*	6.0 (4.0)	6.4 (4.0)	5.0 (5.0-8.0)	0.903	-
ASDAS¶	3.5 (1.1)	3.5 (1.1)	4.1 (3.1-4.7)	0.331	-
BASDAI, 0-10	6.2 (2.5)	6.2 (2.5)	8.2 (4.2-8.5)	0.360	-
BASFI, 0-10	4.8 (3.9)	4.8 (4)	5.4 (3.4-7.1)	0.653	-
Disease activity at the last visit, median (IQR or min-max)					
CRP, *mg/L*	1.6 (3.1)	1.6 (3.0)	4.3 (19.8)	0.416	6.1 (0.3-50.5)
ASDAS¶	1.7 (1.4)	1.6 (1.4)	2.7 (0.7)	0.011	2.8 (2.2-3.3)
PtGA, *0-10*	2.8 (4.0)	2.5 (4.0)	5.5 (1.6)	0.016	5.0 (4.4-6.0)
PhGA, *0-10*	0.5 (1.0)	0.5 (1.0)	1.0 (4.0)	0.529	2.0 (0-4.0)
Current b/tsDMARDs					
None, *n* (%)	36 (17.4)	35 (17.4)	1 (16.7)	NA	0
TNFi, *n* (%)	160 (77.3)	156 (77.6)	4 (66.7)	NA	3 (100)
IL-17i, *n* (%)	6 (2.9)	6 (3)	0	NA	0
JAKi, *n* (%)	4 (1.9)	3 (1.5)	1 (16.7)	NA	0
IL-23i**, *n* (%)	1 (0.5)	1 (0.5)	0	NA	0

axSpA, axial spondyloarthritis; *D2M,* difficult-to-manage, *TR,* treatment refractory; *HLA-B27,* human leucocyte antigen B27; *BMI,* body mass index; *IBD,* inflammatory bowel disease; *b/tsDMARDs,* biologic/targeted synthetic disease modifying anti-rheumatic drugs; *ESR,*

erythrocyte sedimentation rate; *CRP*, C-reactive protein; *PtGA*, patient global assessment; *PhGA*, physician global assessment; *VAS,* visual analogue scale; *ASDAS,* Ankylosing Spondylitis Disease Activity Score; *BASDAI,* Bath Ankylosing Spondylitis Disease Activity Index*; BASFI,* Bath Ankylosing Spondylitis Functional Index; *TNFi,* tumour necrosis factor inhibitors; *IL-17i,* interleukin-17 inhibitors; *JAKi,* janus kinase inhibitors; *IL-23i*, interleukin-23 inhibitor; *NA,* not applicable; *n*, number

[*] compared with non-D2M SpA

[†] comprises peripheral arthritis, enthesitis and dactylitis

[§] comprises Crohn's disease and ulcerative colitis

[‡] comprises hypertension, dyslipidaemia, diabetes mellitus, coronary artery disease and heart failure

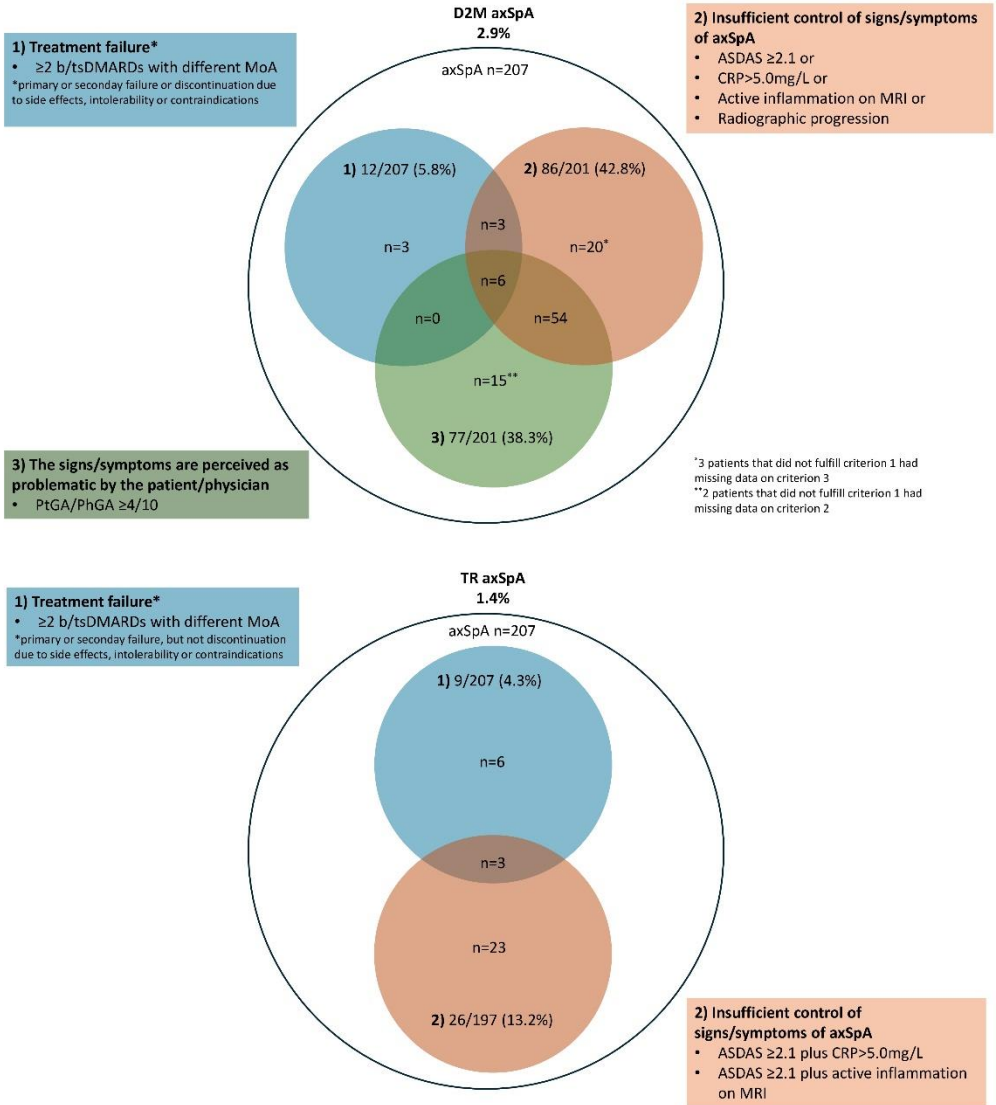
[**] Although IL-23i have no proven efficacy on axSpA, this patient has radiographic axSpA with IBD and is under IL-23i, since she developed psoriasis secondary to TNFi, has contraindication to IL-17i due to IBD and had primary failure to JAKi.

[¶] ASDAS: <1.3 inactive disease; ≥1.3 and <2.1 low disease activity; ≥2.1 and ≤3.5 high disease activity; >3.5 very high disease activity

Statistical significance highlighted in bold (*p*-value <0.05)

Number of missing data per variable: age at symptom onset 0.96% (n=2); HLA-B27 8.2% (n=17); tobacco exposure 4.3% (n=9); BMI 10.1% (n=21); Baseline: ESR 29.9% (n= 62); CRP 28.5% (n=59); PtGA 27.5% (n=57); PhGA 54.5% (n=113); Back pain VAS 28.7% (n=59); ASDAS 33.3% (n=69); BASDAI 25.6% (n=53); BASFI 28.5% (n=59); Last visit: CRP 0.5% (n=1); ASDAS 4.3% (n=9); PtGA 3% (n=6); PhGA 3% (n=6).

Figure 1 - Venn diagram representing the number of patients fulfilling each domain of the ASAS definition for D2M axSpA and TR axSpA.



ASAS - assessment of spondyloarthritis international society, D2M - difficult-to-manage, axSpA - axial spondyloarthritis, TR - treatment-refractory, b/tsDMARDs - biologic or targeted synthetic disease-modifying anti-rheumatic drugs, MoA - mechanisms of action, ASDAS - axial spondyloarthritis disease activity score, CRP - C-reactive protein, MRI - magnetic resonance imaging, PGA - patient global assessment, PhGA - physician global assessment.

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