Eligibility criteria for biological Disease Modifying Anti-Rheumatic Drugs therapy in axial Spondyloarthritis: Going beyond BASDAI

Online Supplementary Material

Online Supplementary Table S1. Baseline patient- and disease-characteristics of the study population

Variables	Reuma.pt axSpA cohort (N=3,138)	'Eligible population' (N=594)	'Non-eligible population' (N=2,544)	p-value ‡
Age in years, mean +/- SD	49 ± 13	49 ± 13	49 ± 13	0.98
Gender (male), n (%)	1,690 (54)	326 (55)	1,364 (54)	0.58
BMI in Kg/m^2, mean +/- SD [N=1,256]	25.9 ± 4.5	25.9 ± 4.7	26.0 ± 4.5	0.77
Current smokers, n (%) [N=2,087]	480 (23)	114 (22)	366 (23)	0.17
Inflammatory back pain, n (%) [N=2,021]	1,656 (82)	436 (84)	1,220 (81)	0.27
Peripheral Arthritis, n (%) [N=2,021]	754 (37)	211 (40)	543 (36)	0.09
HLA-B27, n (%) [N=2,021]	1,241 (61)	347 (67)	894 (60)	**<0.01**
Radiographic sacroiliitis (mNY), n (%) [N=1,769]	1,422 (80)	391 (80)	1,031 (80)	0.95
Sacroiliitis on MRI-SU, n (%) [N=839]	506 (60)	137 (61)	369 (60)	0.84
BASDAI (0-10), mean +/- SD [N=2,082]	5.0 ± 2.4	5.8 ± 2.1	4.7 ± 2.4	**<0.01**
ASDAS-CRP, mean +/- SD [N=1,534]	3.2 ± 1.1	3.5 ± 1.0	3.1 ± 1.2	**<0.01**
ASDAS inactive disease, n (%)	82 (5)	9 (2)	73 (8)	
ASDAS moderate disease activity, n (%)	160 (10)	28 (5)	132 (14)	**<0.01**
ASDAS high disease activity, n (%)	684 (45)	272 (46)	412 (44)	
ASDAS very high disease activity, n (%)	608 (40)	285 (48)	323 (34)	
CRP, mg/dL, mean +/- SD [N=988]	2.2 ± 3.1	2.1 ± 2.9	2.3 ± 3.3	0.47
Elevated CRP, n (%) [N=988] *	715 (72.4)	376 (71.1)	339 (73.9)	0.33
BASFI (0-10), mean +/- SD [N=1,690]	4.6 ± 2.7	5.2 ± 2.5	4.4 ± 2.8	**<0.01**
bDMARD therapy, n (%)	1,519 (48)	529 (89)	990 (39)	**
Infliximab	336 (22)	130 (25)	206 (21)	
Adalimumab	468 (31)	164 (31)	304 (31)	
Etanercept	437 (29)	135 (26)	302 (31)	0.28
Golimumab	247 (16)	91 (17)	156 (16)	
Certolizumab	19 (1)	5 (1)	14 (1)	
Secukinumab, n (%)	12 (1)	4 (1)	8 (1)	
Co-medication [N=1,508]				
NSAIDs	490 (33)	211 (40)	279 (29)	**<0.01**
csDMARDs	607 (40)	271 (51)	336 (34)	**<0.01**
Oral Corticosteroids	279 (19)	108 (20)	171 (18)	0.16

Reuma.pt axSpA cohort: all axSpA patients from Reuma.pt (Rheumatic Diseases Portuguese Register) cohort, irrespective of being treated with bDMARD. 'Eligible population': axSpA patients, irrespective of being treated with bDMARD, with complete 6 months of follow-up and BASDAI/ASDAS data at baseline (irrespective of having ASDAS/BASDAI at any other time point). 'Non-eligible population': axSpA patients from Reuma.pt that did not fulfil the criteria of the eligible population (irrespective of being treated with bDMARD). ‡ comparison between the 'Eligible population' and the 'Non-eligible population' (Independent-samples t-test for continuous variables and Chi2 for categorical variables). * Defined as ≥0.5mg/dL. ** p-value of <0.01 for the categorical variable (treated or not with bDMARD). axSpA, axial spondyloarthritis. BMI, Body Mass Index. HLA-B27, Human Leucocyte Antigen B27. mNY, modified New York criteria for Ankylosing Spondylitis. MRI-SU, Magnetic Resonance Imaging of Sacroiliac joints. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. ASDAS, Ankylosing Spondylitis Disease Activity Score. CRP, C Reactive Protein. BASFI, Bath Ankylosing Spondylitis Functional Index. bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs. NSAIDs, Non-Steroid Anti-inflammatory Drugs. csDMARDs, conventional synthetic Disease Modifying Anti-Rheumatic Drugs.

Online Supplementary Table S2. Baseline patient- and disease-characteristics of the bDMARD treated population

Variables	bDMARD treated (N=529)	bDMARD treated with full data ('Efficacy population') (N=359)
Age in years, mean +/- SD	49 ± 12	49 ± 12
Gender (male), n (%)	287 (54)	195 (54)
BMI in Kg/m^2, mean +/- SD [N=287]	25.9 ± 4.7	25.6 ± 4.4
Current smokers, n (%) †	109 (23)	75 (23)
Number of comorbidities +/- SD * [N=434]	0.3 ± 0.6	0.3 ± 0.6
Disease duration, mean +/- SD †	12.7 ± 9.9	12.7 ± 9.9
Inflammatory back pain, n (%) †	398 (85)	271 (85)
Peripheral arthritis, n (%) †	190 (40)	139 (43)
HLA-B27, n (%) †	309 (66)	207 (65)
Radiographic sacroiliitis (mNY), n (%) [N=487]	363 (82)	250 (82)
Sacroiliitis on MRI-SIJ, n (%) [N=225]	123 (61)	77 (56)
Number of SpA features +/- SD †	2.5 ± 1.3	2.5 ± 1.3
BASDAI (0-10), mean +/- SD	6.0 ± 1.9	6.0 ± 1.8
BASDAI ≥4, n (%)	464 (88)	319 (89)
ASDAS-CRP, mean +/- SD	3.7 ± 0.9	3.7 ± 0.9
ASDAS inactive disease, n (%)	2 (<1)	0 (0)
ASDAS low disease activity, n (%)	9 (2)	7 (2)
ASDAS high disease activity, n (%)	244 (46)	162 (45)
ASDAS very high disease activity, n (%)	274 (52)	190 (53)
CRP, mg/dL, mean +/- SD	2.1 ± 2.9	2.1 ± 2.8
Elevated CRP, n (%) **	376 (71)	260 (72)
BASFI (0-10), mean +/- SD †	5.3 ± 2.4	5.4 ± 2.4
bDMARD, n (%)		
Infliximab	130 (25)	87 (24)
Adalimumab	164 (31)	115 (32)
Etanercept	135 (25)	91 (25)
Golimumab	91 (17)	60 (17)
Certolizumab	5 (1)	3 (1)
Secukinumab	4 (1)	3 (1)
Previous co-medication, n (%):		
NSAIDs	211 (40)	145 (40)
csDMARDs	271 (51)	195 (54)
Oral steroids	108 (20)	80 (22)

bDMARD treated: axSpA patients treated with TNFi, with complete 6 months of follow-up and BASDAI/ASDAS data at baseline (irrespective of having ASDAS/BASDAI at any other timepoint). bDMARD treated with full data ('Efficacy population'): axSpA patients treated with TNFi, with complete 6 months of follow-up and complete data on all response outcomes (every timepoint). † <5% of missing data. * Arterial hypertension and other cardiovascular diseases, dyslipidemia, diabetes mellitus, thyroid disease and malignancies. ** Defined as ≥0.5mg/dL. bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs. BMI, Body Mass Index. HLA-B27, Human Leucocyte Antigen B27. mNY, modified New York criteria for Ankylosing Spondylitis. MRI-SU, Magnetic Resonance Imaging of Sacroiliac joints. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. ASDAS, Ankylosing Spondylitis Disease Activity Score. CRP, C Reactive Protein. BASFI, Bath Ankylosing Spondylitis Functional Index. NSAIDs, Non-Steroid Anti-inflammatory Drugs. csDMARDs, conventional synthetic Disease Modifying Anti-Rheumatic Drugs.

Online Supplementary Table S3. Baseline patient- and disease-characteristics in patients fulfilling the ASAS axSpA Classification Criteria

Variables	All ASAS axSpA (ASAS 'eligible population') (N=463)	ASAS bDMARD treated with full data (ASAS 'efficacy population) (N=286)
Age in years, mean +/- SD	49 ± 12	49 ± 12
Gender (male), n (%)	270 (58)	168 (59)
BMI in Kg/m^2, mean +/- SD [N=254]	25.9 ± 4.6	25.6 ± 4.4
Current smokers, n (%) †	99 (23)	65 (24)
Number of comorbidities +/- SD * [N=239]	0.3 ± 0.6	0.3 ± 0.6
Disease duration in years, mean +/- SD †	13.1 ± 10.6	12.7 ± 9.9
Inflammatory back pain, n (%)	399 (86)	251 (88)
Peripheral arthritis, n (%)	183 (40)	123 (43)
HLA-B27, n (%)	331 (72)	198 (69)
Radiographic sacroiliitis (mNY), n (%) †	373 (86)	236 (87)
Sacroiliitis on MRI-SIJ, n (%) [N=192]	127 (66)	69 (59)
Number of SpA features +/- SD	2.6 ± 1.2	2.6 ± 1.3
BASDAI (0-10), mean +/- SD	5.8 ± 2.1	5.9 ± 1.8
BASDAI ≥4, n (%)	384 (83)	253 (89)
ASDAS-CRP, mean +/- SD	3.6 ± 1.0	3.8 ± 0.9
ASDAS inactive disease, n (%)	4 (1)	0 (0)
ASDAS low disease activity, n (%)	22 (5)	5 (2)
ASDAS high disease activity, n (%)	203 (44)	121 (42)
ASDAS very high disease activity, n (%)	234 (51)	160 (56)
CRP, mg/dL, mean +/- SD †	2.4 ± 3.0	2.4 ± 2.9
Elevated CRP, n (%) ** †	324 (77)	227 (79)
BASFI (0-10), mean +/- SD [N=414]	5.2 ± 2.4	5.4 ± 2.3
bDMARD, n (%)	421 (91)	286 (100)
Infliximab	109 (26)	74 (26)
Adalimumab	123 (29)	86 (30)
Etanercept	102 (24)	68 (24)
Golimumab	81 (19)	54 (19)
Certolizumab Pegol	3 (1)	2 (1)
Secukinumab	3 (1)	2 (1)
Previous co-medication, n (%):		
NSAIDs	169 (40)	116 (41)
csDMARDs	213 (51)	154 (54)
Oral steroids	77 (18)	57 (20)

All ASAS axSpA (ASAS 'eligible population'): axSpA patients according to ASAS criteria, irrespective of being treated with bDMARD, with complete 6 months of follow-up and BASDAI/ASDAS data at baseline (irrespective of having ASDAS/BASDAI at any other timepoint). ASAS bDMARD treated with full data (ASAS 'efficacy population'): axSpA patients according to ASAS criteria treated with bDMARD, with complete 6 months of follow-up and complete data on all response outcomes (every timepoint). † <10% of missing data. * Arterial hypertension and other cardiovascular diseases, dyslipidemia, diabetes mellitus, thyroid disease and malignancies. ** Defined as ≥0.5mg/dL. ASAS, Assessment of SpondyloArthritis international Society. axSpA, axial spondyloarthritis. bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs. BMI, Body Mass Index. HLA-B27, Human Leucocyte Antigen B27. mNY, modified New York criteria for Ankylosing Spondylitis. MRI-SU, Magnetic Resonance Imaging of Sacroiliac joints. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. ASDAS, Ankylosing Spondylitis Disease Activity Score. CRP, C Reactive Protein. BASFI, Bath Ankylosing Spondylitis Functional Index. NSAIDs, Non-Steroid Anti-inflammatory Drugs. csDMARDs, conventional synthetic Disease Modifying Anti-Rheumatic Drugs.

Online Supplementary Table S4. Subgroups according to BASDAI/ASDAS category in patients fulfilling the ASAS axSpA Classification Criteria within the 'eligible population'

	ASDAS ≥2.1	ASDAS <2.1	Total
BASDAI ≥4	381	3	384
BASDAI <4	51	28	79
Total	432	31	**463***

* Subgroups of axSpA fulfilling the ASAS criteria, according to BASDAI/ASDAS category at baseline' (i.e. treated or not with bDMARD, with complete 6 months of follow-up)

Online Supplementary Table S5. Baseline patient- and disease-characteristics in patients fulfilling the ASAS axSpA Classification Criteria within the 'eligible population', and across all subgroups according to BASDAI/ASDAS category

Variables	Overall (N= 463)	ASDAS ≥2.1		ASDAS <2.1		p-value ‡
		BASDAI ≥4 (N=381)	BASDAI <4 (N=51)	BASDAI ≥4 (N=3)	BASDAI <4 (N=28)	
Age in years, mean +/- SD	49 ± 12	49 ± 12	48 ± 13	43 ± 10	49 ± 13	0.84
Gender (male), n (%)	270 (58)	208 (55)	41 (80)	1 (33)	20 (71)	**<0.01**
BMI in Kg/m^2, mean +/- SD [N=254]	25.9 ± 4.6	26.1 ± 4.7	24.3 ± 3.8	. (.)	26.5 ± 3.3	0.08
Current smokers, n (%) † [N=424]	99 (23)	85 (24)	9 (19)	0 (0)	5 (21)	0.03
Age at diagnosis in years, mean +/- SD †	35 ± 12	35 ± 12	33 ± 11	32 ± 17	39 ± 13	0.18
Disease duration in years, mean +/- SD †	13.1 ± 10.6	13.3 ± 10.3	14.1 ± 12.4	13.2 ± 8.5	8.3 ± 9.0	0.12
HLA-B27, n (%)	331 (72)	266 (70)	43 (84)	2 (67)	20 (71)	0.20
Radiographic sacroiliitis (mNY), n (%) †	373 (86)	306 (85)	43 (92)	3 (100)	21 (88)	0.60
Sacroiliitis on MRI-SIJ, n (%) [N=192]	127 (66)	104 (65)	9 (53)	2 (100)	12 (100)	0.03
Number of SpA features +/- SD †	2.6 ± 1.2	6.4 ± 1.5	2.8 ± 0.9	5.0 ± 0.6	2.0 ± 1.3	**<0.01**
BASDAI (0-10), mean +/- SD	5.8 ± 2.1	6.4 ± 1.5	2.8 ± 0.9	5.0 ± 0.6	2.0 ± 1.3	**<0.01**
ASDAS-CRP, mean +/- SD	3.6 ± 1.0	3.8 ± 0.8	3.0 ± 0.6	1.9 ± 0.3	1.6 ± 0.4	**<0.01**
ASDAS inactive disease, n (%)	4 (1)	0 (0)	0 (0)	0 (0)	4 (14)	**<0.01**
ASDAS low disease activity, n (%)	22 (5)	0 (0)	0 (0)	2 (67)	20 (71)	
ASDAS high disease activity, n (%)	203 (44)	156 (41)	42 (82)	1 (33)	4 (14)	
ASDAS very high disease activity, n (%)	234 (51)	225 (59)	9 (18)	0 (0)	0 (0)	
CRP, mg/dL, mean +/- SD †	2.4 ± 3.0	2.3 ± 3.0	3.2 ± 3.5	0.1 ± 0.0	0.6 ± 0.8	0.08
Elevated CRP, n (%) * †	324 (77)	282 (76)	39 (93)	0 (0)	3 (38)	**<0.01**
BASFI (0-10), mean +/- SD † [N=414]	5.2 ± 2.4	5.7 ± 2.2	3.1 ± 2.0	5.2 (.)	2.2 ± 2.1	**<0.01**
bDMARD therapy, n (%)	421 (91)	369 (97)	42 (82)	2 (67)	8 (29)	**
Infliximab	109 (26)	93 (25)	11 (26)	0 (0)	5 (63)	
Adalimumab	123 (29)	110 (30)	12 (29)	0 (0)	1 (13)	
Etanercept	102 (24)	86 (23)	15 (36)	0 (0)	1 (13)	0.19
Golimumab	81 (19)	74 (20)	4 (10)	2 (100)	1 (13)	
Certolizumab	3 (1)	3 (1)	0 (0)	0 (0)	(0)	
Secukinumab, n (%)	3 (1)	4 (1)	0 (0)	0 (0)	4 (1)	
Co-medication (bDMARD treated)**, n (%)**						
NSAIDs	169 (40)	147 (40)	17 (41)	1 (50)	4 (50)	0.94
csDMARDs	213 (51)	185 (50)	21 (50)	2 (100)	5 (63)	0.49
Oral Corticosteroids	77 (18)	68 (18)	7 (17)	1 (50)	1 (13)	0.66

Overall (ASAS 'eligible population'): axSpA patients according to ASAS criteria, irrespective of being treated with bDMARD, with complete 6 months of follow-up and BASDAI/ASDAS data at baseline (irrespective of having ASDAS/BASDAI at any other timepoint). ‡ comparison across all subgroups according to BASDAI/ASDAS category of disease activity (ANOVA test for continuous variables and Chi2 for categorical variables). † <10% of missing values. * Defined as ≥0.5mg/dL. ** p-value of <0.01 for the categorical variable (treated or not with bDMARD). BMI, Body Mass Index. HLA-B27, Human Leucocyte Antigen B27. mNY, modified New York criteria for Ankylosing Spondylitis. MRI-SU, Magnetic Resonance Imaging of Sacroiliac joints. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. ASDAS, Ankylosing Spondylitis Disease Activity Score. CRP, C Reactive Protein.

BASFI, Bath Ankylosing Spondylitis Functional Index. bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs. NSAIDs, Non-Steroid Anti-inflammatory Drugs. csDMARDs, conventional synthetic Disease Modifying Anti-Rheumatic Drugs.

Online Supplementary Table S6. Response to bDMARD in patients fulfilling the ASAS axSpA Classification Criteria within the ‚efficacy population' according to the BASDAI/ASDAS category

Variables	Overall (N=286)	ASDAS ≥2.1		ASDAS <2.1	
		BASDAI ≥4 (N=252)	BASDAI <4 (N=26)	BASDAI ≥4 (N=1)	BASDAI <4 (N=7)
	Probability of response (95% CI)				
Outcomes - 3 months					
ASAS20	62 (56; 67)	63 (57; 68)	58 (43; 73)	*	*
ASAS40	44 (39; 50)	46 (41; 52)	27 (12; 42)	*	40 (7; 73)
ASAS PR	28 (23; 33)	24 (19; 29)	69 (57; 82)	*	*
BASDAI50	62 (57; 67)	62 (57; 68)	62 (47; 76)	*	*
ASDAS CII	65 (60; 70)	66 (60; 71)	73 (59; 87)	*	*
ASDAS MI	41 (35; 46)	42 (36; 48)	38 (26; 51)	*	*
ASDAS ID	31 (27; 36)	27 (22; 32)	69 (56; 83)	*	*
Outcomes - 6 months					
ASAS20	65 (59; 70)	65 (59; 70)	65 (48; 83)	*	*
ASAS40	43 (38; 48)	46 (40; 51)	23 (11; 35)	*	40 (7; 73)
ASAS PR	28 (24; 34)	25 (21; 30)	52 (39; 65)	*	*
BASDAI50	65 (60; 70)	67 (61; 72)	54 (39; 69)	*	*
ASDAS CII	70 (65; 75)	72 (67; 77)	69 (58; 81)	*	*
ASDAS MI	43 (38; 48)	46 (40; 51)	38 (28; 48)	*	*
ASDAS ID	30 (25; 35)	27 (21; 32)	50 (36; 64)	*	*

Overall (ASAS 'efficacy population'): axSpA patients according to ASAS criteria, treated with bDMARD, with complete 6 months of follow-up and complete data on all response outcomes (every time point). Estimated probability of response across all subgroups according to BASDAI/ASDAS category of disease activity using a logistic regression model adjusted for age, gender, CRP and BASFI. * Models fail to converge. 95% CI, 95% confidence interval. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. ASDAS, Ankylosing Spondylitis Disease Activity Score. ASAS PR, ASAS Partial Remission. ASDAS CII, ASDAS Clinical Important improvement. ASAS MI, ASDAS Major Improvement.