2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis

Online supplementary material

1. Introduction

A systematic literature review (SLR) was performed to inform the ASAS/EULAR task force on the new evidence for the efficacy and safety of the treatment of axSpA with biological (b)DMARDs, targeted synthetic (ts)DMARDs and non-biological (including non-pharmacological) interventions[1,2]. In addition, evidence retrieved by the SLR was used to inform the task force on two additional and complementary questions: 1) How is the performance of ASDAS as compared to BASDAI in selecting axSpA patients for treatment with TNFi?; 2) How do the ASDAS response criteria compare to the ASAS response criteria in axSpA patients treated with TNFi and which are the best response criteria to use when monitoring treatment in patients with axSpA?

2. Methods (selection of studies)

Types of studies: Randomized clinical trials, controlled clinical trials and cohort-studies/registries, captured by the SLR[1,2]. In addition, references of the included studies were screened and a hand search was performed for relevant studies.

The study questions were rephrased according to the PICO format:

Table S1. PICO for question 1

Patients	Adults (≥ 18 years) with axial spondyloarthritis.
Intervention	Active disease as defined by: High ASDAS (≥2.1), very high ASDAS (≥3.5), ASDAS≥2.1 + positive expert opinion, ASDAS ≥3.5 + positive expert opinion.
Comparison	Active disease as defined by: BASDAI ≥4, BASDAI≥4 + expert opinion, BASDAI≥4 + spinal pain [on a visual analog scale; during the past week] ≥ 4 cm.
Outcomes	i) Prognostic factors associated with better response to biologic therapy [e.g. lower age, shorter disease duration, lower BASFI, higher CRP, active sacroiliitis on MRI and HLA-B27-positive status, other]; ii) response to TNFi; iii) difference in the number of patients selected by each criterion.

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index CRP, C-reactive protein; MRI, magnetic resonance imaging,

Table S2. PICO for question 2

Patients	Adults (≥ 18 years) with axial spondyloarthritis.
Intervention	ASDAS response criteria (including clinically important improvement, major improvement and inactive disease).
Comparison	ASAS response criteria (including ASAS20, ASAS40, ASAS5/6 and ASAS partial remission), BASDAI resp
Outcomes	Difference in standardized measures of treatment-effect Cohen's Kappa, Intraclass correlation coefficient, sensitivity, specificity.

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASAS, Assessment in SpondyloArthritis international Society; BASDAI resp, BASDAI response (BASDAI 50 or BASDAI 2-point).

3. Results

3.1. Criteria to start biological therapy

Two studies were identified:

i) Study one:

Table S3. Study main characteristics

Study (registry)	Vastesaeger 2014[3] (REGISPONSER)
Study design	Cross-sectional (multi-centre)
Type of patients (sample size)	AS patients (mNY) (N=1,156)
Outcome time-point	NA
Study groups	Cross-tabulation according to ASDAS [inactive disease, moderate disease activity, high disease activity, very high disease activity] and BASDAI (<4 vs ≥ 4)

NA, not applicable; AS, ankylosing spondylitis, mNY, modified New York criteria; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

Table S4. Cross-tabulation between BASDAI and ASDAS

ASDAS disease activity states	BASDAI ≥ 4	BASDAI <4	Total
Moderate disease activity			
ASDAS < 1.3	0 (0%)	142 (25%)	1,014
ASDAS ≥ 1.3	588 (100%)	426 (75%)	142
Total	588	568	1,156
High disease activity			
ASDAS < 2.1	32 (5.4%)	358 (63%)	1,014
ASDAS ≥ 2.1	556 (94.6%)	210 (37%)	142
Total	588	568	1,156
Very high disease activity			
ASDAS < 3.5	316 (53.7%)	552 (97.2%)	1,014
ASDAS ≥ 3.5	272 (46.3%)	16 (2.8%)	142
Total	588	568	1,156

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

- 37% with BASDAI<4 are captured by high disease activity as defined by ASDAS ≥ 2.1 with few (5.4%) being not selected.

Table S5. Characteristics of patients with high disease activity according to BASDAI and ASDAS

Characteristics	BASDAI ≥ 4 (n=588)	ASDAS ≥ 2.1 (n=766)
Age ≤ 40 years	23.1%	26.4%
HLA-B27 positive	83.5%	85.1%
Never had enthesitis	58.2%	61.7%
BASFI < 4.5	37.1%	46.6%
CPR ≥0.6 (mg/dL)	54.4%	62.4%

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein.

- Patients captured by ASDAS ≥ 2.1 are younger, have lower BASFI and higher CRP as compared to those with high disease activity according to BASDAI and these are prognostic markers of a higher likelihood to respond to TNFi[4].

ii) Study two:

Table S6. Study main characteristics

Study (registry)	Fagerli 2012[5] (NOR-DMARD)
Study design	Prospective observational cohort
Type of patients (sample size)	AS patients (rheumatologist's diagnosis) starting first TNFi according to treating rheumatologist (no formal criteria) (N=212)
Outcome time-point	3 months
Outcomes assessed	ASAS20, ASAS40, ASDAS MI, ASDAS CII, ASDAS I, BASDAI resp, Δ ASDAS, Δ BASDAI, Δ BASFI, Δ SF-6D
Study groups	ASDAS ≥ 2.1 AND BASDAI ≥4 ASDAS ≥ 2.1 AND BASDAI <4 ASDAS < 2.1 AND BASDAI ≥4 ASDAS < 2.1 AND BASDAI <4

AS, ankylosing spondylitis, mNY, modified New York criteria; ASDAS, Ankylosing Spondylitis Disease Activity Score; MI, major improvement; CII, clinically important improvement; I, inactive; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI resp, BASDAI response (BASDAI 50 or BASDAI 2-point); SF-6D, Short Form-6 Dimensions.

Table S7. Baseline characteristics of patients with high disease activity according to BASDAI and ASDAS (cross-tabulation)

	ASDAS ≥ 2.1 (n=260)		**ASDAS <2.1 (n=29)**	
Baseline	**BASDAI ≥ 4 (n=212)**	**BASDAI <4 (n=48)**	**BASDAI ≥ 4 (n=4)**	**BASDAI <4 (n=25)**
Age (years), mean (SD)	43.0 (11.5)	40.1 (10.3)	42.8 (9.6)	40.8 (10.6)
Male (%)	64.2	75.0	75.0	80.0
Disease duration (years), mean (SD)	10.2 (10.3)	10.0 (9.3)	6.1 (7.0)	8.2 (9.1)
HLA-B27 (%)	89.7	95.2	75.0	90.5
CRP (mg/L), median (IQR)	9.0 (5.0-18.8)	16.0 (6.0-24.8)	1.0 (1.0-1.8)	5.0 (1.0-6.0)
ASDAS, mean (SD)	3.72 (0.79)	2.83 (0.50)	1.91 (0.14)	1.76 (0.27)
BASDAI, mean (SD)	6.34 (1.28)	2.96 (0.85)	4.94 (0.51)	2.39 (2.20)

BASFI, mean (SD)	4.95 (1.96)	2.73 (1.68)	2.41 (0.89)	2.19 (2.20)

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; SD, standard deviation.

- 65.8% with BASDAI<4 are captured by ASDAS ≥ 2.1 with few (1.9%) being not selected. Patients fulfilling both criteria have higher baseline disease activity (BASDAI and ASDAS), but those fulfilling only ASDAS have higher CRP and lower BASFI, which are factors that predict a higher response rate to TNFi.

Table S8. Three-month outcomes for patients with high disease activity according to BASDAI and ASDAS (cross-tabulation)

	ASDAS ≥ 2.1 (n=260)		**ASDAS <2.1 (n=29)**	
Outcome (3 months)	**BASDAI ≥ 4 (n=212)**	**BASDAI <4 (n=48)**	**BASDAI ≥ 4 (n=4)**	**BASDAI <4 (n=25)**
ASAS20 (%)	67.0	55.3	0.0	13.0
ASAS40 (%)	50.5	34.0	0.0	4.3
ASDAS MI (%)	40.6	18.2	0.0	0.0
ASDAS CII (%)	65.6	75.0	0.0	13.0
ASDAS Inactive (%)	26.7	52.3	0.0	56.5
BASDAI resp (%)	66.8	NA	66.7	NA
Δ ASDAS mean (SD)	-1.63 (1.19)	-1.47 (0.85)	-0.28 (0.24)	-0.31 (0.99)
Δ BASDAI mean (SD)	-3.02 (2.26)	-1.41 (1.09)	-2.67 (1.07)	-0.53 (1.50)
Δ BASFI mean (SD)	-1.99 (2.02)	-0.90 (1.07)	-1.77 (0.72)	-0.29 (1.08)
Δ SF-6D mean (SD)	0.10 (0.10)	0.06 (0.08)	0.07 (0.08)	0.04 (0.09)

ASDAS, Ankylosing Spondylitis Disease Activity Score; MI, major improvement; CII, clinically important improvement; I, inactive; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI resp, BASDAI response (BASDAI 50 or BASDAI 2-point); SF-6D, Short Form-6 Dimensions.

- Better responses among patients fulfilling both criteria but still remarkable responses for the smaller group only fulfilling ASDAS.

iii) Conclusions

- ASDAS high disease activity definition (≥ 2.1) captures more patients otherwise missed by BASDAI (≥4) with only few being 'lost'.
- Patients captured by ASDAS high disease activity (only) show a higher prevalence of features that have been associated with better response to TNFi.
- Patients with high disease activity according to ASDAS show remarkable response rates in different domains only surpassed by those fulfilling both the BASDAI and ASDAS criteria (possibly reflecting baseline features).

3.2. Response criteria

One study identified:

Table S9. Study main characteristics

Study (trial)	van der Heijde 2012[6] (ASCEND)
Study design	Post-hoc analysis of a randomized, double-blind, active-comparator trial
Type of patients (sample size)	AS patients (mNY) included in the ASCEND trial (N=566)
Outcomes time-point	4 months
Outcomes assessed	ASAS20, ASAS40, ASAS5/6, ASAS partial remission, ASDAS MI, ASDAS CII, ASDAS I
Study groups	Etanercept 50 mg/week Sulfasalazine ≤ 3 g/day

AS, ankylosing spondylitis, mNY, modified New York criteria; ASDAS, Ankylosing Spondylitis Disease Activity Score; MI, major improvement; CII, clinically important improvement; I, inactive; ASAS, Assessment in SpondyloArthritis international Society.

Table S10. Adjusted treatment difference across outcomes

Outcome	Adjusted treatment difference, % (SD)
ASDAS CII (≥1.1)	34.3 (47.1)
ASDAS <2.1	29.4 (46.9)
ASAS 40	26.8 (47.9)
ASAS 5/6	22.8 (45.2)
ASDAS MI (≥2.0)	21.9 (38.4)
ASAS 20	21.8 (47.4)

ASDAS <3.5	21.8 (43.3)
ASAS partial remission	17.2 (40.8)
ASDAS inactive (<1.3)	16.4 (34.6)

ASDAS, Ankylosing Spondylitis Disease Activity Score; MI, major improvement; CII, clinically important improvement; ASAS, Assessment in SpondyloArthritis international Society.

Study main findings:

- ASDAS clinical important improvement and ASDAS major improvement have shown a discriminatory ability for treatment effects similar to ASAS 20 and ASAS 40.
- ASDAS inactive disease has shown similar discrimination for treatment effects as compared to ASAS partial remission.

4. References

1. Sepriano A, Regel A, van der Heijde D, et al. Efficacy and safety of biological and targeted synthetic DMARDs: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. 2016, Submitted for publication.

2. Regel A, Sepriano A, Baraliakos X, et al. Efficacy and safety of non-pharmacological and non-biological pharmacological treatment: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. 2016, Submitted for publication.

3. Vastesaeger N, Cruyssen BV, Mulero J, et al. ASDAS high disease activity versus BASDAI elevation in patients with ankylosing spondylitis as selection criterion for anti-TNF therapy Reumatol Clin. 2014;10:204-9.

4. Maneiro JR, Souto A, Salgado E, et al. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. RMD Open. 2015 Feb 18;1(1):e000017.

5. Fagerli KM, Lie E, van der Heijde D, et al. Selecting patients with ankylosing spondylitis for TNF inhibitor therapy: comparison of ASDAS and BASDAI eligibility criteria. Rheumatology (Oxford) 2012;51:1479-83.

6. van der Heijde D, Braun J, Dougados M, et al. Sensitivity and discriminatory ability of the Ankylosing Spondylitis Disease Activity Score in patients treated with etanercept or sulphasalazine in the ASCEND trial. Rheumatology (Oxford) 2012;51:1894-905.