Clinical and Experimental Rheumatology 2010; 28: 752-755.

Active disease requiring TNF-alpha-antagonist therapy can be well discriminated with different ASDAS sets: a prospective, follow-up of disease activity assessment in ankylosing spondylitis

S.Z. Aydin[1,2], M. Can[2], P. Atagunduz[2], H. Direskeneli[2]

[1]*Academic Unit of Musculoskeletal Disease, University of Leeds, Leeds, UK;* [2]*Marmara University Faculty of Medicine, Rheumatology, Istanbul, Turkey.*

Sibel Z. Aydin, MD
Meryem Can, MD
Pamir Atagunduz, Associate Professor
Haner Direskeneli, Professor

Please address correspondence and reprint requests to:
Dr Sibel Zehra Aydin,
University of Leeds,
Academic Unit of Musculoskeletal Disease,
Chapel Allerton, LS7 4SA Leeds,
United Kingdom.
E-mail: drsibelaydin@gmail.com

Received on April 6, 2010; accepted in revised form on May 25, 2010.

Key words: Disease activity assessment, ASDAS, ankylosing spondylitis

Competing interests: none declared.

ABSTRACT

Objective. *To evaluate the validity of different ASDAS sets to assess disease activity in ankylosing spondylitis (AS) in comparison to standard activity assessment tools in routine clinical setting and to determine the best cut-off values for deciding active disease requiring TNF-α antagonist therapy.*

Methods. *Two hundred consecutive AS patients (M/F:104/96) were enrolled. Mean (SD) age was 40.3 (11.7) and disease duration was 11 (8.5) years. Disease activity was assessed by four different ASDAS sets, BASDAI, patient and physicians' global assessments, ESR and CRP. The correlation between different parameters and ASDAS scores of patients requiring TNF-α antagonist therapy were determined.*

Results. *At the time of the assessment 18.5% of the patients were only having NSAIDs, 43% were receiving sulphasalazine and/or methotrexate and 38.5% were under TNF-α antagonists. After the evaluation, 36 (18%) patients were decided to require TNF-α antagonist therapy, 33 (16.5%) patients were started sulphasalazine or methotrexate or their dose increased and 131 (65.5%) patients were decided to be stable without any requirement for a change in therapy. The patients requiring new-TNFa antagonist therapy had significantly higher ASDAS values. The ROC curve analysis revealed best-cut off values for ASDAS sets (ASDAS A: 3.28, ASDAS B: 3.07, ASDAS C: 2.38 and ASDAS D: 3.1) When standardised mean differences were compared, ASDAS B was the best set within the others, but not significantly different from other ASDAS sets and standard assessment tools except acute-phase reactants.*

Conclusion. *ASDAS sets perform well to discriminate TNF-α antagonist requirement in advanced AS patients. However BASDAI and patient's or physician's global assessments also had acceptable performances in our clinical setting.*

Introduction

Ankylosing spondylitis (AS) is an inflammatory rheumatological disorder of the spine with diverse symptoms and findings, complicating the assessment of disease activity. The most commonly used domains are mostly patient-reported and are either single variables, like pain and stiffness, patient's or doctor's global assessment (PatGA, PhyGA) and acute phase reactants or the widely accepted index, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) (1-2). Because of the limited face and construct validity of interpreting a single variable and the variable redundancy of BASDAI, a need for developing a composite disease activity score for the assessment of AS has emerged. With the increasing use of biologic therapies, the necessity of better response assessment is also another important reason to have a disease activity index (3). AS disease activity score (ASDAS) was developed by the Assessment of SpondyloArthritis international Society (ASAS), following a similar approach for DAS28 development in rheumatoid arthritis (4). Four ASDAS scores were modeled (Table I). This weighted index was validated first in OASIS database (5) and in a dataset of patients participating in clinical trials with TNF-α antagonists (4, 6). Despite little differences between ASDAS sets, ASDAS C was voted as the preferred set by the ASAS members because of including CRP levels, mainly based on feasibility and cost issues and having the advantage of including a non-patient reported measure. In a recent study, ASDAS C was tested for its responsiveness on a group of patients recruited in a previous drug trial (BIOSPA) and also found more sensitive to change compared to the conventional measurements (7).

In this study we aimed to evaluate the validity of different ASDAS sets to assess disease activity in AS in comparison to BASDAI, PatGA, PhyGA, ESR and CRP levels in our prospective cohort and determine the best cut-off values to detect the optimum level requiring TNF-α antagonist therapies.

Methods

Consecutive AS patients (n=200, M/F: 104/96) followed in Marmara University between February-May 2009 and diagnosed according to modified New

Table I. Discriminatory ability: Standardised mean difference (SMD) between patients with active and inactive disease according to A) requiring anti-TNF therapy *vs*. no drug modification other than NSAIDs and B) high (>6) versus low (<4) disease activity according to the patient's global assessment (PatGA)

	A) drug modification			B) PatGA		
	no drug modification (n=131)	requiring TNF-α-antagonists (n=36)	SMD	PGA<4 (n=84)	PGA>6 (n=54)	SMD
ASDAS A*	2.33 (1.03)	4.15 (1.2)	1.7	1.84 (0.72)	4.31 (1.02)	2.92
ASDAS B*	2.11 (0.89)	3.88 (1.04)	1.92	1.62 (0.53)	4.04 (0.9)	3.46
ASDAS C*	1.87 (0.86)	3.73 (1.17)	1.72	1.37 (0.74)	3.91 (0.99)	3
ASDAS D*	2.35 (1.06)	4.17 (1.19)	1.67	1.92 (0.79)	4.26 (1.09)	2.58
BASDAI	2.3 (1.85)	5.87 (2.14)	1.87	1.43 (1)	6.24 (1.99)	3.31
PatGA	3.35 (2.15)	7.36 (2.23)	1.86			
PhyGA	2.69 (2.06)	6.64 (2)	1.94	1.56 (1.3)	6.93 (1.51)	3.89
ESR	19.47 (15.38)	36.17 (28)	0.89	16.42 (12.34)	34.81 (28.17)	0.92
CRP	7.43 (11.21)	25.5 (42.31)	0.83	5.73 (7.23)	24.19 (39.71)	0.73

Results are given as mean (SD).
*ASDAS A: Back pain, morning stiffness, patient global, ESR, CRP.
*ASDAS B: Back pain, morning stiffness, patient global, pain/swelling of the peripheral joints, ESR.
*ASDAS C: Back pain, morning stiffness, patient global, pain/swelling of the peripheral joints, CRP.
*ASDAS D: Back pain, morning stiffness, fatigue, ESR, CRP.

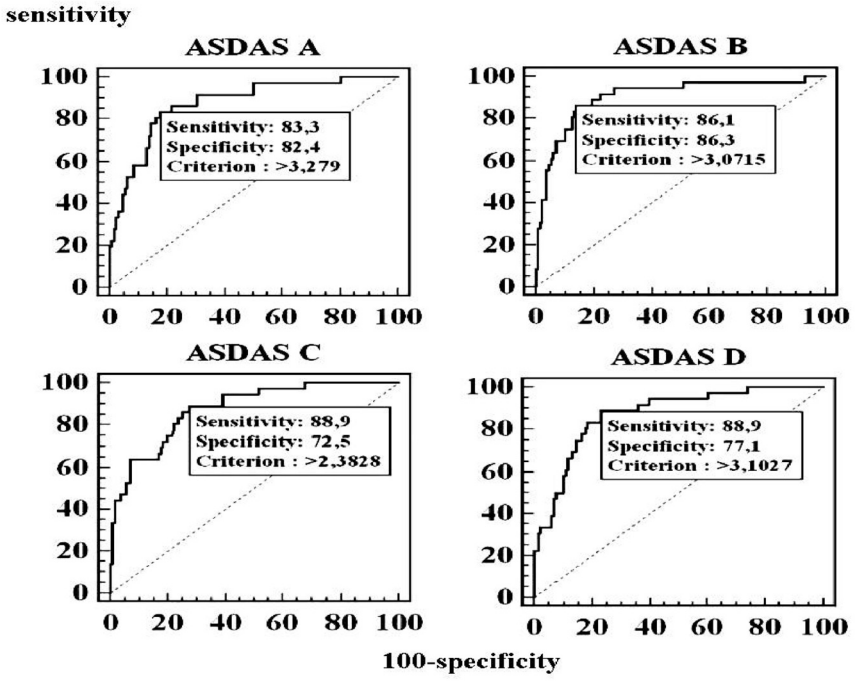

Fig. 1. ROC curves for ASDAS sets: ROC curve, obtained by plotting sensitivity for detecting AS patients requiring anti-TNF therapy (y-axis) against specificity (x-axis). Patients having a stable disease without a drug modification were used as the control group for determining specificity.
A) ROC curve for ASDAS A. Area under curve = 0.884.
B) ROC curve for ASDAS B. Area under curve = 0.899.
C) ROC curve for ASDAS C. Area under curve = 0.875.
D) ROC curve for ASDAS D. Area under curve = 0.789.

York criteria were enrolled (8). Mean (SD) age was 40.3 (11.7) years and disease duration 11 (8.5) years. Fifty-seven percent had peripheral joint involvement. HLA B27 was available in 127 patients and 90 of them (70.9 %) was positive. Mean (SD) BASDAI was 3.4 (2.6), ESR was 24.7 (21.2) mm/h and CRP was 12.2 (23.8) mg/l.

Disease activity was assessed by BASDAI, PatGA, PhyGA for the last week, ESR and CRP levels. Current treatments and decisions for change after assessment including NSAIDs (non steroidal anti-inflammatory drugs), sulphasalazine, methotrexate and TNF-α antagonists were recorded. The need for TNF-α antagonist therapy was decided with a standard protocol as having BASDAI ≥4 and persistent symptoms either due to peripheral arthritis, enthesitis or axial involvement.

The study was approved by the Ethics Committee of Marmara University Medical School and informed consent was obtained from all patients.

Statistical analysis

Four sets of ASDAS were calculated (6). Briefly, the clinical variables used in ASDAS sets were obtained from the BASDAI questions (Back pain-question (Q2), duration of morning stiffness (Q6), peripheral pain / swelling (Q3) and fatigue (Q1) which were all on a numerical rating scale (from 0 to 10).

The correlation between PatGA, PhyGA and all components of BASDAI as well as the combined scores was analyzed by Pearson's correlation test. Active vs inactive disease was defined as: 1. Patients requiring TNF-α antagonist therapy and 2. PatGA for disease activity >6 *vs*. <4. The discriminative value of ASDAS sets to detect patients with active disease was assessed with standardised mean difference (SMD), calculated by dividing the differences of the group means to the pooled SD of the group means. A receiver operating characteristics (ROC) curve was generated to find the best cut-off value of ASDAS sets for deciding TNF-α antagonist therapy requirement. Package MedCalc software (V.4.2.0 for Windows) was used for statistical analyses.

Results

At the time of the assessment 37/200 (18.5%) of the patients were only having NSAIDs, 86/200 (43%) were receiving sulphasalazine and/or methotrexate and 77/200 (38.5%) were under TNF-α antagonists. After the evaluation 36 (18%) patients were decided to require TNF-α antagonist therapy, 33 (16.5%) were decided to start sulphasalazine/methotrexate or their doses increased and 131 (65.5%) were decided to be stable and not require any change in therapy.

Patients requiring new TNF-α antagonist therapy had significantly higher ASDAS values (3.73–4.17 *vs*. 1.87–2.35) (Table I). The ROC curve analysis revealed best-cut off values for ASDAS sets (ASDAS A: 3.28, ASDAS B: 3.07, ASDAS C: 2.38 and ASDAS D: 3.1) (Fig. 1). When SMDs were compared, ASDAS B was only slightly higher within the others, except acute-phase reactants. When active disease was determined according to PatGA, all ASDAS sets had SMDs between 2.58 and 3.46 with a similar SMD for BASDAI (3.31) and PhyGA (3.89).

PatGA and PhyGA had an excellent correlation (0.87). Therefore the correlation between ASDAS sets, BASDAI parameters and both PatGA and PhyGA were found to be similar (Table II). BASDAI had a better correlation with both assessments (0.8) compared to individual BASDAI parameters (0.54–0.75). Among ASDAS sets, ASDAS B had slightly better correlations with PatGA and PhyGA (0.8–0.86). The correlation with acute phase reactants was only fair (0.32–0.39).

Patients with peripheral arthritis had significantly higher BASDAI, ASDAS B and ASDAS C levels (without vs with peripheral arthritis- BASDAI: 2.84±2.38 *vs*. 4±2.62, p=0.002; ASDAS B: 2.41±1.17 *vs*. 2.88±1.22, p=0.005; ASDAS C: 2.2±1.25 *vs*. 2.62±1.39, p=0.035). However, ASDAS A, D and acute phase responses were similar in both groups (without *vs*. with peripheral arthritis – ASDAS A: 2.73±1.28 *vs*. 3.03±1.37, p=0.1; ASDAS D: 2.75±1.32 *vs*. 3.05±1.4, p=0.1; ESR: 24.4±22.2 *vs*. 25.6±21.4, p=0.5; CRP: 10.5±15.5 *vs*. 13.8±29.2, p=1).

Table II. Pearson correlations between the 4 ASDAS scores, the components of BASDAI and the disease activity assessments with patient's global and physician's global scores. PatGA: patient's global assessment. PhyGA: physician's global assessment.

	Patient's global	Physician's global
ASDAS A	0.80	0.75
ASDAS B	0.86	0.80
ASDAS C	0.81	0.77
ASDAS D	0.74	0.71
Patient global (0–10)		0.87
BASDAI (0–10)	0.8	0.8
BASDAI-1 fatique (0–10)	0.69	0.68
BASDAI-2 back pain (0–10)	0.75	0.72
BASDAI-3 pain/swelling peripheral joints (0–10)	0.63	0.62
BASDAI-4 enthesitis (0–10)	0.54	0.56
BASDAI-5 severity of morning stifness (0–10)	0.73	0.75
BASDAI-6duration of morning stifness (0–10)	0.63	0.62
ESR (mm/hr)	0.39	0.36
CRP (mg/lt)	0.35	0.32

Discussion

We assessed ASDAS as a new composite tool with different variables incorporated in a single, composite index in our routine AS outpatient setting. When we determined SMDs, all ASDAS sets performed well to differentiate active disease requiring TNF-α antagonists (SMDs between 1.72–1.9), being ASDAS D the lowest (SMD: 1.67). ASDAS D might have an advantage of including "two non-patient-reported measures", however half of our AS patients had low acute phase response, limiting their use in a composite index. The lowest SMDs in our cohort were observed with acute phase reactants (0.83–0.89) and this might be reflected with the low capacity of ASDAS D having both ESR and CRP. Interestingly, ASDAS A also have two acute-phase reactants and seemed to perform better, suggesting that having "patient global" in ASDAS A instead of "fatigue" in ASDAS D might be a better discriminatory parameter, possibly related to the non-specific feature of "fatigue" in relationship with disease activity.

Both PatGA and PhyGA as well as BASDAI performed comparably to ASDAS A-C in our study (SMDs: 1.86–1.94). This was somewhat different to the previous study by van der Heijde *et al*. which showed a much better discriminatory capacity of ASDAS sets (SMDs 1.50–1.59) compared to BASDAI (1.09), PatGA (1.09) and PhyGA (1.24) and the study by Lukas *et al*. also better with ASDAS sets (1.07–1.18) *vs*. BASDAI (0.81) and PatGA (0.81) (4, 6). When disease activity was determined according to PatGA or TNF-α requirement, all ASDAS sets (except ASDAS D) performed well, similar to BASDAI in our study. In previous sets the discriminatory capacity of BASDAI seemed lower for TNF-α antagonist therapy requirement (which depends on a more complex evaluation usually with acute-phase response) but performed better with PatGA, possibly related to its patient-derived nature.

Our other explanation for discrepant results between our and previous studies might be related to our patient selection which were part of a prospective AS cohort and were given education about self-assessment using BASDAI on a weekly basis. The success of BASDAI in our study with similar SMDs to ASDAS sets may therefore be due to the familiarity of patients to self-disease assessment and may decrease the external validity of our study. Another issue is the high prevalence of peripheral arthritis in our cohort which may limit the generalisation of our results.

PatGA and PhyGA also had a good correlation in our study (0.87). This was also better compared to NORDMARD database analysis (0.3) (6). When PhyGA is compared to different sets and BASDAI, the discriminatory value of ASDAS sets performed better to BASDAI (1.1–1.48 *vs*. 0.75) in other studies. We think, in real practice, high acute-phase response might influence the decision of physicians' for treatment choices especially for TNF-α antagonist requirement. In these settings, ASDAS sets might be better instruments as they all incorporate acute-phase response.

Although no clear decision seems to have emerged on which ASDAS set will dominate in studies and routine clinical practice depending on their performances, most ASAS members

are reported to vote for a single-acute phase reactant, making ASDAS B or C, the choice. ASDAS C which includes CRP level was finally preferred by the ASAS members, and ASDAS B with ESR was suggested to be chosen when CRP level was not available (6). However preference of CRP over ESR by the ASAS group was not based on performances, rather the availability of CRP as a more standard tool that can also be performed in a central laboratory from a stored sample and is better for multicenter studies.

Following this recommendation, the responsiveness of ASDAS C after commencing TNF-α antagonist therapies was tested by Pedersen *et al*., supporting the superiority of ASDAS C compared to the conventional measurements, but other ASDAS sets were not tested in this cohort (7). Our results also confirmed choosing an ASDAS set including an acute phase reactant, as both sets performed best both in discriminating TNF-α antagonist therapy requirement and having a good correlation with PatGA and PhyGA, despite the relatively low SMD's of acute phase reactants when assessed alone. We found slightly better results with ASDAS B compared to ASDAS C, similar to the previous studies (4, 6).

All ASDAS sets except ASDAS D seem to perform well in routine clinical practice. However we could not confirm their higher discriminatory value compared to BASDAI and PatGA/PhyGA.

References

1. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
2. SPOORENBERG A, VAN TUBERGEN A, LANDEWÉ R *et al*.: Measuring disease activity in ankylosing spondylitis: patient and physician have different perspectives. *Rheumatology* 2005; 44: 789-95.
3. KALDEN JR: Biologics in the treatment of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009; 27 (Suppl. 55): 164-7.
4. LUKAS C, LANDEWÉ R, SIEPER J *et al*.: Assessment of SpondyloArthritis international Society. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 18-24.
5. HEIBERG MS, NORDVÅG B-Y, MIKKELSEN K *et al*.: The comparative effectiveness of tumor necrosing factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis. A six-month, longitudinal, observational, multicenter study. *Arthritis Rheum* 2005; 52: 2506-12.
6. VAN DER HEIJDE D, LIE E, KVIEN TK *et al*.: The ASDAS is a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 1811-8.
7. PEDERSEN SJ, SØRENSEN IJ, HERMANN KG *et al*.: Responsiveness of the Ankylosing Spondylitis Disease Activity Score (ASDAS), and clinical and magnetic resonance imaging measures of disease activity in a 1 year follow-up study of patients with axial spondyloarthritis treated with TNF-alpha inhibitors. *Ann Rheum Dis* 2010; 69: 1065-71.
8. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.