Endorsement of Definitions of Disease Activity States and Improvement Scores for the Ankylosing Spondylitis Disease Activity Score: Results from OMERACT 10

PEDRO M.M.C. MACHADO, ROBERT B.M. LANDEWÉ, and DÉSIRÉE M. van der HEIJDE

ABSTRACT. The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a new composite index to assess disease activity in ankylosing spondylitis (AS). Criteria for disease activity states and improvement scores are important for use in clinical practice, observational studies, and clinical trials, and have been proposed by the Assessment of SpondyloArthritis international Society (ASAS). At OMERACT 10, our aim was to obtain endorsement from OMERACT for the ASDAS disease activity states and response criteria proposed by the ASAS membership. This article summarizes the associated discussions, the scientific basis of the validation process, and the results from the voting sessions, and identifies areas for research using the ASDAS. OMERACT participants agreed with the selection of cutoff values, which now have the combined endorsement of ASAS and OMERACT and are ready to be used in clinical practice and in research settings. (J Rheumatol 2011;38:1502–6; doi:10.3899/jrheum.110279)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS
DISEASE ACTIVITY
RESPONSE CRITERIA
OUTCOME ASSESSMENT

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a new composite index to assess disease activity in ankylosing spondylitis (AS)[1]. It combines 5 disease activity variables with only partial overlap, resulting in one single score with better truth (validity), enhanced discriminative capacity, and improved sensitivity to change as compared to single-item variables[1,2]. The Assessment of SpondyloArthritis international Society (ASAS) membership has selected the ASDAS containing C-reactive protein (CRP, mg/l) as the acute-phase reactant as the preferred version, and the one with erythrocyte sedimentation rate (ESR, mm/h) as the alternative version. Apart from the value of CRP or ESR, the 4 additional self-report items included in this index are back pain [visual analog scale (VAS) 0–10 cm, or numerical rating scale (NRS) 0–10], duration of morning stiffness (VAS/NRS), peripheral pain/swelling (VAS/NRS), and patient global assessment of disease activity (VAS/NRS; Table 1)[1,2]. In general, composite indices more accurately reflect the overall state of the disease compared to individual measurements[3,4], which does not dispute the fact that there may be times when single construct measures are more appropriate for judging a specific outcome, because the intervention is directed primarily at one construct and not necessarily to produce a global change.

The next step to consolidate the ASDAS as an instrument to measure disease activity in AS was the development of cutoff values for disease activity states and improvement scores. The selection of cutoffs was driven by patient data supported by a solid methodology, and expert opinion was used only to make decisions about interpretation of the results.

During the 2010 ASAS workshop in Berlin, Germany, cutoff values for the ASDAS were proposed, and cross-validation studies were presented. The methodology and the results were debated by ASAS members and the nomenclature for disease activity states was chosen by consensus: inactive disease, moderate disease activity, high disease activity, and very high disease activity. The 3 values selected to separate these states were < 1.3 between inactive disease and moderate disease activity, < 2.1 between moderate disease activity and high disease activity, and > 3.5 between high disease activity and very high disease activity. Selected cutoffs for improvement scores were a change ≥ 1.1 unit for "minimal clinically important improvement" and a change ≥ 2.0 units for "major improvement"[5].

At the Outcome Measures in Rheumatology Clinical Trials (OMERACT) 10 meeting, in Kota Kinabalu, Malaysia, at a module update, our aim was to obtain endorsement from OMERACT for the ASDAS disease activity states and response criteria proposed by the ASAS membership. This

From the Department of Rheumatology, Coimbra University Hospital, Coimbra, Portugal; Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; and Department of Rheumatology, Maastricht University Medical Center, Maastricht, The Netherlands.

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P.M.M.C. Machado, MD, Department of Rheumatology, Coimbra University Hospital, Department of Rheumatology, Leiden University Medical Center; R.B.M. Landewé, MD, PhD, Department of Rheumatology, Maastricht University Medical Center; D.M.F.M. van der Heijde, MD, PhD, Department of Rheumatology, Leiden University Medical Center.

Address correspondence to Prof. D. van der Heijde, Department of Rheumatology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. E-mail: d.vanderheijde@kpnplanet.nl

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Table 1. The 2 ASDAS formulas selected by the ASAS membership: ASDAS-CRP, the [preferred version, and ASDAS-ESR, the alternative version. Back pain, patient global, duration of morning stiffness and peripheral pain/swelling are all assessed on a visual analog scale (0 to 10 cm) or on a numerical rating scale (0 to 10); back pain, BASDAI question 2; duration of morning stiffness, BASDAI question 6; peripheral pain/swelling, BASDAI question 3.

ASDAS-CRP	$0.12 \times$ back pain $+ 0.06 \times$ duration of morning stiffness $+ 0.11 \times$ patient global $+ 0.07 \times$ peripheral pain/swelling $+ 0.58 \times$ Ln (CRP + 1)
ASDAS-ESR	$0.08 \times$ back pain $+ 0.07 \times$ duration of morning stiffness $+ 0.11 \times$ patient global $+ 0.09 \times$ peripheral pain/swelling $+ 0.29 \times \sqrt{}$ (ESR)

ASDAS: Ankylosing Spondylitis Disease Activity Score; √ (ESR): square root of the erythrocyte sedimentation rate (mm/h); Ln (CRP + 1): natural logarithm of the C-reactive protein (mg/l) + 1; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

article summarizes the discussions and the results from the voting session, and identifies some areas for further research using the ASDAS.

The Module Update Process

Background articles about the development of the ASDAS[1,2] were made available to OMERACT participants as advance reading material. The plenary session started with an introduction reviewing the concept of clinical disease activity and defining the objectives of the module. Next, the methodology used to derive the ASDAS cutoffs was explained, and the results of the cross-validation process were presented for both ASDAS-CRP and ASDAS-ESR.

Participants were then divided into 6 breakout groups, 3 focusing on disease activity states and 3 focusing on improvement scores.

In the breakout sessions, participants were asked if they agreed with the selected cutoffs, taking into account the truth and discrimination filters, and what additional research they recommended. These questions were formulated separately for ASDAS-CRP and ASDAS-ESR. Each group generated a report from their breakout session. A rapporteur for each group reported back in a closing plenary meeting, with further discussion. Finally, the breakout questions were voted on by all OMERACT participants at a second plenary. During the closing plenary, additional questions were posed to explore issues that arose during the first voting session.

Summary of the Development Process and Cross-validation of ASDAS Cutoff Values

The ASDAS was developed by ASAS. To define the cutoffs, we performed receiver-operating characteristic (ROC) analysis against several external criteria, using data from the large Norwegian disease-modifying antirheumatic drug registry (NOR-DMARD)[6]. The registry includes data on patients with ankylosing spondylitis who started treatment with either a conventional DMARD or a tumor necrosis factor-α (TNF-α) blocker.

ASAS members debated and voted to define 4 disease activity states: inactive disease, moderate, high, and very high disease activity. In the ROC analysis, patient and physician global assessments at predefined levels (< 1 cm, < 3 cm, and > 6 cm) were used as external constructs for "inactive disease," to separate "moderate" from "high disease activity," and for "very high disease activity," respectively. Additionally, to determine the cutoff for "inactive disease," ASAS partial remission criteria[7] were also used as an external anchor.

We used several approaches to determine the optimal cutoff — fixed 90% specificity, Youden index, and "closest point to (0,1)"[8]. The final choice was made on clinical and statistical grounds, after voting by ASAS members. Based on the results, the following cutoff values were developed: ASDAS < 1.3 to define inactive disease, 1.3 ≤ ASDAS < 2.1 to define moderate disease activity, 2.1 ≤ ASDAS ≤ 3.5 to define high disease activity, and ASDAS > 3.5 to define very high disease activity.

Regarding improvement scores, the external criterion used for the ROC analysis was a "global rating of change," available in NOR-DMARD. This is a Likert-type scale scored for health change by the patient, according to 5 categories: much better, better, unchanged, worse, and much worse. Selected cutoffs for improvement scores were a change ≥ 1.1 unit for "minimal clinically important improvement" (defined using the patient's report of being better or much better since the start of treatment as an external criterion), and a change ≥ 2.0 units for major improvement (defined using the patient's report of being much better since the start of treatment as an external criterion).

These defined cutoff values were then cross-validated in NOR-DMARD at different timepoints and in the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) database of AS patients participating in a randomized placebo-controlled trial with a TNF blocker[9]. Cross-validation was performed taking into account the aspects of truth and discrimination of the OMERACT filter. The results will be discussed below.

Discussions During Breakout Sessions and Plenary Session

The first part of the discussion was about the aspect of truth[10], i.e., if the proposed ASDAS cutoffs do measure and represent what they are intended to, and if the results are unbiased and relevant.

The ROC analysis was accepted as an adequate method for this type of study. Regarding disease activity states, it was emphasized that there is no universal and broadly accepted "gold standard" for clinical disease activity in AS, and therefore the use of both patient and physician global assessments as external constructs was generally accepted as a valid approach to define the cutoffs. Moreover, it was noted that the

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remarkable consistency among the different external criteria regarding the selection of cutoffs adds to the robustness of the results. The use of arbitrary cutoffs for the external constructs was also discussed, but this was accepted as the only possible approach, and the predefined cutoffs were also accepted by participants to be representative of the disease activity states under study.

Regarding improvement cutoffs, it was highlighted that the use of a "global rating of change" questionnaire (available in NOR-DMARD) from the viewpoint of the patient is a valid approach that has been described as the most adequate method for this purpose[11,12,13]. Another important aspect reemphasizing the validity of the cutoff for "minimal clinically important improvement" (change ≥ 1.1) was that it was beyond the boundaries of measurement error according to several methods that were tested[14,15,16].

The sensitivity and specificity of the cutoffs compared to several external criteria were maintained or even improved in the validation studies, both for disease activity states and for improvement scores.

The discussion about discrimination[10], i.e., whether the measure discriminates between situations of interest, was undertaken mainly by looking at the longitudinal distribution of disease activity states in NOR-DMARD and ASSERT, and by looking at the differences between infliximab and placebo groups and the chi-square values for these differences in the trial population.

In both NOR-DMARD and ASSERT there was a clear longitudinal shift of treated patients from higher disease activity states toward lower disease activity states after initiation of treatments with known efficacy. Moreover, in the trial population, the followup differences between the infliximab and placebo groups clearly discriminated between the 2 treatment arms, and the ASDAS "inactive disease" state was even more discriminative than the ASAS partial remission criteria. Moreover, the comparison between mean values of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and ASDAS across the 4 ASDAS disease activity states during followup showed that ASDAS disease activity states were in agreement with clinically relevant numerical differences in the BASDAI mean values. Regarding improvement scores, the ASDAS-based cutoffs also showed higher discriminatory capacity compared to all currently used response criteria in AS (ASAS20, ASAS40, BASDAI50, and change in BASDAI ≥ 2 units)[7,17,18].

Overall, general comments from the breakout groups highlighted the sound methodology used to develop and validate the cutoff values. The results were considered to be very robust.

Research Agenda for the ASDAS

Participants suggested that the concept of "minimal clinically important worsening" should also be explored, and not only "minimal clinically important improvement." However, this item was not addressed in the current study because there was insufficient data in NOR-DMARD to examine it. It was further suggested that the validation of ASDAS cutoffs should move forward to study its relationship with the concept of quality-adjusted life-years (QALY).

Others suggested research including evaluation of the relationship with activity/inflammation on magnetic resonance imaging, as well as the prognostic validity of ASDAS cutoff levels with regard to structural damage. It was also suggested that the performance of the cutoffs in subgroups of AS patients (e.g., patients with or without elevated CRP, patients treated exclusively with nonsteroidal antiinflammatory drugs, and patients with mild disease) and in other populations (e.g., patients with mechanical back pain) should be investigated further. Finally, it was suggested that the relationship between ASDAS-CRP cutoffs and ASDAS-ESR cutoffs should be investigated with regard to discordant scenarios. In this regard, the module coordinators warned that both formulas should not be used interchangeably in the same patient.

Responses to Plenary Questions

Five questions for each version of ASDAS were posed and voted on at the "module update" closing plenary session. The results are presented in Table 2.

Outstanding Issue

An outstanding issue that required voting was about the use of the word "minimal" in "minimal clinically important improvement." Some participants were concerned about its potential misuse, namely regarding drug reimbursement issues. Therefore, although the expression "minimal clinically important improvement" is widely used and has been used in the past by OMERACT to define the smallest change in measurement that signifies an important and clinically relevant change in a symptom/score, participants were asked to choose and vote for their preferred terminology. The expression "clinically important improvement" received the highest number of votes (42%). Therefore, this was adopted as a synonym of "minimal clinically important improvement." It was remarked that the term "minimal clinically important improvement" is valid for the cutoff as such, but that everything beyond this minimum is a clinically important improvement.

Conclusions

Cutoff levels for disease activity states and improvement scores initially defined and validated among the ASAS membership, which consists of experts in the field of spondyloarthritis[5], were discussed in the OMERACT community, which consists of people with a broader background including clinicians, researchers, and patients.

Disregarding the "don't know" answers, 93% (range 83%–100%) of participants globally agreed with the development process and were in favor of the proposed cutoff values.

After discussing the concept, design, and validation of

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Table 2. Response to plenary questions.

Question 1: Do you agree with the selection of the cutoff for inactive disease versus moderate disease activity? Does it fulfil the truth and discrimination filters sufficiently?

	ASDAS-CRP	ASDAS-ESR
Yes:	75.4%	73.4%
No:	4.6%	3.1%
Don't know:	20%	23.4%

Question 2: Do you agree with the selection of the cutoff for moderate disease activity versus high disease activity? Does it fulfil the truth and discrimination filters sufficiently?

	ASDAS-CRP	ASDAS-ESR
Yes:	70.6%	70.5%
No:	11.8%	0%
Don't know:	17.7%	29.5%

Question 3: Do you agree with the selection of the cutoff for high disease activity versus very high disease activity? Does it fulfil the truth and discrimination filters sufficiently?

	ASDAS-CRP	ASDAS-ESR
Yes:	59.7%	51.5%
No:	10.5%	10.6%
Don't know:	29.9%	37.9%

Question 4: Do you agree with the selection of the cutoff for minimal clinically important improvement? Does it fulfil the truth and discrimination filters sufficiently?

	ASDAS-CRP	ASDAS-ESR
Yes:	77.2%	76.5%
No:	3.0%	1.5%
Don't know:	19.7%	22.1%

Question 5: Do you agree with the selection of the cutoff for major improvement? Does it fulfil the truth and discrimination filters sufficiently?

	ASDAS-CRP	ASDAS-ESR
Yes:	76.6%	69.4%
No:	1.6%	1.6%
Don't know:	21.9%	29%

ASDAS in the ASAS and OMERACT milieu, and after obtaining majority consensus, the developers of the ASDAS feel this measure is ready to be used in clinical practice, observational studies, and clinical trials (Figure 1).

Using the ASDAS and the newly validated cutoff values, we hope that clinicians can better assess the effectiveness of treatments and determine whether they are providing clinically meaningful improvement. The higher discriminatory capac-

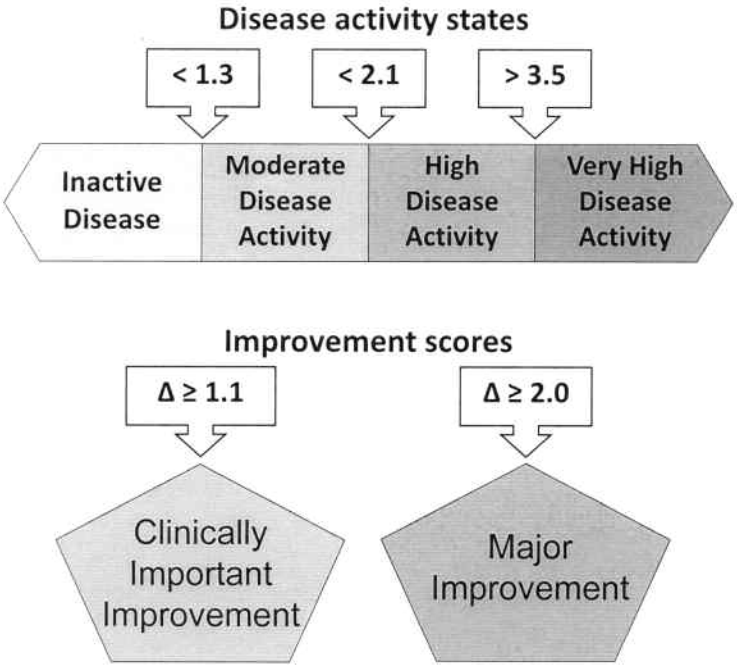

Figure 1. Cutoff values for disease activity states and improvement scores according to the Ankylosing Spondylitis Disease Activity Score (ASDAS).

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ity of the ASDAS compared to classical response criteria in AS may have important implications in reducing sample size calculation for clinical trials. The ASDAS will also allow clinicians, investigators, regulators, and patients to continue communicating about treatment response using the same metric.

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