Construct validity of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) treatment target cut-offs in a BASDAI treat-to-target axial spondyloarthritis cohort: a cross-sectional study

Michielsens, C.A.J.; Bolhuis, T.E.; Gaalen, F.A. van; Hoogen, F.H.J. van den; Verhoef, L.M.; Broeder, N. den; Broeder, A.A. den

Taylor & Francis
Taylor & Francis Group

Scandinavian Journal of Rheumatology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/irhe20

Construct validity of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) treatment target cut-offs in a BASDAI treat-to-target axial spondyloarthritis cohort: a cross-sectional study

CAJ Michielsens, TE Bolhuis, FA van Gaalen, FHJ van den Hoogen, LM Verhoef, N den Broeder & AA den Broeder

To cite this article: CAJ Michielsens, TE Bolhuis, FA van Gaalen, FHJ van den Hoogen, LM Verhoef, N den Broeder & AA den Broeder (2023): Construct validity of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) treatment target cut-offs in a BASDAI treat-to-target axial spondyloarthritis cohort: a cross-sectional study, Scandinavian Journal of Rheumatology, DOI: 10.1080/03009742.2023.2213509

To link to this article: https://doi.org/10.1080/03009742.2023.2213509

Construct validity of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) treatment target cut-offs in a BASDAI treat-to-target axial spondyloarthritis cohort: a cross-sectional study

CAJ Michielsens[1,2], TE Bolhuis[1,2], FA van Gaalen[3], FHJ van den Hoogen[4], LM Verhoef[5], N den Broeder[1,2], AA den Broeder[1,2,4]

[1]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, the Netherlands
[2]Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[3]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands
[4]Department of Rheumatic Diseases, Radboud University Medical Center, Nijmegen, the Netherlands
[5]Department of Research and Innovation, Sint Maartenskliniek, Nijmegen, the Netherlands

Objective: In axial spondyloarthritis (axSpA), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) are recommended for use in treat-to-target (T2T) strategies. However, BASDAI disease states may be a less suitable T2T instrument than ASDAS, since BASDAI contains non-disease activity related items. The objective of our study was to investigate the construct validity of BASDAI and ASDAS disease states.

Method: We performed a single-centre cross-sectional study on BASDAI and ASDAS construct validity in long-term BASDAI T2T-treated axSpA patients. Our hypothesis was that BASDAI is less representative of disease activity than ASDAS owing to the focus on pain and fatigue, and missing an objective item, e.g. C-reactive protein (CRP). This was operationalized using several subhypotheses.

Results: The study included 242 axSpA patients. BASDAI and ASDAS disease states showed a similar relation to Patient Acceptable Symptom State and T2T protocol adherence. The proportions of patients with high BASDAI and ASDAS disease activity fulfilling Central Sensitization Inventory and fibromyalgia syndrome criteria were similar. The correlation with fatigue was moderate for both BASDAI (Spearman's rho 0.64) and ASDAS (Spearman's rho 0.54) disease states. A high ASDAS was strongly correlated with increased CRP (relative risk 6.02, 95% CI 3.0–12.09), while this correlation was not seen for BASDAI (relative risk 1.13, 95% CI 0.74–1.74).

Conclusion: Our study showed moderate and comparable construct validity for BASDAI- and ASDAS-based disease activity states, with the expected exception of association with CRP. Therefore, no strong preference can be given for either measure, although the ASDAS seems marginally more valid.

Axial spondyloarthritis (axSpA) is characterized by inflammation, typically affecting the sacroiliac joints and spine, and can lead to pain, physical disability, and structural damage (1, 2). The current Assessment of SpondyloArthritis international Society–European League Against Rheumatism and American College of Rheumatology guidelines recommend non-steroidal anti-inflammatory drugs (NSAIDs), followed by biological disease-modifying anti-rheumatic drugs (bDMARDs) to suppress disease activity and thereby improve the quality of life and prognosis (3).

In axSpA, current guidelines recommend a treat-to-target (T2T) strategy, although in contrast to rheumatoid arthritis, supporting evidence is nearly absent (4–6). A T2T strategy consists of measuring the outcome of interest, choosing a certain target, and adapting the treatment in case this target is not yet or no longer reached. When executing a T2T strategy, the following aspects have to be taken into account. First, disease

CAJ Michielsens, Department of Rheumatology, Sint Maartenskliniek, PO Box 9011, Nijmegen 6500 GM, the Netherlands.
E-mail: celiamichielsens@gmail.com

Received 30 November 2022; Accepted 10 May 2023

DOI: https://doi.org/10.1080/03009742.2023.2213509

activity should be measured on a regular basis using a valid composite measure. Secondly, the physician and the patient should identify a disease activity target using shared decision making. Finally, if the target is not reached, the physician should adapt the therapy regularly until the target is achieved. The correct T2T instrument and target to use in axSpA are also up for discussion, as two composite disease activity indices are recommended: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) (7, 8). The BASDAI score is the oldest and most frequently used composite index and contains six questions covering axial and peripheral pain, fatigue, and stiffness. The ASDAS was developed more recently than the BASDAI; it is complemented by C-reactive protein (CRP) and the patient's judgement regarding disease activity, and leaves out fatigue and localized tenderness (9, 10). It also uses different weighting for each variable. The incorporation of CRP level in the ASDAS is an advantage as it has been reported to be related to syndesmophyte formation and progression. CRP, however, is only elevated in 40–50% of patients with radiographic axSpA and thus the added value may be limited (11). The exclusion of fatigue and localized tenderness may reduce the association of the ASDAS with central sensitization and fibromyalgia compared to BASDAI. Overall, the ASDAS T2T targets may therefore be a better T2T instrument than the BASDAI (12, 13), although the latter is more feasible (14).

In the Sint Maartenskliniek, Nijmegen, The Netherlands, a BASDAI-guided T2T strategy was implemented in routine clinical care in 2012, and in 2021, the BASDAI was switched to the ASDAS. As, to our knowledge, no other long-term and large T2T axSpA cohorts are available worldwide, this provides a unique opportunity to study aspects of construct validity of the BASDAI and ASDAS in patients who have received a BASDAI-guided T2T strategy. We overall hypothesized that the BASDAI has lower construct validity for disease activity than the ASDAS. Specifically, overestimation of disease activity may occur owing to non-axSpA disease activity-related constructs such as central sensitization playing a role in BASDAI items specifically, thereby influencing BASDAI T2T disease states. Therefore, we set out to study BASDAI disease state construct validity in light of ASDAS disease state construct validity in more detail, using several subhypotheses.

Method

Design and setting

We performed a single-centre cross-sectional study to assess and compare the construct validity of BASDAI- and ASDAS-based disease states. Reporting was conducted in line with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for cross-sectional studies, and a reporting checklist is shown in Online Supplementary Table S1.

Patients

Consenting patients aged ≥ 16 years with a clinical diagnosis of axSpA, operationalized by an electronic diagnosis code (Dutch DOT code 201 or 203), were considered eligible for inclusion. Patients were enrolled between March and September 2021 at the Rheumatology Department of the Sint Maartenskliniek, the Netherlands. Patients were excluded in case of illiteracy or with incomplete questionnaires within 4 weeks of BASDAI and ASDAS measurements. The local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, number 2021-7431) waived the need for formal approval. Written informed consent was acquired.

Procedures

Patients received a patient information letter and a database link (CASTORedc) to an electronic informed consent form. After signing this consent, patients completed questionnaires via CASTORedc within 4 weeks of BASDAI/ASDAS measurement, containing the Central Sensitization Inventory (CSI) criteria, fibromyalgia syndrome (FMS) criteria, and a Patient Acceptable Symptom State (PASS) (15, 16). Furthermore, we extracted patient, disease, and treatment (change) characteristic data from electronic health records. Disease activity was measured with the BASDAI and ASDAS scores in routine care, with a rheumatologist providing the Physician Global Assessment (PGA) at the outpatient visit.

BASDAI/ASDAS disease states

The BASDAI consists of six questions (Q), each with a score ranging from 0 to 10. The final score is calculated by the following formula: (Q1 + Q2 + Q3 + Q4 + (Q5 + Q6)/2)/5. The ASDAS is calculated using the following formula: 0.12 × Visual analogue scale (VAS) back pain (0–10) + 0.06 × Duration of morning stiffness (minutes) + 0.11 × VAS patient global (0–10) + 0.07 × VAS peripheral pain/swelling (0–10) + 0.58 × ln(CRP + 1). Furthermore, if CRP is below the limit of detection or is <2 mg/L (<0.2 mg/dL), the fixed value of 2 mg/L (0.2 mg/dL) is entered.

A BASDAI score ≥ 4 and an ASDAS ≥ 2.1 have been labelled previously as a (very) high disease activity state (7, 17–19). The treatment protocol in the Sint Maartenskliniek has, since 2012, aimed for BASDAI < 4, and since 2021, ASDAS < 2.1, taking into account the physician's judgement of disease activity and patient preferences.

Questionnaires

Central Sensitization Inventory. The CSI is a self-report scale and is designed to assess (i) symptoms and (ii) conditions that relate to central sensitization. The questionnaire has been translated into Dutch (15, 20). A sum score > 40 classifies patients with central sensitization (21).

Fibromyalgia syndrome criteria. The FMS questionnaire used in our study is the 2016 revision of the fibromyalgia diagnostic criteria (16). Criteria are fulfilled if the following three conditions are met: (i) Widespread Pain Index (WPI) ≥ 7 and Symptom Severity Scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9; (ii) generalized pain, defined as pain in at least four out of five regions; and (iii) symptoms have been present for ≥ 3 months. Overall, a higher score indicates more symptoms.

Patient Acceptable Symptom State, physician's judgement, and Physician Global Assessment. The PASS is a self-reported questionnaire consisting of one question, in which a patient can determine whether the current disease activity would be unacceptable or acceptable if it were permanent. In addition, electronic heath records were also searched manually for disease activity state according to the physician's judgement, which was the assessment and recording of patients (low or high disease activity) at their outpatient visit by rheumatologists. Rheumatologists also performed a PGA, ranging from 0 to 10, with a higher score indicating higher disease activity.

Outcomes

Our main outcome concerned various aspects of the construct validity of BASDAI- and ASDAS-based disease states, which we discuss in the following subsections.

Known groups validity. We compared BASDAI and ASDAS disease states to the following reference standards: physician's judgement, PASS, and treatment intensification. Treatment intensification was defined as the start, escalation, or switch of NSAIDs, glucocorticoids (oral/intra-articular/intramuscular), or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)/bDMARDS owing to treatment inefficiency. A perfect agreement is not deemed necessary or even desired, and no specific level of agreement value was aimed for. The recent switch from the BASDAI to the ASDAS in our T2T cohort generated the possibility to compare the agreement between T2T protocol adherence or treatment intensification and disease activity states according to the BASDAI and ASDAS, since this a transition period during which both indices were used.

Discriminative validity. We expect that concomitant chronic central pain disorders (operationalized as FMS and/or CSI criteria positive) may contribute towards measured disease activity, resulting in a higher proportion of patients with a (false) high disease activity according to BASDAI disease activity states, compared to the ASDAS.

Divergent validity. By applying a T2T strategy, we expect a congruent change in objective disease items, but less response in subjective disease items (i.e. fatigue and areas of localized tenderness). Consequently, patients may be classified with high disease activity according to the BASDAI and ASDAS, based disproportionally on fatigue and areas of localized tenderness, when treated according to BASDAI or ASDAS T2T targets.

Convergent validity. We expect that a higher CRP value predominantly reflects higher axSpA disease activity and, therefore, will react more to a T2T strategy. For CRP, patients were categorized as either having a raised CRP or not (with a cut-off CRP ≥ 5 or ≥ 10 mg/L depending on local testing procedures).

Statistical analysis

We powered for an estimation of a dichotomous outcome (proportion). The minimum sample size was considered to be 171 patients, with a maximum sample size of 385 patients, which corresponds to a 95% confidence interval (CI) width of ± 7.5% and ± 5%, respectively, around a proportion point estimate. Analyses were performed using Stata IC version 13 for Windows. Categorical data were presented in 2 × 2 contingency tables as absolute frequencies and percentages. Descriptive statistics and continuous data were described with mean ± standard deviation (sd) or median with interquartile range (IQR), depending on the normality of the distribution. Sensitivity, specificity, and risk ratios (RRs) were used for subhypotheses testing to reflect different aspects of construct validity. Spearman's rank correlation was used to determine the correlation between BASDAI/ASDAS-based disease states and fatigue and areas of localized tenderness.

Results

Patients

During the study period, 337 out of 784 axSpA patients were screened for eligibility and 242 were included. Exclusion of patients was due to the lack of informed consent (n = 35), missing data (n = 14), incomplete data (n = 34), or ≥ 4 weeks between disease activity assessment and fulfilment of the questionnaires (n = 12). The mean ± sd age was approximately 51 ± 14 years, with

a median (IQR) disease duration of 10 (4–22) years. Other study baseline characteristics are shown in Table 1. A selection of the baseline characteristics according to the different BASDAI and ASDAS disease states is shown in Table 2. Notably, the group with an incongruent state of an ASDAS < 2.1 and a BASDAI score ≥ 4 appeared to show a higher percentage of women. Table 3 shows the results of the several sub-hypotheses with the different disease states.

Known groups. The BASDAI and ASDAS disease states showed a similar relation to PASS (unacceptable or acceptable) and treatment intensification (no or yes). The majority of patients who had high BASDAI- and ASDAS-based disease activity were judged to have high disease activity according to the treating physician, with only 18% and 19% of the patients with high BASDAI/ASDAS having their treatment intensified at that visit.

Discriminant validity. Of the patients who had high disease activity according to the BASDAI and ASDAS, approximately 61% fulfilled the CSI criteria. Patients with high disease activity fulfilled CSI criteria approximately four times more often than patients with

Table 1. Baseline characteristics of axial spondyloarthritis (axSpA) patients.

Characteristic	axSpA (N = 242)
Female	109 (45)
Age at inclusion (years)	51 ± 14
Disease duration at inclusion (years)	10 (4–22)
HLA-B27 positivity (*N = 188)	147 (78)
ASAS criteria positive (*N = 236)	213 (90)
Concomitant psoriasis	33 (14)
Concomitant IBD	21 (9)
Sacroiliitis on radiographic imaging (*N = 226)	161 (71)
Disease activity	
BASDAI	4.03 ± 2.06
ASDAS	2.22 ± 0.94
PGA (*N = 177)	2 (1–4)
Current bDMARD use	
None	92 (38)
Adalimumab	76 (31)
Etanercept	26 (11)
Infliximab	13 (5)
Golimumab	11 (5)
Certolizumab pegol	6 (2)
Secukinumab	16 (7)
Ixekizumab	2 (1)
Duration of current bDMARD use (years) (*N = 150)	2.2 (1.1–5.3)
Current csDMARD use	
None	220 (91)
Methotrexate	13 (5)
Hydroxychloroquine	1 (1)
Sulfasalazine	8 (3)
Duration of current csDMARD use (years) (*N = 22)	6.0 (1.4–12.1)
Current NSAID use (*N = 126)	
None	132 (55)
Etoricoxib	31 (13)
Celecoxib	24 (10)
Naproxen	23 (10)
Meloxicam	16 (7)
Piroxicam	10 (4)
Diclofenac	3 (1)
Ibuprofen	2 (1)
Fenylbutazon	1 (1)

Data are shown as n (%), mean ± sd, or median (IQR).
*Number of patients. Missing data were excluded from the percentages.
HLA-B27, human leucocyte antigen-B27; ASAS, Assessment of SpondyloArthritis international Society; IBD, inflammatory bowel disease; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; PGA, Physician Global Assessment; bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug; IQR, interquartile range.

Table 2. Baseline characteristics of axial spondyloarthritis (axSpA) patients according to different Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) disease states.

Characteristic	Overall (N = 242)	Congruent inactive (A < 2.1 and B < 4.0) (N = 92)	Congruent active (A ≥ 2.1 and B ≥ 4.0) (N = 106)	Incongruent A (A ≥ 2.1 and B < 4.0) (N = 23)	Incongruent B (A < 2.1 and B ≥ 4.0) (N = 21)
Female	109 (45)	33 (36)	52 (49)	9 (39)	15 (71)
Age at inclusion (years)	51 ± 14	49 ± 15	54 ± 13	49 ± 17	47 ± 14
Disease duration at inclusion (years)	10 (4–22) (N = 241*)	9.1 (3.9–20) (*N = 91)	14 (4.6–26)	6.3 (2.0–21)	8.9 (3.5–16)
HLA-B27 positivity	147 (78) (*N = 188)	62 (89) (*N = 70)	58 (72) (*N = 81)	14 (67) (*N = 21)	13 (81) (*N = 16)
ASAS criteria positive	213 (90) (*N = 236)	83 (92) (*N = 90)	92 (88) (*N = 104)	22 (100) (*N = 22)	16 (80) (*N = 20)
Concomitant psoriasis	33 (14)	9 (10)	13 (12)	8 (34)	3 (14)
Concomitant IBD	21 (9)	6 (7)	12 (11)	0 (0)	3 (14)
Sacroiliitis on radiographic imaging	161 (71) (*N = 226)	65 (76) (*N = 85)	65 (64) (*N = 101)	20 (95) (*N = 21)	11 (58) (*N = 19)
Disease activity					
BASDAI	4.03 ± 2.06	2.0 ± 1.0	5.9 ± 1.2	3.1 ± 0.8	4.4 ± 0.4
ASDAS	2.22 ± 0.94	1.3 ± 0.5	3.0 ± 0.7	2.5 ± 0.4	1.9 ± 0.2
PGA	2 (1–4) (*N = 177)	1 (1–3) (*N = 65)	3 (2–5) (*N = 83)	3 (2–5) (*N = 17)	2 (1–3.5) (*N = 12)
Current bDMARD use	150 (62)	63 (69)	62 (59)	16 (70)	9 (43)
Duration of current bDMARD use (years)	2.2 (1.1–5.3)	3.0 (1.3–7.2)	2.0 (1.1–5.1)	1.2 (0.7–3.2)	1.5 (0.9–2.6)
Current csDMARD use	22 (9)	5 (5)	15 (14)	1 (4)	1 (5)
Duration of current csDMARD use (years)	6.0 (1.4–12.1)	10 (9.0–11)	3.2 (0.8–12)	4.7	22
Current NSAID use	110 (45)	34 (37)	59 (56)	8 (35)	9 (43)
CSI fulfilled	93 (38)	8 (9)	67 (63)	8 (35)	10 (47)
FMS fulfilled	19 (8)	1 (1)	14 (13)	1 (4)	3 (14)

Data are shown as n (%), mean ± sd, or median (IQR).
*Number of patients. Missing data were excluded from the percentages.
A, ASDAS; B, BASDAI; HLA-B27, human leucocyte antigen-B27; ASAS, Assessment of SpondyloArthritis international Society; IBD, inflammatory bowel disease; PGA, Physician Global Assessment; bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug; CSI, Central Sensitization Inventory; FMS, fibromyalgia syndrome; IQR, interquartile range.

low disease activity. In contrast, few patients with either high or low disease activity fulfilled FMS criteria. However, patients with a high BASDAI fulfilled FMS criteria eight times more often and those with a high ASDAS three times more often than their respective low disease activity states. Despite the big difference in relative risk, the absolute difference was 12% (95% CI 5.3–18.0) for the BASDAI and 8% (95% CI 1.6–14.6) for the ASDAS.

Divergent validity. The BASDAI and ASDAS had a correlation of 0.64 and 0.54 with fatigue and 0.41 and 0.37 with localized tenderness, respectively. Therefore, despite possible incorporation bias for the VAS fatigue in the BASDAI, the correlation with fatigue was relatively similar for BASDAI and ASDAS disease states.

Convergent validity. Patients with a high BASDAI had a negligible relative risk difference and a low absolute difference of having a raised CRP compared with patients with a low BASDAI. In contrast, patients with a low ASDAS had six times the risk of having a raised CRP compared with patients with a low ASDAS.

Discussion

In a cohort of axSpA patients, treated in a clinic that has followed a T2T policy for many years, our results showed moderate construct validity for BASDAI-and ASDAS-based disease states. The construct validity did not seem very different between these measures, although ASDAS tended to perform slightly better in all aspects. All in all, measuring the construct of axSpA disease activity remains difficult, and the ASDAS does not seem to perform much better than the BASDAI, which was also seen in the study by Ortolan et al (22).

In our study, a moderate correlation between treatment intensification with BASDAI and ASDAS T2T targets was seen, despite the relatively high correlation

Table 3. Hypothesis testing for different aspects of construct validity.

	BASDAI			ASDAS		
	< 4.0 (N = 115)	≥ 4.0 (N = 127)	Sens./Spec./RR (95% CI)/r_s	< 2.1 (N = 113)	≥ 2.1 (N = 129)	Sens./Spec./RR (95% CI)/r_s
Known groups						
Unacceptable PASS	12 (10)	59 (46)	Sens.: 83 (72–91) Spec.: 60 (53–68)	12 (11)	59 (46)	Sens.: 83 (72–91) Spec.: 59 (51–67)
T2T protocol adherence/treatment intensified	15 (13)	23 (18)	Sens.: 61 (43–76) Spec.: 49 (42–56)	13 (12)	25 (19)	Sens.: 66 (49–80) Spec.: 49 (42–56)
Physician's judgement	12 (10)	51 (40)	Sens.: 81 (69–90) Spec.: 58 (50–65)	13 (12)	50 (39)	Sens.: 79 (67–89) Spec.: 56 (48–63)
Discriminant						
CSI fulfilled	16 (14)	77 (61)	RR: 4.4 (2.7–7.0)	18 (16)	75 (58)	RR: 3.6 (2.3–5.7)
FMS fulfilled	2 (2)	17 (13)	RR: 7.7 (1.8–33)	4 (4)	15 (12)	RR: 3.3 (1.1–9.6)
Divergent						
Fatigue VAS						
Mean ± sd	3.3 ± 2.1	6.5 ± 1.7	r_s: 0.64*	3.6 ± 2.3	6.3 ± 1.9	r_s: 0.54*
Median (IQR)	3 (2–5)	7 (5–8)		3 (2–5)	6 (5–8)	
Localized tenderness						
Mean ± sd	2.8 ± 2.0	4.8 ± 2.5	r_s: 0.41*	2.9 ± 2.1	4.7 ± 2.5	r_s: 0.37*
Median (IQR)	2 (1–4)	4 (3–6)		2 (1–4)	4 (3–6)	
Convergent						
CRP raised	28 (24)	35 (28)	RR: 1.13 (0.74–1.7)	8 (7)	55 (43)	RR: 6.0 (3.0–12)

Data are shown as n (%), mean ± sd, or median (IQR).
*Significant at $p < 0.0000$.
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; Sens., sensitivity; Spec., specificity; RR, risk ratio; r_s, Spearman's rank correlation; PASS, Patient Acceptable Symptom State; T2T, treat-to-target; CSI, Central Sensitization Inventory; FMS, fibromyalgia syndrome; VAS, visual analogue scale; CRP, C-reactive protein; IQR, interquartile range.

of T2T targets with patient- and physician-based high disease activity. It seems that the physician and patient agree on disease activity assessment, but the physician does not automatically intensify treatment. Although we did not study this, this protocol adherence seems much lower than in rheumatoid arthritis disease activity score-based T2T (60–90% in trials and 30–80% in clinical practice). The drivers for this could be a number of things, including fear of adverse events, cost-effectiveness concerns, or fear of overtreatment.

Although BASDAI- and ASDAS-based disease states seem to have similar discriminative ability for axSpA disease activity, patients with high disease activity according to both the BASDAI and ASDAS were more likely to fulfil fibromyalgia and central sensitization criteria than patients with low disease activity. In a conference abstract, Baraliakos et al reported similar findings with regard to the BASDAI T2T targets (23). The fulfilment of fibromyalgia criteria may be caused by the severity and duration of chronic pain, which is often present in axSpA. In turn, this could hamper disease activity assessment and could lead to overtreatment (24). However, the fulfilment of criteria seems to be the case for both BASDAI and ASDAS T2T targets, and consequent with fatigue and tenderness are comparable. Therefore, construct validity may be influenced by non-specific chronic pain due to central sensitization in the same and comparable way for BASDAI- and ASDAS-based disease states (25). Physicians should be aware of the influence of central sensitization when interpreting disease activity and be cautious of stringent treatment with remission as target, as this carries a risk of overtreatment. However, it is also important to recognize and treat secondary FMS in patients, because although it is not mediated by the inflammatory system, or modifiable with NSAIDs or DMARDs, it is a true burden for patients.

A sex difference was seen in the group with an ASDAS < 2.1 and a BASDAI ≥ 4. Besides there being a higher percentage of women, current bDMARD use was also lower in this subgroup, with no difference in fulfilment of the CSI and FMS criteria between groups. Other studies have shown that women have overall worse patient-reported outcomes, and lower efficacy, response rate, and drug survival for tumour necrosis factor inhibitors compared to men (26, 27). In our study, this difference could be caused by underestimation of the disease burden and therefore bDMARD undertreatment/delay or perhaps bDMARD treatment failure.

Strengths of our study included the adequate sample size, prospective measurements of all domains, and low proportion of missing data. The non-selective inclusion criteria contribute towards the generalizability. In addition, these patients had been treated for up to 10 years

with BASDAI-based T2T, which is a unique characteristic of this cohort.

A limitation of our study is the lack of a gold standard to measure disease activity. Furthermore, the absence of information on transition of disease activity after the start or intensification of treatment, which is inherent to the cross-sectional design of our study, is another limitation. We could therefore not assess whether treatment intensification in the case of high disease activity according to the BASDAI would impact the disease activity less in comparison with the ASDAS (T2T longitudinal construct validity). This would be a pivotal experiment, as it would most closely fit with the goal of these disease measures, i.e. predicting response in clinical practice. Moreover, the stronger correlation with magnetic resonance imaging (MRI)-determined disease progression of the ASDAS compared to the BASDAI, reported by Machado et al and Pedersen et al, could not be investigated, as no MRI scans were performed (28, 29). A practical limitation of the ASDAS is the inclusion of the PGA for calculation of the total score, which could easily be forgotten in daily clinical practice and thus be absent from research databases. However, as was seen with the disease activity score in rheumatoid arthritis, an alternative score was proposed and tested by Ortolan et al. They developed an alternative ASDAS using the total BASDAI score as a replacement for the PGA in the case of missing values, which proved to be a discriminative and feasible instrument for use in research databases (30, 31). The choice of ASDAS low disease activity rather than remission as the cut-off could be a limitation if treating physicians were only to target remission, which hinders generalizability. Furthermore, this could cause a lack of difference compared to the BASDAI, since another group of patients is selected by disease activity. However, especially with the performance of a T2T strategy, remission as cut-off is, in axSpA, often seen as too stringent and not feasible for use in clinical practice. We did not assess other forms of validity, since construct validity was deemed most applicable to our hypotheses, with the different types of construct validity showing comparable results for both the BASDAI and ASDAS. Finally, it may be argued that our COSMIN-based criteria are not optimal to evaluate the construct validity of a binary criterion. However, standardized criteria for assessment are lacking, although these are in development. Future research should focus on finding T2T targets that better capture the concept of biological–clinical disease activity in axSpA and longitudinally assessing such T2T targets.

Conclusion

BASDAI and ASDAS T2T targets showed moderate and surprisingly comparable construct validity for axSpA disease activity. Although the ASDAS seems to be somewhat better, both measures could for be used for axSpA T2T. In light of some advantages of the ASDAS (CRP addition, available cut-offs also for remission, and for flare and improvement) and the trend towards better construct validity, using the ASDAS may still be preferred over the BASDAI (32).

Acknowledgement

We thank A Verkerk for data collection.

Disclosure statement

FvG is a member of the ASAS executive committee. AdB has received research grants (to the institution) from AbbVie, Amgen, Roche, Biogen, Lilly, Novartis, Sanofi, and Gilead. The remaining authors have no potential conflicts of interest to declare.

Author contributions

CM, TB, NdB, LV, and AdB were involved in the study design. CM was involved in the data collection. CM and TB performed the data analyses. All authors were involved in writing, revision, and final approval of the manuscript. CM is the study guarantor. CM contributed to all aspects of the study.

Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author according to FAIR principles.

Ethics approval

This study was reviewed by the CMO region Arnhem-Nijmegen and was officially exempted from formal review (CMO number 2021-7431).

ORCID

CAJ Michielsens http://orcid.org/0000-0001-8625-034X

TE Bolhuis http://orcid.org/0000-0003-3911-3515

FA van Gaalen http://orcid.org/0000-0001-8448-7407

N den Broeder http://orcid.org/0000-0001-7126-2209

References

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379–90.
2. de Koning A, Schoones JW, van der Heijde D, van Gaalen FA. Pathophysiology of axial spondyloarthritis: consensus and controversies. Eur J Clin Invest 2018;48:e12913.
3. van der Heijde D, Ramiro S, Landewe R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978–91.
4. Smolen JS, Schols M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral

spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018;77:3–17.
5. Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis 2014;73:6–16.
6. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis 2016;75:16–22.
7. 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.
8. Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.
9. van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811–18.
10. Fernandez-Espartero C, de Miguel E, Loza E, Tomero E, Gobbo M, Descalzo MA, et al. Validity of the Ankylosing Spondylitis Disease Activity Score (ASDAS) in patients with early spondyloarthritis from the Esperanza programme. Ann Rheum Dis 2014;73:1350–5.
11. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Marker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German spondyloarthritis inception cohort. Arthritis Rheum 2009;60:717–27.
12. Marona J, Sepriano A, Rodrigues-Manica S, Pimentel-Santos F, Mourao AF, Gouveia N, et al. Eligibility criteria for biologic disease-modifying antirheumatic drugs in axial spondyloarthritis: going beyond BASDAI. RMD Open 2020;6:e001145.
13. Fagerli KM, Lie E, van der Heijde D, Heiberg MS, Kaufmann C, Rodevand E, et al. Selecting patients with ankylosing spondylitis for TNF inhibitor therapy: comparison of ASDAS and BASDAI eligibility criteria. Rheumatology (Oxford) 2012;51:1479–83.
14. Pedersen SJ, Sorensen IJ, Hermann KG, Madsen OR, Tvede N, Hansen MS, et al. Responsiveness of the Ankylosing Spondylitis Disease Activity Score (ASDAS) and clinical and MRI measures of disease activity in a 1-year follow-up study of patients with axial spondyloarthritis treated with tumour necrosis factor alpha inhibitors. Ann Rheum Dis 2010;69:1065–71.
15. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, et al. The development and psychometric validation of the Central Sensitization Inventory. Pain Pract 2012;12:276–85.
16. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RL, et al. Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46:319–29.
17. Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002;359:1187–93.
18. Braun J, Pham T, Sieper J, Davis J, van der Linden S, Dougados M, et al. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Ann Rheum Dis 2003;62:817–24.
19. Machado P, Landewe R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis 2011;70:47–53.
20. Kregel J, Vuijk PJ, Descheemaeker F, Keizer D, van der Noord R, Nijs J, et al. The dutch Central Sensitization Inventory (CSI): factor analysis, discriminative power, and test-retest reliability. Clin J Pain 2016;32:624–30.
21. Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain 2013;14:438–45.
22. Ortolan A, Navarro-Compan V, Sepriano A, Landewe RBM, van der Heijde D, Ramiro S. Which disease activity outcome measure discriminates best in axial spondyloarthritis? A systematic literature review and meta-analysis. Rheumatology (Oxford) 2020;59:3990–2.
23. Baraliakos XTS, Gkelaki M, Dukatz P, Kiltz U, Braun J. Performance of standardized scores for disease assessment and pain in patients with spondyloarthritis and fibromyalgia [abstract]. Arthritis Rheumatol 2021;73 (suppl 9).
24. Alunno A, Carubbi F, Stones S, Gerli R, Giacomelli R, Baraliakos X. The impact of Fibromyalgia in spondyloarthritis: from classification criteria to outcome measures. Front Med (Lausanne) 2018;5:290.
25. Kieskamp SC, Paap D, Carbo MJG, Wink F, Bos R, Bootsma H, et al. Central sensitization, illness perception and obesity should be considered when interpreting disease activity in axial spondyloarthritis. Rheumatology (Oxford) 2021;60:4476–85.
26. Rusman T, van Bentum RE, van der Horst-Bruinsma IE. Sex and gender differences in axial spondyloarthritis: myths and truths. Rheumatology (Oxford) 2020;59:iv38–iv46.
27. Maguire S, Wilson F, Gallagher P, O'Shea FD. Worse scores but similar patterns of disease activity: interpreting outcomes in women with axial spondyloarthropathy. Scand J Rheumatol 2023;52:142–9.
28. Machado P, Landewe RB, Braun J, Baraliakos X, Hermann KG, Hsu B, et al. MRI inflammation and its relation with measures of clinical disease activity and different treatment responses in patients with ankylosing spondylitis treated with a tumour necrosis factor inhibitor. Ann Rheum Dis 2012;71:2002–5.
29. Pedersen SJ, Sorensen IJ, Garnero P, Johansen JS, Madsen OR, Tvede N, et al. ASDAS, BASDAI and different treatment responses and their relation to biomarkers of inflammation, cartilage and bone turnover in patients with axial spondyloarthritis treated with TNFalpha inhibitors. Ann Rheum Dis 2011;70:1375–81.
30. Ortolan A, Ramiro S, van Gaalen F, Kvien TK, Landewe RBM, Machado PM, et al. Development and validation of an alternative ankylosing spondylitis disease activity score when patient global assessment is unavailable. Rheumatology (Oxford) 2021;60:638–48.
31. Ortolan A, Ramiro S, Ramonda R, van der Heijde D. External validation of the alternative ankylosing spondylitis disease activity score in three randomised clinical trials of ixekizumab. Rheumatology (Oxford) 2022 Oct 25:keac618.
32. Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 2023;82:19–34.

Supplementary material

Supplemental data for this article can be accessed online at https://doi.org/10.1080/03009742.2023.2213509