Optimisation of rheumatology assessments – the actual situation in axial spondyloarthritis including ankylosing spondylitis

J. Braun, U. Kiltz, X. Baraliakos, D. van der Heijde

ABSTRACT

The spondyloarthritides (SpA) are currently differentiated into axial and peripheral SpA. Patients with axial SpA (axSpA) may be further classified into the classical form ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA). The SpA are genetically linked, and the subtypes including psoriatic arthritis (PsA) share characteristic clinical symptoms such as inflammatory back pain (IBP) and enthesitis. IMP can be due to sacroiliitis and spondylitis, enthesitis may occur with or without arthritis, and anterior uveitis, as well as other extraarticular manifestations such as psoriasis and chronic inflammatory bowel disease (IBD). In addition to clinical findings, imaging, mainly radiography and magnetic resonance imaging (MRI), and laboratory data, mainly HLA B27 and CRP, are important diagnostic tools for SpA. The Assessment of SpondyloArthritis international Society (ASAS), an international group of experts in the field of SpA since 1995, has published on assessments and outcome parameters in SpA. The publication of classification criteria for axSpA has widened the spectrum of this condition (8, 9), which had been guided largely by the 1984 classification criteria for AS. The established part of axSpA has definite structural changes in the sacroiliac joints (SIJ, 10). In addition, non- radiographic axSpA (nr-axSpA), the subset in which no such changes are present, is now recognised. The primary rationale to develop new criteria has been the considerable delay until AS is diagnosed (11).

Since imaging plays an important role in all criteria sets, ASAS has recently organised expert consensus groups to agree on definitions for inflammatory changes in the sacroiliac joints (SIJ) and the spine (13). Patients with nr-axSpA, who appear to have somewhat fewer signs of inflammation in comparison to those with established AS, may represent axSpA in early disease stages, who will develop structural changes and AS in the near future, or female patients who may never develop such changes (14). The term ‘undifferentiated SpA’ (15) is therefore no longer used for patients with nr-axSpA, but is now still used for patients with peripheral SpA who do

Introduction

Ankylosing spondylitis (AS) has long been considered as the prototype of a heterogeneous group of diseases termed spondyloarthritides (SpA). The SpA are genetically linked (1), and share characteristic clinical features such as inflammatory back pain (IBP) due to sacroiliitis and spondylitis (2), others such as enthesitis, arthritis, anterior uveitis, as well as other organ manifestations such as psoriasis and chronic inflammatory bowel disease (IBD, 3, 4). In addition to clinical findings, imaging, mainly radiography and magnetic resonance imaging (MRI) and laboratory data, mainly HLA B27 and CRP, are important diagnostic tools for SpA (5-7).

The publication of classification criteria for axial SpA (axSpA) has widened the spectrum of this condition (8, 9), which had been guided largely by the 1984 classification criteria for AS. The established part of axSpA has definite structural changes in the sacroiliac joints (SIJ, 10). In addition, non-radiographic axSpA (nr-axSpA), the subset in which no such changes are present, is now recognised. The primary rationale to develop new criteria has been the considerable delay until AS is diagnosed (11).
Fig. 1.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Purpose/content</th>
<th>Method of administration</th>
<th>Respondent burden</th>
<th>Administrative burden</th>
<th>Score interpretation</th>
<th>Reliability evidence</th>
<th>Validity evidence</th>
<th>Ability to detect change</th>
<th>Strengths</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASDAS</td>
<td>Measures of disease activity</td>
<td>Hand/computer score</td>
<td>&lt;2 minutes</td>
<td>Score from 0 (no disease activity), higher values reflecting higher disease activity</td>
<td>Not reported in text</td>
<td>Content, construct validity</td>
<td>ES 2.04, SRM 1.45 for improvement with anti-TNF therapy, clinically important improvement 1.1 units, major improvement 2.0 units</td>
<td>Measures important concept with stronger content validity than the BASDAI, extensive validity evidence, appropriate for research use</td>
<td>Still being validated Reliability evidence not reported Use in a clinical setting requiring further assessment Information on MCID and PASS is lacking</td>
<td></td>
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<tr>
<td>ASQoL</td>
<td>Measures of quality of life</td>
<td>Hand score</td>
<td>Median 4 minutes (range 2–18 minutes)</td>
<td>0–18, higher values reflecting greater impairment of quality of life</td>
<td>Internal consistency, test–retest stability</td>
<td>Content, construct validity</td>
<td>mSRM 0.35 (improvement) mSRM 0.57 (deterioration)</td>
<td>Measures important concept, psychometric properties sound, appropriate for clinical and research use</td>
<td>Score based solely on patient report may omit important objective elements of disease activity Less sensitive in the well AS patient</td>
<td></td>
</tr>
<tr>
<td>BASDAI</td>
<td>Measures of disease activity</td>
<td>Hand score</td>
<td>Mean 67 seconds (range 30 seconds–2 minutes)</td>
<td>0 (none or no symptoms) to 10 (very severe symptoms)</td>
<td>Internal consistency, test–retest stability</td>
<td>Content, construct validity</td>
<td>mSRM 0.74 (improvement) mSRM 0.60 (deterioration) ES 1.06, SRM 1.36 for improvement with anti-TNF therapy MCID 10 mm (22.5%) PASS cut off 34.5 mm</td>
<td>Measures important concept, psychometric properties sound, appropriate for clinical and research use</td>
<td>Score based solely on patient report may omit important objective elements of disease activity Less sensitive in the well AS patient</td>
<td></td>
</tr>
<tr>
<td>BASFI</td>
<td>Measures of functional status</td>
<td>Hand score</td>
<td>&lt;3 minutes</td>
<td>0 (no functional impairments) to 10 (maximal impairment)</td>
<td>Internal consistency, test–retest stability, internal reliability</td>
<td>Content, construct, and criterion validity</td>
<td>ES 0.36, SRM 0.46 (improvement) ES 0.70, SRM 0.72 (deterioration) MCID 7 mm (17.5%)</td>
<td>Measures important concept, psychometric properties sound, appropriate for clinical and research use</td>
<td>Less sensitive in the well AS patient</td>
<td></td>
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<tr>
<td>BAS-G</td>
<td>Effect of AS on well-being</td>
<td>Hand score</td>
<td>&lt;1 minute</td>
<td>0 (no effect on well-being) to 10 (very severe effect on well-being)</td>
<td>Test–retest stability</td>
<td>Construct validity</td>
<td>MCID 15 mm (27.5%)</td>
<td>Measures important concept, psychometric properties sound, appropriate for use in a clinical setting</td>
<td>Less well evaluated than other scales</td>
<td></td>
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<tr>
<td>BASMI</td>
<td>Spinal Physical mobility measures</td>
<td>Hand score</td>
<td>5–10 minutes</td>
<td>0 (normal spinal mobility) to 10 (severely restricted spinal mobility)</td>
<td>Internal reliability, test–retest stability</td>
<td>Content, construct, and criterion validity</td>
<td>ES 0.66 (BASMI), ES 0.95 (BASMI), ES 1.04 (BASMI)</td>
<td>Measures important concept, appropriate for use in a research setting</td>
<td>Limited by the lack of thoracic spine measures</td>
<td></td>
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<td>DFI</td>
<td>Measures of functional status</td>
<td>Hand score</td>
<td>Not stated</td>
<td>0–40, higher values reflecting higher functional impairment</td>
<td>Internal reliability, test–retest stability</td>
<td>Content, construct, and criterion validity</td>
<td>ES 0.30, SRM 0.33 (improvement) ES 0.47, SRM 0.59 (deterioration)</td>
<td>Measures important concept, psychometric properties sound, appropriate for research use</td>
<td>5-point Likert scale likely better than original 3-point, but less well validated Information on use in clinical care is lacking</td>
<td></td>
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<tr>
<td>HAQ-S</td>
<td>Measures of functional status</td>
<td>Hand score</td>
<td>Not stated</td>
<td>0–3, higher values reflect higher impairment</td>
<td>Test–retest stability</td>
<td>Content, construct, and criterion validity</td>
<td>ES 0.20, SRM 0.28 (improvement) ES 0.28, SRM 0.72 (deterioration)</td>
<td>Measures important concept, psychometric properties sound, appropriate for research use</td>
<td>Information on MCID, PASS, and use in clinical care is lacking</td>
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* ASDAS = Ankylosing Spondylitis Disease Activity Score; ES = effect size; SRM = standardized response mean; TNF = tumor necrosis factor; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASQoL = Ankylosing Spondylitis Quality of Life scale; MCID = minimum clinically important difference; PASS = patient acceptable symptom state; BASFI = Bath Ankylosing Spondylitis Functional Index; AS = ankylosing spondylitis; BAS-G = Bath Ankylosing Spondylitis Global Score; BASMI = Bath Ankylosing Spondylitis Metrology Index; DFI = Dougados Functional Index; HAQ-S = Health Assessment Questionnaire for the Spondyloarthropathies.
not have psoriasis, IBD or a preceding infection.

However, the vast majority of assessment tools in the field has been developed for AS and psoriatic arthritis (PsA), the latter not being the subject of this paper.

The Assessment of SpondyloArthritis international Society (ASAS) is an international group of experts in the field of SpA. Founded in 1995 the group has published several landmark papers on assessment tools and outcome parameters starting with the definition of domains (16) and core sets for AS (17-20). The most relevant assessment tools have been recently listed (Fig. 1) and described (21). The most important domains in AS are disease activity, function, spinal mobility, structural damage, and quality of life. This review discusses the relative value of the two major currently widely-used existing tools to assess disease activity the BASDAI (22, Fig. 2) and the ASDAS (23,24, Fig. 3), the one for function, the BASFI (25, Fig. 4), and mobility measures including the BASMI (26, Fig. 5). A rather new development, the AS Health Index (AS-HI), is subject of another paper in this supplement (27).

**Disease activity**

In daily clinical routine the judgment how active the disease is usually a synthesis based on a combination of information from several sources, including clinical variables, laboratory markers, imaging information, and overall impression. However, as frequently discussed over the last decades in regard to rheumatoid arthritis (RA; 28, 29), clinical judgment varies considerably between assessors.

Different types of disease activity measures are available: single measures (e.g. back pain, CRP), self-report (patient) instruments (e.g. BASDAI) and composite indices (e.g. ASDAS). Examples of diseases for which single single measures are available include hypertension and hypercholesterolemia. In axial SpA there is no simple gold standard for measuring disease activity in all individual patients, since disease activity in axial SpA is the sum of many different aspects and a complexity that cannot be represented by a single variable.

Composite indices include information provided by the evaluator, the patient, and laboratory investigations. In general, composite indices capture disease activity better than single measures in individual patients, because of superior reliability, validity, applicability across patients and sensitivity to change.

EULAR/ACR collaborative recommendations for assessment of disease activity in clinical trials in RA have been recently proposed (30). Expectedly use of the RA disease activity score DAS28 (31) has been recommended as one of several choices. The DAS28 has been the first quantifiable combined disease activity measure in RA that was based on a statistical approach, ensuring that the most informative variables were included with the optimal weighting (32). Composite disease activity measures facilitate comparisons between patients and treatments, consistent treatment
decisions, longitudinal follow-up, assessment of treatment efficacy, and discrimination at the low end of the disease activity spectrum.

As discussed recently (33), patient assessment in axial SpA is multidimensional, and the evaluation of disease activity is complex and multifactorial due to a large phenotypic heterogeneity of the disease, differences in the predominance of individual clinical manifestations, possible misrepresentation when using individual variables, and differences in the perspective of patient and physicians (33). Indeed, a recent study with axSpA patients (34) showed that the correlation between patient’s and physician’s global assessment of disease activity was only 0.30, similar to RA (35).

The BASDAI, a fully patient-reported measure has been published 20 years ago (22). As recently discussed (33), it measures only part of the domain disease activity. BASDAI does not weigh individual clinical manifestations, as the variables are simply summed, without taking the relative importance, redundancy and dependency into account. Finally, it lacks specificity for inflammatory processes (33).

Development of the ASDAS published 5 years ago (23, 24) aimed to improve the construct validity of disease activity measures in AS. To avoid that only one part of the construct disease activity is measured, several assessments were combined in one score to increase the validity of the score and enhance discriminative capacity and sensitivity to change (24). The statistical development of the ASDAS ensures that each item of ASDAS adds extra information not yet captured by the other items, and, thus, is not redundant. The ASDAS maximises the available information (the signal) and reduces the random error associated with measurement (the noise), it performed well methodologically and is feasible (24). However, the main relative advantage of BASDAI is that there is no need to wait for a lab result (CRP or ESR). Being highly discriminatory and sensitive to change (36), the ASDAS appears the best method to be used in clinical trials (37), and, if used as primary endpoint and therefore for sample size calculations, it would reduce the number of patients that need to be included by about 50% (37).

In a recent report from the OASIS cohort, disease activity measures were significantly longitudinally associated with radiographic progression (38, Fig. 6), adjusted for possible confounders including medication. The models with ASDAS fitted data better than BASDAI, CRP or BASDAI plus CRP. An increase of one ASDAS unit led to an increase of 0.72 mSASSS (modified Stokes AS scoring system, 39) units/2 years. A very high disease activity state (i.e. ASDAS >3.5) compared with ‘inactive disease’ (i.e. ASDAS <1.3) resulted in an additional 2-year progression of 2.3 mSASSS units. The effect of ASDAS on mSASSS was higher in males and in patients with long symptom duration (38).

A major topic of discussion has been the choice of a level of cut-off for consideration of anti-TNF therapy. Since all studies have used the BASDAI formal cut-off of 4, this is the method that is currently used most frequently. How-
ever, there is some evidence that the ASDAS could be the superior measure (37, 40-43) – especially since an elevated CRP has been reported to be a good predictor of response (44).

**Advantages of ASDAS**

- Validated response and status scores of ASDAS available (33, 37, 40)
- ASDAS showed the highest responsiveness compared to BASDAI and single assessments, MRI inflammation and damage scores in both the lumbar spine and in the sacroiliac joints (33, 37, 40)
- ASDAS changes correlated significantly with changes in MRI inflammation in SI joints and spine in contrast to BASDAI and CRP (45-47)
- Reflects the inflammatory disease processes better than the BASDAI (33, 37)
- ASDAS performed well in patients with/without peripheral arthritis, and normal/abnormal CRP (48)
- ASDAS was shown to work in AS, nr-axSpA, axial psoriatic arthritis (49)
- ASDAS performed in most studies better, sometimes equal to BASDAI (33, 37)
- the correlation of ASDAS to patient and physician global assessment is more balanced than BASDAI (33, 37)
- ASDAS predicts response to biologic therapy (44)
- ASDAS may perform better in the selection of patients for anti-TNF treatment (41-43)
- ASDAS can be used as a treatment target and to evaluate treatment response
- ASDAS is related to progression of mSASSS (38)

Another major difference between BASDAI and ASDAS is that the latter is entirely in the public domain while the BASDAI, since 2011, is only free of charge to academic users while industry has to pay because of a copyright held by A. Calin represented by the MAPI trust (Mapi Research Trust, 27 rue de la Villette, 69003 Lyon, France). The same applies for BASFI and BASMI (see below).

A recent report proposed approaches to address missing items of BASDAI and BASFI in large clinical studies (50). In conclusion, there is evidence that the ASDAS provides objective information on the level of disease activity and is superior to other measures in the assessment of patients with axial SpA, since it is more reliable to determine their disease activity status. ASDAS appears superior to determine the effectiveness of treatments, and provides better information on the level of disease activity than single variables. However, in certain situations the composite score might not give accurate information – e.g. in cases with concomitant chronic pain syndrome (as seen with any index that includes a patient estimate of pain and/or global status) or elevated ESR due to hypergammaglobulaemia. Finally, ASDAS proved to be a predictor of radiographic damage. The ASDAS is available for everybody, while use of BASDAI is restricted. Finally, future work should also put the definition of flare (51) into the context of disease activity measures.

**Function**

The first AS functional index was the Dougados functional index (DFI), proposed in 1988 (52). However, it was largely supplanted by the BASFI first published in 1994 (25), with reference charts reported some years later (53). Systematic comparisons favoured the BASFI (54, 55). High intraindividual week-to-week variability in BASFI values was found in one (56) but not in other studies (57, 58). In the former
study, 8 performance measures based on items used in the BASFI showed good reproducibility. In the other study the BASFI underwent rigorous psychometric testing (57), and was also found to have good reproducibility. In that study, BASFI responses showed an even spread of scores across patients but they were positively skewed. Although being unidimensional according to the Rasch model, the BASFI had several items displaying differential item functioning (58). Category disordering was apparent with the BASFI which also displayed disordered item thresholds. The authors discouraged the use of BASFI as an interval measure (58). The tool was found to have a tower of thresholds and several thresholds were marking the same point on the underlying disability construct (58).

To overcome the problem about reducing function to physical function, the categories of the International Classification of Functioning, Disability, and Health (ICF) has been used to describe a wide spectrum of functioning focusing on physical, emotional and social functioning. Validated and widely used instruments measuring physical functional ability in AS have been linked to the ICF and the contents have been compared. Based on the results of the linking process (59), 55 different ICF categories were linked: 7 belonged to body functions, 43 to activities and participation, and 5 to environmental factors. The component body structure was not contained in any of the four instruments. In an attempt to determine the comprehensive classification of functioning in AS (60) 127 ICF categories were identified to represent the relevant items from the patients’ perspective. The results underscored the need to address the 4 ICF components when classifying functioning and to emphasise that functioning implies more than physical functioning.

Some further studies have taken the ICF as the best basis to study function in AS in a more complex way including the definition of an ICF core set for AS (61–64). The most recent result of these investigations has been development of an AS health index which is introduced in another paper of this supplement (27). A major advantage of the newer index is that 5 items came in that were proposed by patients which do not appear in any other index published on function and disability in AS. Given the possibilities provided by the ICF there seems to be reason to develop another questionnaire to assess function in AS that is based on the relevant items provided by the patients. It is now well established that function is influenced by both disease activity and structural damage in AS (65, 66). It is more likely that inflammation plays a larger role in early disease, and new bone formation a stronger role in more advanced disease. However, it may be difficult to differentiate the two major influencing factors, in an individual patient. The observation that patients who were classified as non-responders to anti-TNF therapy had definitely improved physical function seems interesting in that regard (67). The influence of psychological factors on function and mobility has only rarely been studied in AS (68, 69).

The use of electronic patient questionnaires for function and other psychometric tests is increasingly studied and has already been successfully practised (70, 71).

In conclusion, although the BASFI is currently the most frequently used tool to assess function in AS, it seems likely that other approaches to assessment of function based on the ICF core set for AS will be developed.

**Spinal mobility**

A list of measures that have been used for the assessment of spinal mobility in AS can be found in the Table. In an early study with patients undergoing intensive physiotherapy, the spinal measurements (72) most sensitive to change were finger to floor distance, chest expansion, thoracolumbar rotation (TLR), and lateral flexion, while cervical rotation, hip internal rotation (HRI) and intermalleolar distance were considered to be also useful for short term clinical trials, while the Schober tests, thoracolumbar flexion, and occiput-wall distance were not sensitive. TLR and HRIs were the only measurements that correlated markedly with disease duration, but not with age (72).

The reproducibility of spinal metrology measures was tested in an international exercise (73) which showed that, overall, the measures of spinal mobility used in AS performed well with respect to interobserver reliability, and they were equally reproducible when applied to PsA patients with axial involvement (73).

In a recent cross-sectional study conducted among normal individuals aged 20–69 years (n=393) reference intervals (RIs) for spinal mobility measures as recommended for patients with axSpA were established (74). Eleven spinal mobility measures were assessed. The recruitment was stratified by gender, age and height. Age-specific RIs and percentiles were derived for each measure. Since all spinal mobility measures...
were shown to decrease with increasing age, age specific RIs were developed. The 95% RIs (2.5th and 97.5th percentiles), and the 5th, 10th, 25th, 50th, 75th and 90th percentiles for each spinal mobility measure and different ages are presented in that paper (74). Mobility percentile curves were plotted for each measure. For instance, the 95% RI for lateral spinal flexion was 16.2–28.0 cm for a 25-year-old subject, 13.2–25.0 cm for a 45-year-old subject and 10.1–21.9 cm for a 65-year-old subject. After adjustment for age, there was no need for gender specific RIs, while RIs of some measures are height-adjusted. Age specific RIs and percentiles for the commonly used spinal mobility measures in axSpA may guide clinicians when assessing the mobility of such patients. The RIs may serve as cut-off levels for ‘normal’ versus ‘abnormal’, whereas the mobility percentile curves may be used to assess the level of mobility of patients with axSpA (74). The individual patient does serve as the baseline for serial measures to observe change in status.

Population-based percentile reference values for selected spinal mobility measures in a nationally representative sample of 5103 U.S. adults aged 20–69 years were part of examinations performed in the 2009–10 U.S. National Health and Nutrition Examination Survey (NHANES, 75). All spinal measures were also significantly associated with gender, age, ethnicity, height, and body mass index. An OWD of >0 was present in only 3.8% of participants and 8.8% of participants had an out of range value (threshold 2.5 cm) for TE. The 95th percentile of OWD measurement (Table I) was 0 while the 5th percentile measurements for TE and ALF were 1.9 and 2 cm, respectively. Exclusion of individuals with severe obesity (BMI >35) slightly increased these values (75).

The BASMI has been published in its original form in 1995 (26). A clinimetric evaluation based on a study with two different doses of pamidronate (76) showed that the responsiveness of the original BASMI was poor with both scoring systems (2-step and 10-step, see below). Lumbar side flexion was the most responsive of the BASMI components. Changes in the BASMI and its individual components were not correlated with changes in functional outcomes. These authors from Edmonton/Canada have proposed a different scoring system, the EDASMI (Edmonton AS mobility index), that is not frequently used (77).

Lateral spinal mobility and chest expansion are most responsive to anti-TNF therapy (78). Changes to the 2-step scoring system into a 10-step and a linear calculation have been recently proposed (78) and evaluated (79). In an anti-TNF clinical trial with golimumab, lumbar flexion, tragus-to-wall distance, lumbar side flexion, intermalleolar distance, and cervical rotation angle measurements at baseline, week 14, and week 24 were used to calculate the BASMI 2-step (BASMI(2)), 10-step (BASMI(10)), and linear (BASMI(lin)) scores. BASMI(2) scores were generally lower than BASMI(10) and BASMI(lin) scores, which were nearly identical. Median changes from baseline to week 14 in the combined golimumab group were similar to those in the placebo group when using the BASMI(2) calculation method. The combined golimumab group showed significantly greater improvement from baseline to week 14 than the placebo group when using the BASMI(10) and BASMI(lin) calculation methods, with the latter showing the greatest difference between golimumab and placebo. Guyatt’s effect size was better for the BASMI(lin) and the BASMI(10) versus the BASMI(2) in the combined golimumab group, despite the relatively short period to assess changes in spinal mobility. Taken together, the BASMI(lin) method was the most sensitive to changes in range of motion exhibited by patients with AS (79). The main criticism over the years have been that it is not a pure measure for spinal mobility since the hip joints are included (intermalleolar distance), and that the chest expansion is not included. Thus, there seems room for the development of new composite scores that may differ from the current BASMI.

Finally, we would like to mention that a recent analysis on the performance of the MDHAQ (Multidimensional Health Assessment Questionnaire) score for physical function (FN), pain, Patient Global Estimate (PAGT), and RAPID3 (Routine Assessment of Patient Index Data, a composite of these 3 measures) documented improvement in patients with different rheumatic diseases including SpA and gout, similarly to RA (80), very well. Extensive experience with simple patient questionnaires (81) that are incorporated into standard care (82) suggests that use of such quantitative data should supplement traditional narrative descriptions in daily practice hereby improving care of patients with rheumatic diseases.

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