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The ASAS Criteria for Axial Spondyloarthritis: Strengths, Weaknesses, and Proposals for a Way Forward

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Abstract Classification criteria should facilitate selection of similar patients for clinical and epidemiologic studies, therapeutic trials, and research on etiopathogenesis to enable comparison of results across studies from different centers. We critically appraise the validity and performance of the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial spondyloarthritis (axSpA). It is still debatable whether all patients fulfilling these criteria should be considered as having true axSpA. Patients with radiographically evident disease by the ASAS criteria are not necessarily identical with ankylosing spondylitis (AS) as classified by the modified New York criteria. The complex multi-arm selection design of the ASAS criteria induces considerable heterogeneity among patients so classified, and applying them in settings with a low prevalence of axial spondyloarthritis (SpA) greatly increases the proportion of subjects falsely classified as suffering from axial SpA. One of the unmet needs in non-radiographic form of axial SpA is to have reliable markers that can identify individuals at risk for progression to AS and thereby facilitate early intervention trials designed to prevent such progression. We suggest needed improvements of the ASAS criteria for axSpA, as all criteria sets should be regarded as dynamic concepts open to modifications or updates as our knowledge advances.

Keywords Assessment of SpondyloArthritis international Society (ASAS) · ASAS classification criteria · Spondyloarthritis (SpA) · Axial spondyloarthritis (axSpA) · Ankylosing spondylitis (AS)

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Introduction

In the past decade, major progress has been made in the recognition, classification, and treatment of spondyloarthritis (SpA). The concept of axial spondyloarthritis (axSpA) and the criteria proposed by the Assessment of SpondyloArthritis international Society (ASAS) for its classification have contributed to a better understanding of its wider disease spectrum [1, 2•]. Ankylosing spondylitis (AS), usually defined by modified New York criteria [3], is the prototype of SpA [4, 5]. Genetic factors play major roles in disease susceptibility, disease activity, and severity [6, 7]. Radiographic sacroiliitis is considered a hallmark in AS, but it takes, on average, 6 to 8 years between the onset of chronic inflammatory back pain and establishing a definite diagnosis of AS. This diagnostic delay results mainly from the relatively late appearance of definite radiographic sacroiliitis on conventional plain radiographs [8, 9]. Such images show structural damage, not inflammation. Active inflammatory lesions of the sacroiliac joints on magnetic resonance imaging (MRI) predict a later appearance of radiographic sacroiliitis [10]. A proportion of such patients (11.6 % over 2 years in one report) do progress to radiographic sacroiliitis and thus fulfill the modified New York criteria [3, 11]. The ASAS criteria for axial SpA were developed with the goal of improving the ability to define such cases for clinical and research purposes, particularly in the absence of radiographic sacroiliitis (Table 1) [1, 2•].

In 1985, we observed in our family studies of human leukocyte antigen-B27 (HLA-B27+) probands with AS an occurrence of symptomatic disease but with normal looking sacroiliac joints on plain radiography among some of the first degree relatives, quite often women [12]. More recently, this form of what we had called "spondylitic disease without radiologic evidence of sacroiliitis" [12] has been termed *non-radiographic axSpA* (nr-axSpA) [9, 13, 14•] while the term axial spondyloarthritis (*axSpA*) encompasses this nr-axSpA as well as the classic AS (by modified New York criteria). There is a major unmet need to recognize and treat patients with nr-axSpA as they often have active disease that can be treated if current therapies used for AS are utilized. However, an unknown proportion of patients with nr-axSpA may never progress to classical AS or may go on to spontaneous remission. The ASAS criteria also encompass presentations with symptoms of axSpA, but caused by non-inflammatory conditions. Further understanding such aspects of axSpA requires valid criteria. Moreover, it needs to be pointed out that patients with radiographically evident axSpA by the ASAS criteria are not necessarily identical with ankylosing spondylitis (AS) as classified by the modified New York criteria. For example, a patient who has chronic back pain with onset before age 45 and radiographic sacroiliitis in the presence of at least 1 SpA feature can be classified as radiographic axSpA, but not as AS according to the modified New York criteria, unless the patient's chronic back pain is inflammatory in nature (e.g., improves with exercise and not relieved at rest).

Classification Criteria for axSpA

Candidate variables for the ASAS criteria were derived by experts in the field of SpA after they had evaluated 71 "paper patients" with possible axSpA, most of whom were lacking definite radiographic sacroiliitis [1]. ASAS members from 25 centers in 16 countries then provided 649 patients with chronic (more than 3 months) back pain (CBP) and of unknown origin that began before age 45. Upon diagnostic work-up and based on experts' opinion, axSpA was diagnosed in 391 of these 649 patients (60.2 %). HLA-B27 was present in 65.9 % of the 391 patients with axSpA, 61.9 % had normal CRP levels, 52.4 % were males, and 30 % fulfilled the modified New York criteria for AS [2•]. Among the remaining 258 patients with CBP considered not to have axSpA, 27.7 % possessed HLA-B27, quite a high proportion. Any variance in the prevalence of HLA-B27 within and between the 16 countries and any inter-observer variation in the diagnosis of axSpA were not reported [2•].

The sensitivity and specificity of these ASAS criteria were reported as 82.9 and 84.4 %, but for the imaging arm alone, they were 66.2 and 97.3 %, respectively [2•]. These figures were obtained from the same data set from which these criteria were developed. Figures for the clinical arm were reported as 56.6 % for sensitivity and 83.3 % for specificity [14•]. It was concluded that "the new ASAS classification criteria for axSpA can reliably classify patients for clinical studies and may help rheumatologists in clinical practice in diagnosing axSpA in those with chronic back pain" [2•]. Moreover, it was added that "the new criteria will also perform quite well as diagnostic criteria if applied by rheumatologists, and if a prevalence of axSpA of 60 % in the rheumatology setting is assumed as was the case in our study" [2•].

It is worth noting, however, that a prevalence (or pretest probability) of 60 % for axSpA among patients with CBP with onset before age 45 being seen outside of the specialized referral center for axSpA is unrealistically high. The a priori chance of axSpA will likely be much lower in settings with lower referral rates of axSpA. This will result in considerably higher figures for "false-positives" ("look-alikes"), i.e., those patients who fulfill the ASAS criteria but do not suffer from true axSpA.

Four categories listed in Table 2 should be considered in creating classification criteria for the full spectrum of axSpA. Valid classification criteria should define homogeneous phenotypes with common etiology (or pathogenesis), similar prognosis, and similar response to identical treatments. Since axSpA has been proposed to encompass a wider spectrum of AS, it should have a verifiable biologic relationship with

Table 1 ASAS classification criteria for axSpA (in patients with back pain for at least 3 months and age at onset <45 years)

Sacroiliitis on imaging	OR	HLA-B27
Plus		Plus
At least one other SpA feature		At least 2 other SpA features
Sacroiliitis on imaging		SpA features
Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA		Inflammatory back pain
OR		Arthritis
Definite radiographic sacroiliitis according to modified New York criteria		Enthesitis (heel)
		Uveitis
		Dactylitis
		Psoriasis
		Crohns disease/ulcerative colitis
		Good response to NSAIDs
		Family history for SpA
		HLA-B27
		Elevated CRP‡

ASAS Assessment of SpondyloArthritis international Society, *SpA* spondyloarthritis, *CRP* C-reactive protein, *HLA-B27* human leukocyte antigen-B27, *IBP* inflammatory back pain, *MRI* magnetic resonance imaging, *NSAIDs* nonsteroidal anti-inflammatory drugs

‡ Elevated CRP is considered a SpA feature in the context of chronic back pain

classical AS and not encompass other conditions that may resemble axSpA. Such criteria are needed to facilitate selection of similar patients for clinical studies, therapeutic trials, epidemiologic studies, and research on etiopathogenesis of a disease, and for comparison of results across studies from different centers. There is increasing evidence that the ASAS criteria for axSpA lack such validity, and we, therefore, suggest needed improvements, as criteria sets should be regarded as dynamic concepts open to modifications or updates as our knowledge advances.

The ASAS Classification Criteria Multi-arm Design Increases Heterogeneity

The ASAS classification criteria have been applied in several studies and settings, and the reported prevalence of axSpA has been estimated to be at least two to three times that of classical AS (by modified New York criteria) [15–17]. In line with our earlier findings among patients with "spondylitis disease without radiographic sacroiliitis" [12], there is a relative preponderance of women among patients with nr-axSpA as compared to those with AS [16, 17]. The prevalence of HLA-B27 among axSpA patients in population-based studies varies widely depending on how such patients were ascertained [15–17].

Table 2 Categories within the spectrum of axSpA, with or without peripheral arthritis

- Classical AS (by modified New York criteria) with syndesmophytes
- Classical AS (by modified New York criteria) without syndesmophytes
- "Early" not yet radiographic AS/axSpA
- AS/axSpA without ever developing radiographic sacroiliitis

A study from Tromsø, northern Norway, evaluated the utility of the ASAS criteria for axSpA in 807 patients reporting back pain lasting more than 4 weeks and who had undergone clinical, laboratory, and radiographic evaluation, but MRI was not available (Table 3) [16]. Altogether, 332 of these patients had CBP and aged 20–45 years; 163 (49 %) were males, and 56 (17.1 %) possessed HLA-B27. The prevalence of HLA-B27 in the general population of northern Norway is 15.9 % [16]. Twenty-eight of these 332 patients (8.4 %) met the ASAS criteria for axSpA; all but one of them (96 %) were HLA-B27+. Twenty of these 28 patients (71 %) belonged to the nr-axSpA (Table 3), and 4 of them (20 %) did develop radiographic sacroiliitis after a median period of 8 years of follow-up [16]. Overall, among the 56 HLA-B27+ patients with CBP and aged 20–45, axSpA was present in 27 (48.2 %) of them.

In a Dutch study, in the Rotterdam region, case records of 12,477 patients from general practitioners' registers were reviewed, and 1106 of them (8.9 %) were found to have ever been registered with non-specific low back pain and they were invited by letter [17]. Eligibility was further checked via an interview by telephone, and responders were eligible if they had current CBP for >12 weeks and had no contraindications for MRI, had no back injury, and were not pregnant.

Table 3 Applying ASAS classification criteria with or without MRI in two different populations

Country	Norway	Netherlands
Source	Population survey	Primary care
HLA-B27+ in general population:	15.9 %	8.8 %
Back pain	*N*=807	*N*=1106
Back pain >3 months; onset <45 years	332/807 (41 %)	364/1106 (33 %)
Mean age±SD (year)	40.8±8.2	36.3±6.8
HLA-B27+	56/332 (17 %)	20/364 (5.5 %)
Male sex	49 %	43 %
AS (mNY)	8/332 (2.4 %)	24/364 (6.6 %)
HLA-B27+	7/8 (87.5 %)	≤7/24 (≤29 %)
Male sex	75 %	38 %
♦ Axial SpA by ASAS Criteria	28/332 (8.4 %)	86/364 (23.6 %)
Mean age±SD (yr)	37.4	36.6±6.6
HLA-B27+	27/28 (96 %)	17/86 (20 %)
Male sex	57 %	38 %
♦ Non-radiographic axSpA	20/332 (6.0 %)[a]	56/364 (15.4 %)
♦ HLA-B27 positive + ≥2 SpA features	20/332 (6.0 %)[b]	10/364 (2.7 %)
Male sex	50 %	60 %
♦ Axial SpA when HLA-B27+ CBP[b]	27/56 (48.2 %)	17/20 (85 %)
♦ Non-axial SpA CBP	304/332 (91.6 %)	278/364 (76.4 %)
HLA-B27+	29/304 (9.5 %)	3/278 (1.1 %)
♦ Non-axial SpA when HLA-B27+ CBP[c]		
Number of patients observed[c]	29	3
Number of patients expected	48 (15.9 % of 304)	24 (8.8 % of 278)
	$p<0.01$	$p<0.001$

Please note that the reported prevalence of axSpA in these two studies (8.4 versus 23.6 % is dependent on which arms (imaging or clinical) of the ASAS classification criteria one uses for the study

ASAS Assessment of SpondyloArthritis international Society, *AS* ankylosing spondylitis, *mNY* modified New York criteria, *SpA* spondyloarthritis, HLA-B27 human leukocyte antigen-B27, *CBP* chronic back pain, *MRI* magnetic resonance

[a] No magnetic resonance imaging was performed; only clinical arm of ASAS axial SpA classification criteria were applied

[b] HLA-B27+CBP=HLA-B27 positive patient with chronic back pain >3 months and onset at <45 years of age

[c] In the Norwegian study, 304 of 332 CBP patients did not fulfill the ASAS criteria for axial SpA; 29 of them were HLA-B27+, whereas the expected number was 48 HLA-B27+ CBP patients given a HLA-B27 prevalence of 15.9 % in the regional Norwegian population ($p<0.01$). In the Dutch study, 278 of 364 CBP patients did not fulfill the ASAS criteria for axial SpA; 3 of them were HLA-B27+, whereas the expected number was 24 HLA-B27+ CBP patients given a HLA-B27 prevalence of 8.8 % in the general Dutch population ($p<0.001$)

Altogether, 364 patients met the eligibility criteria. They completed questionnaires for inflammatory back pain (IBP), and an experienced rheumatologist performed clinical evaluation (clinical history containing all potential features of axSpA, namely IBP, arthritis, family history, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, uveitis anterior, and response to NSAIDs), performed swollen joint count and spinal mobility measurements, and ordered laboratory tests (including ESR, CRP, HLA-B27 typing), conventional pelvic radiography, and MRI (T1, T2, and STIR images) of the sacroiliac joints [17]. The ASAS criteria for axSpA were satisfied in 86 of the 364 (23.6 %) patients; and 56 of these 86 (65 %) patients had nr-axSpA (Table 3) [17]. The data also show that 17 of 20 (85 %) HLA-B27+ patients with CBP and onset before age 45 met the ASAS criteria for axSpA. The prevalence of HLA-B27 among the 278 patients who did not have axSpA was only 1.1 %, i.e., only 3 patients (Table 3) [17]; the expected number would have been 24 patients (0.088 multiplied by 278) since the frequency of HLA-B27 in the general Dutch population is 8.8 % [18]. It is also

note-worthy that only 38 % of the 86 patients with axSpA were male.

The observed proportion of CBP patients meeting the ASAS criteria for axSpA in the two studies differs considerably (8.4 versus 23.6 %). This indicates that enrollment through different arms of the ASAS criteria leads to heterogeneity and incomparability across studies. This violates the primary aim of all classification criteria, i.e., creating homogeneity. Utilization of MRI of the sacroiliac joints may result in a considerably higher prevalence rate of axSpA, along with a higher proportion of females and lower prevalence figures for HLA-B27 among patients classified as having axSpA. Furthermore, there is a risk of biased inclusion. The performance of the ASAS criteria in both studies showed that, as expected, HLA-B27+ patients with CBP are very much prone to axSpA, but oddly, somehow, they seem to be relatively "protected" from the ubiquitous non-specific CBP (Table 3). This distortion can also occur if axSpA patients have a markedly increased likelihood of being included in chronic back pain cohorts. This type of bias is unlikely in the Norwegian study as the 17 % prevalence of HLA-B27 in the group of patients with CBP with onset before age 45 is almost the same as in the general population (15.9 %) of that region [16]. In the Dutch study, on the other hand, the prevalence of HLA-B27 of only 5.5 % in the group of patients with CBP with onset before age 45 is even lower than in the general Dutch population (8.8 %) (Table 3) [17, 18]. This finding is most likely due to misclassification bias where the ASAS criteria misclassified HLA-B27+ non-axSpA as axSpA, i.e., if the criteria lack discriminative power to differentiate between non-specific CBP and "true" axSpA. HLA-B27+ patients with CBP are at increased risk of being misclassified as axSpA (e.g., if their back pain responds well to NSAIDs and they happen to have a second feature such as heel pain).

Clinical Dissimilarities Among Patients Enrolled by the Two Arms of the ASAS Classification Criteria

Dissimilarities between the two arms of the ASAS criteria were seen not only in population-based studies [16, 17] but also noted in a prospective cohort of early IBP (<3 years duration) with high probability of SpA [19••]. Patients in the imaging arm were younger (30.6 versus 32.6 years), more frequently male (59.2 versus 41.6 %), and had higher mean CRP levels (11.6 versus 5.2 mg/L), when compared with those in the clinical arm [19••]. Within the imaging arm, the subset of patients with a positive MRI but negative X-ray also had higher male prevalence (56.2 versus 41.6 %) and mean CRP levels (10.5 versus 5.2 mg/L) than those in the clinical arm [19••].

Results obtained in an early axSpA cohort depict the differences between the imaging and the clinical arms of the nr-axSpA with regard to the structural MRI lesions at this early symptom stage [20]. Prevalence of any type of MRI lesions in the sacroiliac joints (bone edema, fatty changes, erosion, or fusion) in the patients meeting the clinical arm was found to be quite similar to that in the group with possible or no SpA [20].

To date, four randomized placebo controlled trials (RCTs) of tumor necrosis factor (TNF) inhibitors have been conducted in patients with nr-axSpA, as defined by the ASAS criteria [21•, 22•, 23•, 24]. Comparison of the results of these studies with those observed in the major RCTs in patients with AS identifies some prominent differences between AS and nr-axSpA, such as a relatively diminished male prevalence [21•, 22•, 23•, 24] and lower CRP levels [21•, 22•, 23•] in some studies of patients with nr-axSpA (Table 4). HLA-B27 prevalence in the imaging arm of nr-axSpA (54–73.5 %) reported in these trials [21•, 23•, 24] was lower than those reported in patients with AS (79–87 %) (Table 4) [22•, 25–28]. HLA-B27 prevalence among patients defined by the clinical arm of nr-axSpA is by definition, 100 %.

Heterogeneity regarding demographics and disease characteristics exists also across the nr-axSpA trials, which may partly be a result of differences in the relative size of each arm (clinical and imaging) in the study population. Although both ABILITY-1 trial of adalimumab [21•] and a similar etanercept trial [23•] involved patients with nr-axSpA, the composition of the study populations was markedly different, with 49 and 81 % of the patients meeting the imaging arm, respectively. Use of additional inclusion components in some of the trials, such as elevated CRP or positive MRI [22•], disease duration [23•, 24], or age [24], probably contributed to the observed heterogeneity.

Thus, it becomes clear that the ASAS criteria create heterogeneity not only between the radiographic and non-radiographic forms of axSpA but also between the imaging and the clinical arms. The complex multi-arm selection design of the axSpA classification criteria and its broad spectrum may lead to differences among the composition of patients in different clinical trials and other studies.

Heterogeneity in Clinical Response to Treatment

Clinical response to anti-TNF agents seems to be better in patients with AS than in those with nr-axSpA, as suggested by a significantly greater ASAS40 response rate observed in AS patients (48.1 versus 29.6 %; $p=0.02$) in a recent study [29••]. Another study noted differences even between the imaging and the clinical arms of the subgroups of nr-axSpA because of higher response to anti-TNF therapy in patients with positive imaging findings than in those without [30]. Of note, the delta values for ASAS20 responses in AS trials seem to be greater than those observed in nr-axSpA trials

Table 4 Comparison of patient characteristics and efficacy data from randomized placebo controlled trials of TNF inhibitors conducted in patients with non-radiographic axSpA and those with AS

	Demographics		Disease characteristics					ASAS20 response rate[a] (%)		
	Male (%)	Age (years)	Disease duration (years)	HLA-B27 prevalence (%)	BASDAI	BASFI	CRP (mg/dL)	Placebo	anti-TNF	Delta
• Non-radiographic axial SpA										
Adalimumab [21•]	45.5	38.0	10.1	58.2[c]	6.5	4.7	0.7	31.0	52.0	21.0
Certolizumab [22•]	48.3	37.4	5.5[b]	53.7[c]	6.5	4.9	1.2[b]	40.0	62.7[d]	22.7[d]
Etanercept [23•]	60.4	32.0	2.5	64.9[c]	6.0	4.0	0.7	36.1	52.4	16.3
Golimumab [24]	57.0	31.2	<1 year[b]	73.5[c]	6.5	5.0	1.4	40.0[e]	71.1[e]	31.1[e]
• Ankylosing spondylitis										
Etanercept [25]	76.0	42.0	10.3	84.0	5.9	5.4	2.0	28.0	59.0	31.0
Infliximab [26]	80.6	40.3	9.2	87.1	6.6	5.8	1.6	19.2[f]	61.2[f]	42.0[f]
Adalimumab [27]	74.9	42.3	10.9	78.7	6.3	5.3	1.9	20.6	58.2	37.6
Golimumab [28]	71.6	38.7	12.1	83.4	6.8	5.1	1.0	21.8[g]	59.7[g]	37.9[g]
Certolizumab [22•]	72.5	41.5	9.1[b]	81.5	6.4	5.7	1.4[b]	36.8	64.3[d]	27.5[d]

Some of the data included in the table are not given in the original study but are estimated from the presented data in that study. Unless stated otherwise, values are the mean

AS ankylosing spondylitis, *SpA* spondyloarthritis, *TNF* tumor necrosis factor, *CRP* C-reactive protein, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Functional Index, *HLA-B27* human leukocyte antigen-B27, *ASAS20* ASAS criteria for 20 % improvement

[a] ASAS20 response rate at week 12 except where otherwise indicated

[b] median value

[c] In the group of patients with non-radiographic axial SpA fulfilling the imaging arm

[d] for the 400 mg every 4 weeks arm

[e] ASAS response rate at week 16

[f] ASAS20 response rate at week 24 (almost identical to that at week 12 as shown in a graph in the cited publication)

[g] ASAS response rate at week 14

(Table 4). Consistently higher ASAS20 responses obtained with placebo in the nr-axSpA trials compared with those observed in the AS trials (Table 4) may suggest a more fluctuating disease course in patients with nr-axSpA.

There are also differences in clinical response to anti-TNF therapy between AS and nr-axSpA patients, particularly in the setting of normal baseline CRP levels. The probability of achieving a BASDAI50 response in classical AS patients with normal CRP and short disease duration (≤5 years) was estimated to be as high as 65 %, based on a combined analysis of the data from two early randomized controlled trials of infliximab and etanercept [31]. Another RCT [32] and data from the British Biologics Registry [33] also showed significantly greater clinical responses in patients with classical AS who have normal baseline CRP values. In contrast, in the nr-axSpA trials of the adalimumab [21•] and etanercept [23•], ASAS40 response rates at week 12 obtained in patients with normal CRP levels at baseline were only minimally higher in the active treatment arms as compared to the placebo arms (27 versus 18 and 20.7 versus 12.5 %, respectively) [21•, 23•]. Of note, the mean disease duration in the adalimumab trial was 10.1 versus only 2.5 years in the etanercept trial (Table 4). Such disparity in clinical response to anti-TNF agents between patients with AS and nr-axSpA underlines the heterogeneity between these two clinical entities. This heterogeneity precludes comparability of results across studies, as patients included in those studies differ for variables such as gender, imaging results, proportion HLA-B27+, CRP levels, and, importantly, also in clinical responsiveness to treatment.

Critical Appraisal and Performance of the ASAS Classification Criteria in the "Real World"

It is not yet known how well the ASAS classification criteria really capture what we have called "spondylitic disease without radiographic sacroiliitis" [12]. There are no data on their performance in settings with a lower prevalence of disease (a priori likelihood) or among patients with "look-alike" conditions with signs and symptoms resembling axSpA, including patients with ubiquitous or mechanical back pain or fibromyalgia. Mislabeling of such conditions as axSpA due to a relative lack of specificity of the ASAS criteria in settings with lower prevalence of disease will be associated with health and financial costs of potential mismanagement of the disease. Recommendations for the development and validation of criteria sets have been proposed based upon the current standards of measurement science [34, 35].

Issues With Validity of the ASAS Classification Criteria

A number of validity issues need to be addressed and appraised critically; these include face validity, construct validity, criterion validity, and content validity.

Face Validity This aspect assesses whether the criteria are sensible and reflect the attributes of the disease and also show coherence of the separate criteria items. The multi-arm design of the ASAS classification criteria creates several different phenotypes, which contrast with the primary aim of classification to promote homogeneity. This multi-arm design is more appropriate for diagnostic tools.

Construct Validity It addresses whether the criteria identify those with the disease (sensitivity) and those without (specificity). One should also evaluate how often the criteria are met as false-positives in clinical entities that should be considered in the differential diagnosis. In contrast to an expert-center setting, in more community settings, the prevalence of axSpA generally will be lower. The predictive value of the criteria will as a consequence be lower, resulting in a higher proportion of false-positive diagnoses and possibly inappropriate management. However, the sensitivity and specificity may also change due in relation to the proportion of patients who have mild versus severe forms of the disease.

Up to now, the ASAS criteria for axSpA are built upon experts' opinion only. Proper assessment of validity of these criteria has not yet been reported. Some of the clinical features of axSpA criteria lack specificity. For example, about 11 % of healthy sportsmen ("orienteers") have been reported to have back pain that meets the definition of inflammatory back pain [36]. If such physically active sportsmen happen to be HLA-B27+ and also happen to have mechanical heel pain and a good response of their "inflammatory"-type back pain to NSAIDs, then they classify as having axSpA without any requirement for further confirmative imaging evidence, or even if imaging tests including MRI are negative.

Criterion Validity A few examples may illustrate what is meant by criterion validity. A new measure proposed to assess bone quality will have criterion validity if it could demonstrate a strong correlation of this new measure with an external measure such as the incidence of fractures. The same holds true for demonstrating strong correlations with the typical distribution of the affected joints and the levels of uric acid when developing new classification criteria for acute gout. Another

theoretical example might be validation of the clinical components of a certain candidate set of clinical criteria for classical AS. Suppose for a moment that pelvic radiographs were non-existent. In that case, a proposed set of clinical criteria for AS should have a strong correlation with HLA-B27, and most patients meeting these new criteria should turn out to be HLA-B27+. In this last example, the genetic factor HLA-B27 supports the criterion validity. However, objective markers that are included in the ASAS criteria (HLA-B27, CRP, and MRI of sacroiliac joint) are not sufficient enough to strongly support criterion validity. CRP is not elevated in a sizeable percentage of axSpA patients and has very low specificity; the overwhelming majority of HLA-B27+ people remain healthy, and "positive MRI" results of sacroiliac joints also lack high specificity. For example, bone marrow edema was noted in 23 % of patients with mechanical back pain and in 7 % of healthy volunteers, whereas erosion was recorded in 4 and 2 % of these individuals, respectively [37] A data-driven endeavor is required to define the features that constitute a positive MRI in axSpA [38].

Content Validity It refers to the comprehensiveness of the criteria, and it evaluates whether all the domains of the disease have been represented. The ASAS classification criteria sample a number of relevant domains: clinical, imaging, and genetic (HLA-B27). But evidence is still required to demonstrate that axSpA criteria really encompass the wider spectrum of AS, exclude other conditions, and define a homogenous group of patients. The recent genome-wide association study (GWAS) results have linked at least 40 genetic loci to AS [39, 40], and a large proportion of the genetic variants that contribute to the disease have yet to be identified. Although some of the genetic variants may be associated with disease activity and severity [6, 7], it seems reasonable to postulate that most of them should also be present in patients with broader spectrum of the disease and thus also occur in patients with nr-axSpA. One may, therefore, expect a high degree of genetic similarity among the subgroups of axSpA. Genes do not work independently but in a concert, just like in an orchestra [41]. The first two genes to be discovered to show association with AS, i.e., *HLA-B27* and *ERAP1*, show epistasis (gene-gene interaction) and together contribute to approximately 75 % of the population attributable risk to AS [39–41]. While all genetic associations other than *HLA-B27* are of low individual effect, in combination, they have significant discriminatory capacity in distinguishing AS cases from healthy individuals. This discriminatory capacity is progressively increasing as a higher proportion of the genetic risk for AS is defined.

Moving Forward From Concept to Valid Criteria

Table 5 lists our proposed steps that are needed to improve the validity of the ASAS criteria. The concept of axSpA that encompasses both the classical AS [3] and the "spondylitic disease without radiographic sacroiliitis" [12] is attractive and also important for clinical research and management decisions. However, the current construct of the ASAS criteria for this clinical entity, as discussed above, lacks construct, criterion, content, and face validity. Moreover, its multi-arm selection design induces considerable heterogeneity among enrolled patients in different studies, and this can be reduced by inclusion of patients through stratification by separate arms, but it would be contrary to the rationale of encompassing the wider spectrum of axSpA into one group.

One of the unmet needs in nr-axSpA is the lack of reliable markers that can identify individuals at risk for progression to AS and facilitate early intervention trials designed to prevent such progression. Emerging evidence that available therapy may slow radiographic progression of axSpA heightens the importance of recognizing axSpA at an early stage, but potential benefits and risks of early identification need careful considerations [42]. We recommend exploration of genomics, proteomics, and selected biomarkers as tools to differentiate between "true" axSpA and mimicking conditions. Appropriate assessment of criterion validity of the "construct" axSpA would include verification of its biologic association with AS genetics, including MHC and non-MHC gene variants, and proteomic or other biomarkers that turn out to be typical for and occur frequently in classical AS. Candidate biomarkers, mostly hypothetical at this stage, are listed in Table 6 [39, 40, 43–54]. Some of these biomarkers may turn out to have prognostic value, and those will be most suitable as predictors of outcome, not as candidates for classification criteria that are intended to create homogeneity, not prognostication.

Table 5 Proposed steps to move forward in improving validity of the ASAS classification criteria for axSpA

- Assess sensitivity, specificity, and predictive value in settings with lower prevalence of axSpA and use controls, including patients with fibromyalgia
- Evaluate MHC- and non-MHC genes and other candidate biomarkers, individually and in combination, that typically are met in classical AS
- Establish specificity in HLA-B27+ and HLA-B27- controls (unselected for the ASAS axSpA classification criteria)
- Appraise AS biomarkers separately in patients meeting the "imaging" arm versus the "clinical" arm of current ASAS axSpA criteria
- Investigate the performance of different MRI criteria in classifying patients with radiographic and non-radiographic axSpA to determine optimal "imaging" arm of the classification criteria
- Adjust the current ASAS axSpA classification criteria as needed to firmly establish a close biological relationship of non-radiographic axSpA with classical AS

Table 6 Biomarkers to consider for improving validity of the ASAS classification criteria for axSpA

- Genomics (MHC and non-MHC) [39, 40]
- Proteonomics [43]
- Specific Biomarkers
  - Vascular endothelium growth factor [44]
  - Matrix metalloproteinase-3 [45, 46]
  - Sclerostin [47, 48]
  - Calprotectin [49]
  - Citrullinated vimentin [50]
  - Dikkopf-1 [51]
  - Anti-CD74 antibodies [52–54]

Studies are needed to assess the clinical course of the full spectrum of axSpA. Furthermore, any inter-observer variation in the assessment of axSpA has to be established. Such studies will contribute towards reducing concerns raised by the FDA with regard to the classification of non-radiographic axSpA [55••]. Improved and truly validated classification criteria will facilitate discovery of appropriate new and more effective ways to manage patients at very early stages of axSpA.

Conclusion

Major progress has been made during the past decade in the recognition, classification, and treatment of SpA. The concept of axSpA and the criteria proposed by ASAS for its classification have contributed to a better understanding of its wider disease spectrum. Classification criteria should facilitate selection of similar patients for clinical and epidemiologic studies, therapeutic trials, and research on etiopathogenesis to enable comparison of results across studies from different centers. We have hereby provided critical appraisal of the validity and clinical performance of the ASAS classification criteria for axSpA. It is still debatable whether all patients fulfilling these criteria should be considered as having true axSpA [56••, 57, 58••, 59••, 60••, 61••].

The complex multi-arm selection design of the ASAS criteria for axSpA induces considerable heterogeneity among patients so classified. Application of these criteria in a setting with a low prevalence of axial SpA would greatly increase the proportion of subjects falsely classified as suffering from axial SpA. One of the unmet needs in nr-axSpA is to have reliable markers that can identify individuals at risk for progression to AS and thereby facilitate early intervention trials designed to prevent such progression. We suggest needed improvements of the ASAS criteria for axSpA and propose steps that are needed to improve the validity of the criteria, summarized in Tables 4 and 5, because all criteria sets should be regarded as dynamic concepts open to modifications or updates as our knowledge advances. It is feared that the current criteria may provoke a prominent axSpA "Gestalt" that may impact the diagnostic process even if one correctly does not apply (or "box") classification criteria to establish a clinical diagnosis for an individual patient. Incidentally, a recent publication has very nicely explained the distinctions between the diagnostic and the classification criteria [62••].

Finally, regarding the nomenclature: axSpA or AS? What is in a name? What we call a rose would smell as sweet by any other name (William Shakespeare). What we call "Axial SpA" or "Ankylosing Spondylitis" abbreviates as "AS" by both names. To be or not to be, that is the question! (Hamlet, William Shakespeare).

Compliance with Ethics Guidelines

Conflict of Interest Sjef van der Linden: None

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- • Of importance
- •• Of major importance

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