ASAS classification criteria for axial spondyloarthritis: a look at the unfilled part of the glass

Sirs,

The concept of "spondyltic disease without radiographic evidence of sacroiliitis" was first published in 1985 (1), and was more recently redefined as "non-radiographic axial spondyloarthritis (nr-axSpA)", while the term ankylosing spondylitis (AS) is considered to be synonymous with the presence of radiographic sacroiliitis in a patient with axial spondyloarthritis" (axSpA) (1, 2). This has led to the new Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA as a disease entity that encompasses patients with AS, and also those that may or may not show evidence of sacroiliitis on MRI (but not on pelvic radiography) (3). So a patient with chronic back pain with age at onset of <45 years can be classified as having axSpA if the "imaging arm" (the presence of sacroiliitis as detected by either x-ray or by MRI plus ≥1 SpA feature(s)) or the "clinical arm" (the presence of HLA-B27 plus ≥2 SpA features and the imaging arm) features are fulfilled.

The primary objective of all classification criteria is to identify a homogeneous patient population for basic research and clinical trials. Therefore, the patients so selected must be equivalent in terms of demographics, clinical characteristics, treatment response and prognosis. A comparison of the patient sub-populations [defined by the two different subgroups of axSpA (AS *vs*. nr-axSpA), as well as those within the nr-axSpA (clinical arm *vs*. imaging-MRI only)] is needed to validate these components of the ASAS criteria.

There has been some recent debate on the similarities and differences between AS and nr-axSpA. It has been suggested that nr-axSpA and AS are different, though overlapping, entities, based on female predominance, weaker association with HLA-B27, greater diversity with regard to disease progression, and lower response to treatment in the nr-axSpA group (4). However, another recent publication reached an opposite conclusion, claiming that nr-axSpA is the same entity as AS, but with a self-limiting or a slower disease progression, possibly due to female predominance and lower inflammatory response (5). But both of these publications acknowledged the presence of greater heterogeneity among the patients with nr-axSpA.

Recent data from DESIR cohort (6) suggest that patients in the clinical arm of the ASAS criteria for axSpA may account for some of the reported differences between nr-axSpA and AS (7). Despite similarities in many clinical variables, the patients in the imaging arm of the ASAS criteria for axSpA were significantly younger (30.6 *vs*. 32.6 years), more frequently male (59.2% *vs*. 41.6%) and had higher mean CRP levels (11.6 mg/dl *vs*. 5.2 mg/dl), when compared with those in the clinical arm. On analysing patients within the imaging arm, those with only positive MRI also had a higher male prevalence (56.2%) and mean CRP levels (10.5 mg/dl) than those in the clinical arm.

A study of another cohort (SPACE) assessed the prevalence of structural lesions on MRI among patients with early axSpA, and those with possible or no SpA (8, 9). The prevalence of any type of MRI-spine lesions (fatty changes, erosion or syndesmophyte) in the patients meeting the clinical arm was very similar to those with possible or no SpA, but lower than those observed in the AS patients or nr-axSpA patients in the imaging arm (8). MRI lesions in the sacroiliac joints (fatty lesion, sclerosis, erosions or ankylosis) were also less common in the clinical arm as compared to each subgroup of the imaging arm (9). These results obtained in an early axSpA cohort are of interest as they depict the differences between the two arms of the nr-axSpA with regard to the structural MRI lesions in the axial skeleton at an early symptom stage.

Nr-axSpA patients belonging to the two arms of the ASAS criteria for axSpA, may also differ in their natural history. A recent retrospective analysis of patients

Table I. Composition of patient populations in recent trials of TNF inhibitors for axSpA.

	ABILITY-1 n=185	RAPID-axSpA n=325	Etanercept n=215	INFAST n=156
Anti-TNF agent	Adalimumab	Certolizumab	Etanercept	Infliximab
Target population	Nr-axSpA	axSpA	Nr-axSpA	axSpA-Imaging arm
Trial specific Inclusion criteria[1]	None	Presence of MRI lesions or high CRP	Disease duration <5 yrs	Disease duration <3 yrs NSAID naïve[4]
Clinical arm[2]	51%	20% (46%)[3]	19%	0%
Imaging-nraxSpA	49%	25% (54%)[3]	81%	40%
Imaging-AS	0%	55%	0%	60%

[1] Those not used in pivotal registration trials of anti-TNF agents for AS; [2]Many patients in the clinical arm had an unknown MRI status; [3]Percentage in the nr-axSpA group only; [4]NSAIDs not previously used or used in submaximal doses.

Table II. Some patient characteristics in recent trials of TNF inhibitors for axSpA.

	ABILITY-1	RAPID-axSpA[1]	Etanercept	INFAST
Age, mean (yrs)	38	37.4	32	31.4
Male gender	46%	48%	61%	72%
HLA-B27 positivity	78%	75%	72%	86%
Symptom duration mean (yrs)	10.1	5.5[2]	2.4	1.8
CRP mean (mg/dl)	7.2	11.9[2]	6.6	1.9

[1]The data shown are for the nr-axSpA subgroup only; [2]Median value.

Table III. Prevalence of HLA-B27 among patients in different subgroups of axSpA in recent trials of TNF inhibitors for nr-axSpA.

	ABILITY-1	RAPID-axSpA	Etanercept	INFAST
Nr-axSpA (Imaging arm)	58%	54%[1]	66%	NR
AS	NA	82%	NA	NR
All axSpA	78%	79%	72%	86%

[1]Many patients in the clinical arm had an unknown MRI status; NA: not applicable; NR: not reported.

who had presented with inflammatory back pain and possible early AS, reported that after 5–10 years of follow-up 87.5% of patients with sacroiliitis on MRI at baseline developed grade II or higher sacroiliitis, compared to only 30% in those with no sacroiliitis on MRI (10). This is in line with some other studies indicating an association of baseline MRI findings with future development of radiographic sacroiliitis (11, 12).

Limited evidence suggests that the two subgroups of nr-axSpA may also differ in their response to anti-TNF therapy. In the ABILITY-1 trial of adalimumab, which included nr-axSpA patients, there was a trend for a higher response in patients with a baseline MRI SPARCC SI joint score ≥2 than in those with a score <2 (11). Another study reported higher response rates to TNF inhibitors in patients with positive imaging findings than those without. However, imaging in that study included also standard radiographs and CT-scans (13).

The ASAS classification criteria for axial SpA were primarily developed to facilitate the conduct of clinical trials, especially for those in the pre-radiographic stage. To date, four randomised controlled trials have been conducted using the new classification criteria (14-17). However, they mostly targeted different subgroups of the disease using different inclusion criteria (Table I). This lead to selection of heterogeneous patient populations across these four studies, which makes the comparison rather difficult (Table II). ABILITY-1 trial of adalimumab and the etanercept trial both involved patients with nr-axSpA; however the composition of their study populations were markedly different, with 49% and 81% of the patients meeting the imaging arm, respectively (Table I). In some of these studies the prevalence of HLA-B27 in the imaging arm was much lower than expected for AS (Table III). Moreover, most of these trials adopted additional inclusion criteria for patient selection, which were not used in pivotal registration trials of anti-TNF agents for the treatment of AS. This may indirectly indicate a difference in treatment response between AS and nr-axSpA, or point out the need for an increase in the specificity of the criteria set for nr-axSpA. Thus, the broad spectrum and the complex multi-arm selection design of the axSpA classification criteria may lead to different composition of patients in different trials, which may contribute to the heterogeneity of the observed results. Criteria sets should be regarded as dynamic concepts open to modifications or updates as our knowledge advances. The clinical entity of AS is well established within the concept of axSpA, with good sensitivity and high degree of specificity, as defined by the modified New York criteria (18). Classification criteria that target a narrower clinical spectrum may better serve their primary objectives; *i.e.* to facilitate enrolment of homogenous patient populations into clinical trials, and communication within the scientific community. Until such criteria have been developed, all we have are the current classification criteria for axSpA that encompass AS and nr-axSpA. In the end, it needs to be emphasised that as yet there are no diagnostic criteria for these clinical entities.

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