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SPONDYLOARTHRITIS (MA KHAN, SECTION EDITOR)

Looking Into the New ASAS Classification Criteria for Axial Spondyloarthritis Through the Other Side of the Glass

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Abstract The new concept of axial spondylitis (axSpA) and the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA have induced new clinical research that has broadened our understanding of spondyloarthritis (SpA) and has had indeed a positive impact on earlier diagnosis and treatment of patients with axSpA who have not yet developed radiographic sacroiliitis. The primary goal of any valid classification criteria for any disease is to provide a homogeneous study population with a common etiopathogenesis, similar prognosis, and similar response to identical treatment. Without such a homogeneous study population, robust clinical and basic science research in any subtype of SpA is not possible. All criteria are dynamic concepts that need updating as our knowledge advances and our review of the ASAS classification criteria of axSpA indicates that complex multi-selection design and unclear (not mutually exclusive) definitions of the imaging and clinical arms of the criteria results in patient heterogeneity across study populations. Therefore, there is a need to improve the validity of the ASAS criteria for axSpA. It is our opinion that in the meantime, the clinically well-established entity of AS, as defined by the modified New York (mNY) criteria, should be preserved for the most accurate comparison of the new research studies with those conducted over the last three decades, and that the use of the ASAS criteria should be restricted to patients with nr-axSpA, who are not recognized by the mNY criteria.

Keywords Spondyloarthritis · Axial spondyloarthritis · Ankylosing spondylitis · Classification criteria

> "When I use a word" Humpty Dumpty said, in rather a scornful tone "it means just what I choose it to mean—neither more nor less."
> "The question is," said Alice, "whether you can make words mean so many different things."
> Through the Looking-Glass, and What Alice Found There (1871).—Lewis Carroll (1832–1898)

Introduction

The term axial spondyloarthritis (axSpA) encompasses the wider clinical spectrum of ankylosing spondylitis (AS) that includes patients who have predominantly axial involvement but their pelvic radiograph does not show sacroiliitis [1, 2]. This non-radiographic form is actually not new and was introduced as "spondyltic disease without radiographic evidence of sacroiliitis" 30 years ago [3]. The emergence of magnetic resonance imaging (MRI) as a new imaging tool that facilitates early detection of sacroiliac inflammation, and the introduction of tumor necrosis factor (TNF) inhibitors as very effective therapeutic agents for symptoms of AS, and possibly disease modifying, when started early, have renewed interest in the non-radiographic phase of the disease. Therefore, the Assessment of Spondyloarthritis International Society

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(ASAS) has developed a new classification criteria for axSpA that encompasses patients with definite radiographic sacroiliitis (radiographic axSpA) as well as those with "spondyltic disease without radiographic evidence of sacroiliitis" (non-radiographic (nr-axSpA)) [4] (Table 1).

Undoubtedly, the new concept of axSpA (2) and the classification criteria within this concept (4) have induced new clinical research, which has broadened our understanding of SpA and has had a positive impact on earlier diagnosis and treatment of patients with nr-axSpA. Thus, the European Medicines Agency (EMA) has approved the use of three TNF inhibitors (i.e., etanercept, adalimumab, and certolizumab) for the treatment of patients with nr-axSpA. However, in the USA, the Food and Drug Agency (FDA) raised several key concerns, including the ASAS criteria for axSpA, and did not approve to the use of adalimumab and certolizumab for such indication [6••]. A number of recent articles had also raised some concerns about the ASAS classification criteria and the concept of nr-axSpA [7••, 8, 9•, 10•]. The aim of this article is to review and discuss the different viewpoints on this topic and implications for clinical practice.

Classification Criteria

Classification criteria should provide a framework that reflects current knowledge and understandings. Their primary objective is to identify a homogeneous patient population for basic research and clinical trials. Therefore, the patients so selected must be equivalent in terms of clinical characteristics, including age and gender distribution, as well as treatment response and prognosis. They are not meant to be used for diagnosing disease in an individual patient but are being utilized by clinicians as an aid to diagnosis because of absence of diagnostic criteria; a good example is the diagnosis of AS defined by the modified New York (mNY) classification criteria [11]. When members of the Spondyloarthritis Research and Treatment Network (SPARTAN), which comprises practicing rheumatologists interested in AS and related spondyloarthritis (SpA), were asked in a survey how often do they use mNY classification criteria to determine whether or not a patient has definite AS in their daily clinical practice, 65 % answered "most of the time," and 16 % answered "always" [12]. Another core principle for classification criteria is clarity and simplicity so that they can facilitate communication and education. Therefore, terms and concepts used in classification criteria should refer to entities with clearly defined boundaries that avoid any mixture or overlap between each other. To what extent the ASAS classification criteria for axSpA align with the core principles of classification criteria is open to interpretation.

According to the ASAS classification criteria for axSpA [4, 5•], 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

Table 1 ASAS criteria for predominantly axial spondyloarthritis

Patients with Back Pain ≥ 3 Months and Age at Onset < 45 Years

Sacroiliitis on Imaging Plus ≥1 SpA Feature	**OR**	**HLA-B27 Plus ≥2 other SpA Features**
Sacroiliitis on Imaging • Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA • OR Definite radiographic sacroiliitis according to modified New York criteria		SpA Features • Inflammatory back pain • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn's 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

presence of HLA-B27 plus ≥2 SpA features) are fulfilled (Table 1). The patients who show sacroiliitis on X-ray are considered as having radiographic axSpA, and those who do not are labeled as non-radiographic axSpA. The concept of peripheral SpA can perhaps be seen as an attempt to encompass the full spectrum of SpA. A patient with arthritis or enthesitis or dactylitis can be classified as having peripheral SpA, if ≥1 of the following SpA features are present: uveitis, psoriasis, Crohn's/ulcerative colitis, preceding infection, HLA-B27, sacroiliitis on imaging; or if ≥2 of the following SpA features are present: arthritis, enthesitis, dactylitis, inflammatory back pain (IBP) ever, and family history for SpA. No age limit for disease onset is defined in the classification criteria for peripheral SpA, in contrast with the criteria for axSpA. By the way, there are no such subsets in the European Spondyloarthritis Study Group (ESSG) criteria [13] and the Amor criteria for SpA [14].

Performance of the ASAS Criteria for Axial Spondyloarthritis

The sensitivity and specificity of the ASAS classification criteria for axSpA are 82.9 and 84.4 %, respectively, for the entire set and 66.2 and 97.3 %, respectively, for the imaging arm alone [4]. The corresponding figures for the clinical arm were not given in the original manuscript but were later reported to be 56.6 and 83.3 %, respectively, in a recent review article [15•]. Of note, these latter figures were based on all patients fulfilling the clinical arm, regardless of their imaging status. If the analysis is restricted to those patients who did not fulfill the imaging arm, the sensitivity for the (pure) clinical arm decreases to 48.4 %, without a notable change in specificity (86.7 %) (Martin Rudwaleit, personal communication).

It should be pointed out that the sensitivity of 66.2 % for the imaging arm does not refer to only those with nr-axSpA, who were the primary target of the new criteria, but to all axSpA patients, both with radiographic or non-radiographic sacroiliitis. However, in real clinical practice, patients with radiographic sacroiliitis would already have been diagnosed as having AS, and only those without definite radiographic sacroiliitis would undergo MRI. In such a case, the sensitivity of the imaging arm for classifying patients with non-radiographic sacroiliitis, which is more relevant in the real clinical setting, can be calculated after excluding the 116 patients with definite radiographic sacroliitis (≥grade 2 bilateral or ≥grade 3 unilateral) in the ASAS cohort. Given the sensitivity of 66.2 % for the imaging arm and the number of axSpA patients (n=391), there should be 259 patients (391×66.2 %) fulfilling the imaging arm. Then the sensitivity of the imaging arm alone for classifying patients with nr-axSpA decreases to 56.8 % (153/269), with no change in specificity. It should be underlined that the decrease in the sensitivity of the imaging arm for nr-axSpA based on such calculation does not change the sensitivity and specificity of the entire set if the two arms are used in combination. This results from the multi-arm structure of the ASAS classification criteria. However, if the patient populations selected by the imaging and clinical arms are somewhat dissimilar, then the multi-selection design of the criteria set will lead to violation of the primary purpose of the classification criteria, which is to create homogenous patient populations for basic as well as clinical research. It is worth adding that the ASAS criteria for peripheral SpA also demonstrate a balanced sensitivity (77.8 %) and specificity (82.9 %).

The ASAS classification criteria performed better than both the original and the modified versions of the ESSG and the Amor criteria, whether applied to the patients with peripheral or axial disease or to the entire ASAS cohort (Table 2). However, when the performance of the ASAS criteria for peripheral arthritis was compared against that of the classification criteria for Psoriatic Arthritis (CASPAR) in diagnosing psoriatic arthritis (PsA) in an early arthritis cohort, it showed a much lower sensitivity (52 versus 88.7 %) [16].

The New Unified Concept of Axial Spondyloarthritis Comes with a New Divide

ESSG and Amor criteria were developed to classify the whole spectrum of SpA, covering all patients with a specific SpA subtype or those with an undifferentiated form of SpA [13, 14]. The new ASAS classification criteria lumped together all forms of SpA and then divided the entire group into axial and peripheral SpA on the basis of predominant symptoms. This approach represents a paradigm shift from recognizing all the subtypes of SpA as distinct diseases and contrasts sharply with the popular trend in medicine to try to subdivide diseases into subtypes to avoid heterogeneity in genetic and immunological studies as well as clinical trials.

This new division of the SpA spectrum into axial and peripheral disease is a consequence of the presumption that SpA patients with axial symptoms are most likely to develop evidence of sacroiliitis that can be detected earlier by MRI than by conventional radiography, and thus facilitate earlier disease recognition [17]. However, it should be kept in mind that peripheral joint involvement is a presenting feature in about 15 % of the AS patients [18] and a significant proportion of patients with axSpA (36 % in the ASAS cohort) report (past or current) peripheral arthritis [4]. In a study including 119 HLA-B27-positive patients with oligoarthritis, 25.2 % developed AS over 2 to 6 years; further follow-up for another 6 years of the 31 patients who had experienced recurrent oligoarthritis attacks identified five more patients who progressed to AS, making the progression rate of 29.4 % in the whole cohort [19].

Table 2 Performance of several criteria sets for spondyloarthritis in the ASAS Cohort [4, 5•]

	Axial		Peripheral		Entire cohort	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
ESSG	72.4	66.3	55.1	81.1	66.7	72.0
Modified ESSG[a]	85.1	65.1	62.5	81.1	79.1	68.8
Amor	69.3	77.9	35.2	97.8	55.6	86.7
Modified Amor[b]	82.9	77.5	39.8	97.8	67.5	86.7
ASAS	82.9	84.4	77.8	82.2	79.5	83.3

ASAS Assessment of SpondyloArthritis International Society, *ESSG* European Spondylarthropathy Study Group

[a] The ESSG criteria were modified so that active sacroiliitis on MRI was added to the list of parameters of which at least one is required in addition to one entry criterion

[b] The Amor criteria were modified so that active sacroiliitis on MRI was included with a scoring point of 3, similar to definite radiographic sacroiliitis

The new concept of axSpA, encompasses all the patients with early and late forms of AS, no matter whether the AS is "primary" or is "secondary" (i.e., associated with psoriasis, IBD, or reactive arthritis (ReA) [20, 21]. But these two forms are not completely identical; for example, there is relatively more severe axial involvement in primary AS, as compared with secondary AS [21]. It is well known that patients with psoriatic spondylitis differ from primary AS patients by some of their clinical and radiologic features; such as milder symptoms and the presence of asymmetrical sacroiliitis, non-marginal syndesmophytes, asymmetrical syndesmophytes, paravertebral ossification, and more frequent involvement of cervical spine, and also a weaker association with HLA-B27 [22•, 23]. Dissimilarities between the clinical and radiological features of the two entities have been discussed in detail in a number of recent review articles [22•, 24].

The heterogeneity between the nr-axSpA patients with and without an associated SpA-related disease is probably even greater than between the patients with primary and secondary AS. PsA, enteropathic arthritis, and ReA are known to have a more self-limiting disease course and therefore are less likely to progress to AS. Chronic axial pain is common in patients with psoriasis [25] or PsA [26]. A recent study reported that 52 % of patients with PsA had back pain or stiffness. Of the patients who initially had back pain, 54 and 67 % became free of back pain after 5 and 10 years of follow-up, respectively [26]. Of note, back pain persisted in patients with radiographic sacroiliitis [26]. Sacroiliitis diagnosed by MRI is also commonly observed in PsA (38 %) [27]. Clinical features of sacroiliitis were observed in 33 % of the patients with normal MRI scans and in only 39 % of those with abnormal MRI scans (p=0.7) [27], suggesting that silent MRI sacroiliitis is also a feature of PsA, as has previously been shown for asymptomatic radiographic sacroiliitis [23]. Subclinical sacroiliitis detected by X-ray or MRI has been reported also in 24 and 16.5 % of patients with IBD, respectively [28, 29]. It is of interest that no correlation was found between the prevalence of HLA-B27 and radiological sacroiliitis in these studies [23, 27, 28]. Therefore, patients with psoriasis/PsA or IBD suffering from chronic back pain from any reason may be misclassified as having axSpA.

Non-radiographic Axial Spondyloarthritis Versus Ankylosing Spondylitis

The concept of axSpA, since it was first proposed, presumed the occurrence of radiographic sacroiliitis mainly as a function of time, with some influence of severity factors [1, 2]. A recent article challenged this view and suggested that nr-axSpA and AS are different, though overlapping, entities [7••]; the differing features include female predominance, weaker association with HLA-B27, greater diversity with regard to disease progression, and lower response to treatment among patients with nr-axSpA [7••]. The gender and genetic differences were acknowledged also in the recent joint SPARTAN/ASAS statement, but it was argued that these differences should be seen only as prognostic factors that define two subsets of the same disease, axSpA [6••]. Whether they are overlapping but distinct entities, or are two subsets of the same disease, the extent and nature of differences between nr-axSpA or AS can be appreciated only if these two subsets are included as clearly defined distinct populations and analyzed so.

Disease Progression

The natural history is yet to be explored in patients classified as nr-axSpA on the basis of the new ASAS classification criteria. However, the existence of such cases has long been known and long-term outcome in these patients has been assessed in a number of those studies [30–37, 38•, 39•], but they largely differ in their design, inclusion criteria, as well as, in demographics and disease characteristics, such as mean age

and mean symptom duration at study entry, gender distribution, HLA-B27 prevalence, presence of low-grade radiographic sacroiliitis at baseline, and duration of follow-up, which are all likely to have an effect on disease progression (Table 3). Therefore, it is not possible to make a meaningful comparison of results across these studies. None of these studies used ASAS criteria for patient inclusion. One of the most recent studies included patients with a definite clinical diagnosis of axial SpA, who were classified as having nr-axial SpA on the basis of fulfillment of the ESSG criteria, and who had a maximum duration of symptoms (mostly back pain) of <5 years [38•]. It should be underlined that the ESSG criteria in this study were applied with minor modifications, so that HLA-B27 positivity, acute anterior uveitis, and dactylitis were added to the list of parameters, of which at least one must be present in patients who fulfill the entry criterion of IBP [38•, 39•, 40]. The population of this study was composed of a majority (66 %) of female patients in contrast to those of other studies (with 19 to 48 % females). This study estimated the rate of progression from nr-axSpA to AS as 11.6 % over 2 years. Despite the claims that genetic and gender differences between the nr-axSpA and AS should be perceived as only differences in prognostic factors between the two subsets of the same disease [6••], in this study male gender was associated with a significantly lower probability of progression to radiographic sacroiliitis in patients with nr-axSpA (odd ratio (OR), 0.10 (95 % confidence interval (CI), 0.01 to 0.82); p=0.032 in the univariate analysis and OR, 0.11 (95 % CI, 0.01 to 0.85); p=0.035 in the multivariate analysis) [38•]. However, the univariate and multivariate analyses suggested a trend for male gender to be a positive predictor of sacroiliitis progression in AS patients. Moreover, no clear association was found between HLA-B27 and radiographic progression of sacroiliitis [38•]. These data are not in support of the explanation for the genetic and gender differences between the two subsets of axSpA, as being barely a reflection of prognostic factors. The same study identified elevated C-reactive protein (CRP) as the only one strong predictor of progression of sacroiliitis in patients with nr-axSpA and AS [38•]. Some other recent studies indicated that baseline MRI findings also predict future development of radiographic sacroiliitis [36, 37, 38•, 39•]. In line with these studies, a recent retrospective analysis of patients who had presented with IBP 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, as compared with only 30 % in those with no sacroiliitis on MRI [41•]. Thus, clinical and imaging subgroups of nr-axSpA may differ in their natural history.

Clinical Arm Versus the Imaging Arm of the ASAS Criteria

The imaging and the clinical arms of the ASAS criteria for axSpA were compared in two recent studies [42, 43••] from

Table 3 Studies assessing the progression from non-radiographic disease to ankylosing spondylitis

Ref #	Inclusion criteria	Males (%)	Mean age (years)	Mean disease duration (years)	Axial symptoms at baseline (%)	HLA-B27 (%)	Follow-up (years)	Progression rate (%)
[30]	B27-unclassifed arthritis	65	35	2	NA	100	1-4	52
[19]	B27-oligoarthritis	81	NA	NA	NA	100	2–6	25
[31]	Possible ankylosing spondylitis	75	29	8	89 %	69	10	59
[32]	IBP plus HLA-B27 (+) plus MRI (+)	56	36	4[b]	100	100	3	45
[33]	uSpA (ESSG)	86	17[b]	0.7[b]	100	100[c]	11[b]	68
[34]	uSpA (ESSG±Amor)	78	31	5	74	54	2	10
[35]	uSpA (Clinical/ESSG)	52	20	5	92	64	3–5	42
[36]	IBP <2 years	63	31	0.5	100	58	7.7[e]	33
[37]	uSpA (ESSG±Amor)	81	27	3	29 (68[d])	61	5–10	24
[38•]	axSpA (clinical/modified ESSG[a]+symptoms <5 years	34	39	3	100	73	2	12
[39•]	IBP <2 years	72	32	0.5	100	62	7.7[e]	14

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

uSpA undifferentiated spondyloarthritis, *IBP* inflammatory back pain, *ESSG* European Spondyloarthritis Study Group

[a] See text

[b] Median value

[c] Among patients tested

[d] At follow-up

[e] Mean value

two cohorts including patients with early axSpA; The SpondyloArthritis Caught Early (SPACE) [42] and DEvenir des Spondylarthropathies Indiffe´rencie´es Re´centes (DESIR) [44]. Although both are early axSpA cohorts, there are some differences between the two populations. SPACE cohort included patients referred because of chronic back pain (≥3 months but ≤2 years, onset <45 years) [42], whereas the DESIR cohort included patients with IBP (≥3 months, but <3 years), aged 18 to 50 years with symptoms suggestive of SpA according to the local investigator's assessment [44].

In the SPACE cohort, all patients underwent HLA-B27 typing and MRI examination of the sacroiliac joints. So, it was possible to compare the patients fulfilling either the clinical or imaging arm only. In the DESIR cohort, of the 475 patients fulfilling the axSpA classification criteria, 435 had no missing data in respect with imaging and HLA-B27, enabling categorization of these patients into a specific arm correctly. The data from these patients were analyzed in a later study to assess the validity of the different arms of the ASAS classification criteria set for axSpA [43••].

Despite many similarities regarding the clinical features and disease activity measures of the two arms in both studies, the proportion of males was significantly greater in the imaging arm than in the clinical arm in both cohorts; 63.3 versus 33.3 % (p=0.02) in the SPACE cohort, and 59.2 versus 41.6 % (p=0.0003) in the DESIR cohort Moreover, the patients in the imaging arm of the DESIR cohort were slightly, but significantly younger (30.6 versus 32.6 years; p=0.005), and had higher mean CRP levels (11.6 versus 5.2 mg/L; p<0.0001), than those in the clinical arm. On analyzing patients within the imaging arm, those with only positive MRI also had a significantly higher male prevalence (56.2 versus 41.6 %; p=0.027) and higher mean CRP levels (10.5 versus 5.2 mg/L; p<0.0007), as compared with those in the clinical arm. In the SPACE cohort, the imaging arm included patients with a longer symptom duration and a lower prevalence of positive family history for SpA than among the patients fulfilling the clinical arm. Of interest, in the DESIR cohort within the clinical arm, but not within the imaging arm, women had higher disease activity and functional scores than men [45]. Imaging abnormalities on MRI examination at the sacroiliac and spine levels were compared between the subgroups of axSpA in the DESIR cohort [43••] and the prevalence of structural changes in the sacroiliac joints and inflammatory lesions in the spine were found to be greater among patients with non-radiographic axSpA fulfilling the imaging arm as compared with those fulfilling the clinical arm (34.8 versus 3.5 % and 34.1 versus 12.9 %, respectively). This study did not include a healthy control group.

Two studies from SPACE cohort, both published in abstract forms, also produced results in the same direction [46, 47]. One of these studies found the prevalence of any type of MRI-spine lesion (bone marrow edema, fatty changes, erosion, or syndesmophyte) among patients meeting the clinical arm to be very similar to those with possible or no SpA but lower than those observed among patients with AS or nr-axSpA in the imaging arm [46]. The other study which assessed the structural MRI lesions in the sacroiliac joints showed that fatty lesions, sclerosis, erosions, or ankylosis in sacroiliac joints were also less common among patients in the clinical arm as compared with each subgroup of the imaging arm (X-ray+ and MRI−/X-ray+) [47]. These results from both cohorts are of interest as they reveal the differences between the two arms of the nr-axSpA with regard to the structural MRI lesions in the axial skeleton even at an early symptom stage.

Treatment Response Across the Spectrum of Axial Spondyloarthritis

Current evidence suggests that at the group level radiographic and non-radiographic axSpA may differ in their response to anti-TNF therapy, and a similar difference may also exist between the two subgroups of nr-axSpA [48–51, 52•, 53•, 54•, 55]. To date, four randomized controlled trials (RCTs) of TNF inhibitors have been conducted in patients with nr-axSpA [52•, 53•, 54•, 55]. Comparison of the results of these studies with those observed in the main RCTs of patients with AS also point out some differences between classical AS and nr-axSpA, as reflected by diminished male prevalence [52•, 53•] and lower CRP levels [53•, 54•] (Table 4). Another study reported higher response rates to TNF inhibitors in patients with positive imaging findings than those without; although imaging studies included standard radiographs and CT scans [56]. The prevalence of HLA-B27 among nr-axSpA patients is lower than in patients with AS, especially when only the imaging arm is analyzed (Tables 4 and 5). Moreover, the delta values for ASAS20 responses observed in trials of nr-axSpA patients seem to be lower than those in AS trials (Table 4). One could speculate that the consistently higher ASAS20 response rates in the placebo arms of the nr-axSpA trials may be a sign of a more fluctuating disease course in this group of patients. A better clinical response to TNF inhibitors in patients with AS, as compared with those with nr-axSpA is suggested also by a recent Swiss study, which reported a significantly greater ASAS40 response in AS patients (48.1 versus 29.6 %; p=0.02) [57••]. Most notably, the difference was more marked between the patients with normal baseline CRP levels (41.9 versus 21.3 %; p=0.07) as compared with those with elevated CRP levels (51.6 vs 38.5 %; p=0.29). Probability of achieving a BASDAI 50 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 RCTs of infliximab and etanercept [58]. In one of the early trials of etanercept in AS, ASAS 40 response rate at week 24 in the

Table 4 Comparison of patient characteristics and efficacy data from randomized placebo-controlled trials of TNF inhibitors conducted in patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)

	AS					Nr-axSpA			
	ETN [48]	IFX [49]	ADA [50]	GLM [51]	CZP [52•]	ADA [53•]	CZP [52•]	ETN [54•]	GLM [55]
Male (%)	76.0	80.6	74.9	71.6	72.5	45.5	48.3	60.4	57.0
Age (years)	42.0	40.3	42.3	38.7	41.5	38.0	37.4	32.0	31.2
Disease duration (years)	10.3	9.2	10.9	12.1	9.1[a]	10.1	5.5[a]	2.5	<1 year[a]
HLA-B27 (+; %)	84.0	87.1	78.7	83.4	81.5	58.2[b]	53.7[b]	64.9[b]	73.5[b]
BASDAI	5.9	6.6	6.3	6.8	6.4	6.5	6.5	6.0	6.5
BASFI	5.4	5.8	5.3	5.1	5.7	4.7	4.9	4.0	5.0
CRP (mg/L)	20	16	19	10	14[a]	7	12[a]	7	14
ASAS 20 response rate at week 12 (where otherwise indicated)									
Placebo	28.0	19.2[c]	20.6	21.8[d]	36.8	31.0	40.0	36.1	40.0[f]
Anti-TNF	59.0	61.2[c]	58.2	59.4[d]	64.3[e]	52.0	62.7[f]	52.4	71.1[f]
Delta	31.0	42.0[c]	37.6	37.6[d]	27.5[e]	21.0	22.7[f]	16.3	31.1[f]

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

ADA adalimumab, *CZP* certolizumab pegol, *ETN* etanercept, *GLM* golimumab, *IFX* infliximab, *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* Assessment of Spondyloarthritis International Society criteria for 20 % improvement

[a] Median value

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

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

[d] ASAS response rate at week 14 for GLM 50 mg

[e] For the 400-mg every 4 weeks arm

[f] ASAS response rate at week 16

Table 5 Comparison of baseline characteristics of patients with non-radiographic axial spondyloarthritis included in recent randomized controlled trials of TNF inhibitors

Trial-specific inclusion criteria*	ABILITY ADA (*n*=185) None	RAPID-axSpA[a] CZP (*n*=147) Presence of MRI sacroiliitis or high CRP	ETN (*n*=215) Disease duration <5 years	GO-AHEAD GLM (*n*=198) 18–45 years of age, disease duration <5 years
Age (years)	38.4	37.4	32	31.2
Male gender (%)	45.5	48.3	60.4	57.0
Disease duration (years)	10.1	5.5[b]	2.5	<1 year[b]
CRP (mg/L)	7.2	11.9[b]	6.6	13.9
Elevated CRP (%)	38.9	63.3	42.7	40.9
HLA-B27 (+; %)				
Whole group	78	74.8	71.7	82.3
Imaging arm-MRI+	58.2	53.7	64.9	73.5
Imaging arm-MRI+ (*n*)/clinical arm (*n*)	0.96	1.19[c]	4.24	2

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

ADA adalimumab, *CZP* certolizumab pegol, *ETN* etanercept, *GLM* golimumab

[a] Data from the nr-AxSpA subgroup only

[b] Median value

[c] Many patients in the clinical arm had an unknown MRI status

etanercept group was 52 % in AS patients with normal CRP values at baseline. This was very similar to the 57 % response rate that was observed in the whole etanercept group but higher than the 22 % response rate in the placebo group at the same time point [59]. In line with these results, the data from the British Biologics Registry reported that 47 % of the AS patients without raised inflammatory markers at baseline achieved a BASDAI50 response at 6 months [60]. However, ASAS40 response rates at week 12 with etanercept and adalimumab in patients with nr-axSpA who had normal CRP levels at baseline were not very different from the rates obtained in patients receiving placebo (20.7 versus 12.5 % and 27 versus 18 %, respectively) [53•, 54•]. Mean disease duration in the etanercept trial of nr-axSpA patients was only 2.5 years. Disparity in clinical response to anti-TNF agents between patients with AS and nr-axSpA, including those with normal CRP levels underline the heterogeneity between the two conditions.

Heterogeneity regarding demographics and disease characteristics exists also across the populations of the nr-axSpA trials, which may partly be due to the differences in the relative size of each arm (imaging and clinical) in the study population (Table 5). ABILITY-1 trial of adalimumab, and the etanercept trial, both involved patients with nr-axSpA; however, the composition of the study populations was markedly different, with 49 and 81 % of the patients meeting the imaging arm criteria, respectively. Certainly, the use of additional inclusion criteria in some of the trials in regard with CRP or MRI [52•], disease duration [54•, 55], or age [55] are likely to have contributed to the heterogeneity between the studies.

Complex Structure of the ASAS Classification Criteria as a Source of Heterogeneity

Given the dissimilarities described above in terms of demographics, clinical characteristics, treatment response between the two subgroups of axSpA (AS versus nr-axSpA), as well as the two subgroups within the nr-axSpA (clinical arm versus imaging-MRI only), the complex multi-arm structure of the ASAS criteria may also be a potential source of heterogeneity, due to possible differences in composition of the subgroups in different studies. Disparities between physicians in their applications of the criteria are also likely to contribute to heterogeneity across different study populations. In a setting where HLA-B27 testing and imaging examinations are performed in every patient, the patient population fulfilling the imaging arm will be different than that defined in a setting where MRI is mostly performed only in patients who have not fulfilled the clinical arm. In this latter situation, the imaging arm will have a lower HLA-B27 prevalence, due to the selection of more HLA-B27-negative patients for MRI examination. Then, patient populations defined in different settings will not be comparable.

The criteria for peripheral SpA can be applied to patients with peripheral manifestations only, and the criteria for axSpA can be applied to patients with predominantly axial manifestations with or without peripheral manifestations. About 36 % of patients with axSpA in the original ASAS cohort reported (past or current) peripheral arthritis [4]. Among patients with peripheral SpA in the same cohort, definite radiographic sacroiliitis (≥grade 2 bilateral or ≥grade 3 unilateral) was detected in 19.5 % and MRI evidence of sacroiliitis in 44 % (of those who underwent radiographic and MRI exams) of the patients, although none reported current back pain. But it is well known that the predominant symptoms change over the course of SpA, and it is not clear how to deal with patients whose symptoms change from peripheral to axial or vice versa along the course of a study [8]. In the ASAS cohort, of the 34 patients with peripheral SpA, who had definite radiographic sacroiliitis, seven reported IBP in the past, but none was considered as having AS. Another disputable scenario could be an HLA-B27-negative patient with Crohn's disease with monoarthritis of the knee, current IBP, but normal imaging of the sacroiliac joints who would not be classified as SpA, even if he met the peripheral SpA criteria, because the ASAS criteria for peripheral SpA can be applied only to patients with peripheral manifestations with no current axial symptoms [61].

The terms "radiographic axSpA" and "AS" are widely used interchangeably as if they are synonymous. However, this is not true in strict sense, since a patient with chronic back pain and radiographic sacroiliitis in the presence of at least one SpA feature can be classified as radiographic axSpA, but not as AS according to the mNY criteria, unless the patient's back pain is of inflammatory nature (improves with exercise and not relieved at rest) [11]. For example, in a recent Dutch cohort of patients with chronic low back pain, whereas 30 were classified as having radiographic axSpA, only 24 of them were classified as having AS [62].

It is apparent from these discussions that ASAS classification criteria have a quite complex, rather than a simple, structure. This complex multi-selection design and unclear (not mutually exclusive) definitions of the clinical and imaging arm may lead to heterogeneity across study populations.

Advantages and Disadvantages of the ASAS Classification Criteria

The advantages of the new concept of SpA, which is divided into axial and peripheral SpA include early access to effective therapies for patients who have axial disease without radiographic sacroiliitis, and to allow for clinical trials to be conducted in patients fulfilling the criteria for either axial or peripheral SpA, irrespective of the underlying distinct SpA form. The first advantage has been realized in Europe, where

adalimumab, etanercept, and certolizumab have been approved for their use in nr-axSpA, though only for those patients with evidence of inflammation as reflected by elevated CRP or presence of acute (active) lesions on MRI. A number of double-blind RCTs were indeed conducted in patients representing the whole spectrum of axSpA [52•, 53•, 54•, 55, 56, 57••, 58–63], but these studies used additional inclusion criteria, such as presence of elevated CRP or inflammatory lesions on MRI and disease duration, which were not required in major trials in patients with AS. Registration trials of adalimumab, etanercept, and golimumab included only patients with nr-axSpA [53•, 54•, 55]. There seems to be no benefit from inclusion of both subtypes of axSpA (AS and nr-axSpA) within a single study, unless one wishes to compare the two subgroups.

The major disadvantage of the new ASAS classification criteria is the potential heterogeneity due to the grouping together of patients with different SpA subtypes (such as primary AS, and those with associated ReA, psoriasis, and IBD) under a single category of SpA (either predominantly axial or peripheral).

Although the existing literature shows an overlap in genetic risk factors and pathophysiologic mechanisms, as well as clinical features between the specific subtypes of SpA, the extent of differences between them can only be recognized if they are included as distinctly defined populations in research studies. If there are some effective therapies that work in certain subtype(s) but not in others, their efficacy may not be appreciated truly in trials including patients based on classification criteria that do not differentiate between the specific subtypes. Such a disadvantage can be avoided by restricting the inclusion of patients with a specific subtype to some studies, but then one would question the rationale for developing one set of criteria to encompass the wider spectrum of axSpA as a single disease entity.

An old Canadian study of patients with AS had reported that after 38 years of disease, 41 % of the surviving patients develop severe spinal restriction and suggested that the extent of spinal restriction is a good predictor of future progression because 74 % of the patients who had mild spinal restriction after 10 years did not show progression [64]. This finding has been supported by recent studies that have demonstrated a leading role of baseline syndesmophytes as a predictor of radiographic progression in the spine [65, 66]. Therefore, we can extrapolate from these data that we can expect a more benign disease course for patients with nr-axSpA, at least for those who have not developed radiographic sacroiliitis within the first 10 years of the disease. However, if these patients perceive their disease being the same entity as AS, under the diagnosis of axSpA, then they may have worries that are unnecessarily at a similar level to those patients who have AS, with regard to their future physical appearance and employability, which are among the most prevalent quality of life concerns in patients with AS [67]. It has been well accepted that currently there are no long-term studies on axSpA patients that could clarify the natural history of the disease [6••]. The data on the nr-axSpA in this regard are even more sparse and hence the rate of spontaneous remission, as well as the rate of progression to severe disease with spinal deformities are yet largely unknown.

The primary goal of a valid classification criteria for any disease is to provide a homogeneous study population with a common etiopathogenesis, similar prognosis, and similar response to identical treatment. Without such a homogeneous study population, robust clinical and basic science research in any subtype of SpA is not possible. All criteria are dynamic concepts that need updating as our knowledge advances. We have provided a review of the ASAS classification criteria of axSpA that indicates that its complex multi-selection design and unclear (not mutually exclusive) definitions of the imaging and clinical arms result in patient heterogeneity across study populations. Therefore, there is a need to improve the validity of the ASAS classification criteria for axSpA. It is our opinion that in the meantime, the clinically well established entity of AS, as defined by the mNY criteria, should be preserved for the most accurate comparison of the new research studies with those conducted over the last three decades, and hence the use of the ASAS criteria should be restricted to patients with nr-axSpA, who are not recognized by the mNY criteria.

Compliance with Ethics Guidelines

Conflict of Interest Nurullah Akkoc declares the receipt of consulting and/or speaking fees and/or honoraria from Pfizer, AbbVie, MSD, and UCB, as well as research funding from Pfizer and UCB. Muhammad A Khan declares the receipt of consulting fees from AbbVie, Amgen, Celgene, Novartis, and Crescendo Bioscience, as well as fees from speaker's bureaus of AbbVie and Amgen.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. Ann Rheum Dis. 2004;63(5):535–43. doi:10.1136/ard.2003.011247.
2. Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? Arthritis Rheum. 2005;52(4):1000–8. doi:10.1002/art.20990.

3. Khan MA, van der Linden SM, Kushner I, Valkenburg HA, Cats A. Spondylitic disease without radiologic evidence of sacroiliitis in relatives of HLA-B27 positive ankylosing spondylitis patients. Arthritis Rheum. 1985;28(1):40–3.
4. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777–83. doi:10.1136/ard.2009.108233. **This study proposes new classification criteria for axial SpA that include radiographic and non-radiographic stages of the disease**.
5.• Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25–31. doi:10.1136/ard.2010.133645. **This study proposes new classification criteria for SpA that have peripheral manifestations. The performance of the combined use of the axial and peripheral SpA are assessed, also relative to the ESSG and Amor Criteria**.
6.•• Deodhar A, Reveille JD, van den Bosch F, Braun J, Burgos-Vargas R, Caplan L, et al. The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of Spondyloarthritis International Society in response to the US Food and Drug Administration's comments and concerns. Arthritis Rheum. 2014;66(10):2649–56. doi:10.1002/art.38776. **This special article summarises the discussions that took place at the meeting between SPARTAN and ASAS leadership, which was held to explore the consensus and also the differences regarding the concept of axial SpA after the FDA's rebuttal of approving TNF inhibitors for the treatment of nonradiographic axial SpA**.
7.•• Robinson PC, Wordsworth BP, Reveille JD, Brown MA. Axial spondyloarthritis: a new disease entity, not necessarily early ankylosing spondylitis. Ann Rheum Dis. 2012;72(2):162–4. doi:10.1136/annrheumdis-2012-202073. **This point of view article discusses the differences between the radiographic and non-radiographic subgroups of axial SpA and suggests that the modified New York criteria for ankylosing spondylitis should remain for clinical use and research studies**.
8. Zeidler H, Amor B. The Assessment in Spondyloarthritis International Society (ASAS) classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general: the spondyloarthritis concept in progress. Ann Rheum Dis. 2011;70(1):1–3. doi:10.1136/ard.2010.135889.
9.• Taylor WJ, Robinson PC. Classification Criteria: Peripheral Spondyloarthropathy and Psoriatic Arthritis. Current Rheumatology Reports. 2013;15(4). **This critical review of the implications of the ASAS classification criteria, with particular reference to psoriatic arthritis, suggest that there are more advantages in distinguishing particular subsets of SpA than there are in unifying them into a single disorder.**
10.• Akkoc N, Khan MA. ASAS classification criteria for axial spondyloarthritis: a look at the unfilled part of the glass. Clin Exp Rheumatol. 2014;32(Suppl 87(6)):14–5. **This brief letter points out the differences between the clinical and imaging arms of axial SpA and concludes that complex multi-arm structure of the ASAS classification criteria is a potential source of heterogeneity**.
11. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27(4):361–8.
12. Deodhar A. Axial spondyloarthritis criteria and modified NY criteria: issues and controversies. Clin Rheumatol. 2014;33(6):741–7. doi:10.1007/s10067-014-2661-8.
13. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum. 1991;34(10):1218–27.
14. Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondylarthropathies. Rev Rhum Mal Osteoartic. 1990;57(2):85–9.
15.• Sieper J, van der Heijde D. Review: nonradiographic axial spondyloarthritis: new definition of an old disease? Arthritis Rheum. 2013;65(3):543–51. doi:10.1002/art.37803. **This review addresses the several questions that have been raised regarding the new definition of nonradiographic axial SpA as part of the axial SpA**.
16. van den Berg R, van Gaalen F, van der Helm-van Mil A, Huizinga T, van der Heijde D. Performance of classification criteria for peripheral spondyloarthritis and psoriatic arthritis in the Leiden Early Arthritis cohort. Ann Rheum Dis. 2012;71(8):1366–9. doi:10.1136/annrheumdis-2011-201081.
17. Zochling J, Brandt J, Braun J. The current concept of spondyloarthritis with special emphasis on undifferentiated spondyloarthritis. Rheumatology (Oxford). 2005;44(12):1483–91. doi:10.1093/rheumatology/kei047.
18. Ginsburg WW, Cohen MD. Peripheral arthritis in ankylosing spondylitis. A review of 209 patients followed up for more than 20 years. Mayo Clin Proc. 1983;58(9):593–6.
19. Schattenkirchner M, Kruger K. Natural course and prognosis of HLA-B27-positive oligoarthritis. Clin Rheumatol. 1987;6(Suppl 2):83–6.
20. Helliwell PS, Hickling P, Wright V. Do the radiological changes of classic ankylosing spondylitis differ from the changes found in the spondylitis associated with inflammatory bowel disease, psoriasis, and reactive arthritis? Ann Rheum Dis. 1998;57(3):135–40.
21. Perez Alamino R, Maldonado Cocco JA, Citera G, Arturi P, Vazquez-Mellado J, Sampaio-Barros PD, et al. Differential features between primary ankylosing spondylitis and spondylitis associated with psoriasis and inflammatory bowel disease. J Rheumatol. 2011;38(8):1656–60. doi:10.3899/jrheum.101049.
22.• Lubrano E, Spadaro A. Axial psoriatic arthritis: an intriguing clinical entity or a subset of an intriguing disease? Clin Rheumatol. 2012;31(7):1027–32. doi:10.1007/s10067-012-1990-8. **A comprehenesive review on the diagnosis and treatment of axial psoriatic arthritis**.
23. Queiro R, Belzunegui J, Gonzalez C, De DJ, Sarasqueta C, Torre JC, et al. Clinically asymptomatic axial disease in psoriatic spondyloarthropathy. A retrospective study. Clin Rheumatol. 2002;21(1):10–3.
24. Gladman DD. Axial disease in psoriatic arthritis. Curr Rheumatol Rep. 2007;9(6):455–60.
25. Thom N, Ritchlin CT, Zhang X, Reveille J, Weisman MH. Prevalence of chronic axial pain, inflammatory back pain and spondyloarthritis in diagnosed psoriasis. Arthritis Care Res (Hoboken). 2014. doi:10.1002/acr.22528.
26. Chandran V, Barrett J, Schentag CT, Farewell VT, Gladman DD. Axial psoriatic arthritis: update on a longterm prospective study. J Rheumatol. 2009;36(12):2744–50. doi:10.3899/jrheum.090412.26.
27. Williamson L, Dockerty JL, Dalbeth N, McNally E, Ostlere S, Wordsworth BP. Clinical assessment of sacroiliitis and HLA-B27 are poor predictors of sacroiliitis diagnosed by magnetic resonance imaging in psoriatic arthritis. Rheumatology (Oxford). 2004;43(1):85–8. doi:10.1093/rheumatology/keg475.
28. Queiro R, Maiz O, Intxausti J, de Dios JR, Belzunegui J, Gonzalez C, et al. Subclinical sacroiliitis in inflammatory bowel disease: a clinical and follow-up study. Clin Rheumatol. 2000;19(6):445–9.
29. Leclerc-Jacob S, Lux G, Rat AC, Laurent V, Blum A, Chary-Valckenaere I, et al. The prevalence of inflammatory sacroiliitis assessed on magnetic resonance imaging of inflammatory bowel

disease: a retrospective study performed on 186 patients. Aliment Pharmacol Ther. 2014;39(9):957–62. doi:10.1111/apt.12680.
30. Sany J, Rosenberg F, Panis G, Serre H. Unclassified HLA-B27 inflammatory rheumatic diseases: follow up of 23 patients. Arthritis Rheum. 1980;23(2):258–9.
31. Mau W, Zeidler H, Mau R, Majewski A, Freyschmidt J, Stangel W, et al. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year follow up. J Rheumatol. 1988;15(7):1109–14.
32. Oostveen J, Prevo R, den Boer J, van de Laar M. Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. J Rheumatol. 1999;26(9):1953–8.
33. Kumar A, Bansal M, Srivastava DN, Pandhi A, Menon A, Mehra NK, et al. Long-term outcome of undifferentiated spondylarthropathy. Rheumatol Int. 2001;20(6):221–4.
34. Sampaio-Barros PD, Bertolo MB, Kraemer MH, Marques-Neto JF, Samara AM. Undifferentiated spondyloarthropathies: a 2-year follow-up study. Clin Rheumatol. 2001;20(3):201–6.
35. Huerta-Sil G, Casasola-Vargas JC, Londono JD, Rivas-Ruiz R, Chavez J, Pacheco-Tena C, et al. Low grade radiographic sacroiliitis as prognostic factor in patients with undifferentiated spondyloarthritis fulfilling diagnostic criteria for ankylosing spondylitis throughout follow up. Ann Rheum Dis. 2006;65(5):642–6. doi:10.1136/ard.2005.043471.
36. Bennett AN, McGonagle D, O'Connor P, Hensor EM, Sivera F, Coates LC, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. Arthritis Rheum. 2008;58(11):3413–8. doi:10.1002/art.24024.
37. Sampaio-Barros PD, Bortoluzzo AB, Conde RA, Costallat LT, Samara AM, Bertolo MB. Undifferentiated spondyloarthritis: a longterm follow up. J Rheumatol. 2010;37(6):1195–9. doi:10.3899/jrheum.090625.
38.• Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Marker-Hermann E, Zeidler H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis. 2011;70(8):1369–74. doi:10.1136/ard.2010.145995. **This study reported that progression of radiographic sacroiliitis by at least one grade over 2 years only in a small percentage of patients with early axial spondyloarthritis and that elevated level of CRP, was found to be a strong positive predictor of progression**.
39.• Aydin SZ, Maksymowych WP, Bennett AN, McGonagle D, Emery P, Marzo-Ortega H. Validation of the ASAS criteria and definition of a positive MRI of the sacroiliac joint in an inception cohort of axial spondyloarthritis followed up for 8 years. Ann Rheum Dis. 2012;71(1):56–60. doi:10.1136/ard.2011.153064. **This study reported that a positive baseline MRI had 100 % sensitivity but a low specificity for subsequent radiographic sacroiliitis, both with global assessment or ASAS definition of a positive MRI. This study estimated the progression rate to radiographic sacroilitiis in the Leeds cohort as 14.2 % over eight years, after excluding the patients, who fulfilled the modified New York criteria at baseline**.
40. 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(3):717–27. doi:10.1002/art.24483.
41.• Gong Y, Zheng N, Chen SB, Xiao ZY, Wu MY, Liu Y, et al. Ten years' experience with needle biopsy in the early diagnosis of sacroiliitis. Arthritis Rheum. 2012;64(5):1399–406. doi:10.1002/art.33453. **This study evaluated the usefulness of needle biopsy in the diagnosis of early sacroiliitis and showed that MRI, though of low sensitivity, is specific for the diagnosis of early sacroiliitis and that evidence of MRI sacroiliitis is associtaed with future progression of sacroiliitis detected by computerized tomography**.
42. van den Berg R, de Hooge M, van Gaalen F, Reijnierse M, Huizinga T, van der Heijde D. Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. Rheumatology (Oxford). 2013. doi:10.1093/rheumatology/ket164.
43.•• Molto A, Paternotte S, van der Heijde D, Claudepierre P, Rudwaleit M, Dougados M. Evaluation of the validity of the different arms of the ASAS set of criteria for axial spondyloarthritis and description of the different imaging abnormalities suggestive of spondyloarthritis: data from the DESIR cohort. Ann Rheum Dis. 2014. doi:10.1136/annrheumdis-2013-204262. **This study compares the patient characteristics between the patients fulfilling the imaging and clinical arms of the patients with axial SpA in the DESIR cohort and also report on the prevalence of the different imaging abnormalities in the two arms**.
44. Dougados M, D'Agostino MA, Benessiano J, Berenbaum F, Breban M, Claudepierre P, et al. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. Joint Bone Spine: Rev Rhum. 2011;78(6):598–603. doi:10.1016/j.jbspin.2011.01.013.
45. Tournadre A, Pereira B, Lhoste A, Dubost JJ, Ristori JM, Claudepierre P, et al. Differences between women and men with recent-onset axial spondyloarthritis: results from a prospective multicenter French cohort. Arthritis Care Res (Hoboken). 2013;65(9):1482–9. doi:10.1002/acr.22001.
46. de Hooge M, van den Berg R, Navarro-Compan V, Reijnierse M, van Gaalen F, Fagerli K, et al. Prevalence of structural lesions seen on MRI-spine in patients with (possible) axial spondyloarthritis (axSpA) included in the SPACE-cohort. Arthritis Rheum. 2013;65:S1237–S.
47. van den Berg R, de Hooge M, Navarro-Compan V, Reijnierse M, van Gaalen F, Fagerli K, et al. Prevalence of structural lesions on MRI of the sacroiliac joints in patients with early axial spondyloarthritis and patients with back pain. Arthritis Rheum. 2013;65:S1238–S.
48. Davis Jr JC, Van Der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum. 2003;48(11):3230–6. doi:10.1002/art.11325.
49. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005;52(2):582–91. doi:10.1002/art.20852.
50. van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54(7):2136–46. doi:10.1002/art.21913.
51. Inman RD, Davis Jr JC, Heijde D, Diekman L, Sieper J, Kim SI, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum. 2008;58(11):3402–12. doi:10.1002/art.23969.
52.• Landewe R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study. Ann Rheum Dis. 2014;73(1):39–47. doi:

10.1136/annrheumdis-2013-204231. **This is the first trial of a TNF inhibitor that included patients with ankylosing spondylitis and non-radiographic axSpA in one single study, which reported that certolizumab is effective in treating the signs and symptoms of axial SpA**.

53.• Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013;72(6):815–22. doi:10.1136/annrheumdis-2012-201766. **The first clinical trial that utilized the ASAS axial SpA criteria in classifying nr-axSpA patients which showed that adalimumab has a positive benefit–risk profile in active nr-axSpA patients with inadequate response to NSAIDs**.

54.• Dougados M, van der Heijde D, Sieper J, Braun J, Maksymowych WP, Citera G, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2014;66(8):2091–102. doi:10.1002/art.38721. **In this randomized controlled trial etanercept showed good efficacy in patients with nonradiographic axial SpA over 12 weeks with clinical/functional improvement continuing through 24 weeks**.

55. Sieper J, van der Heijde D, Dougados M, Maksymowych WP, Boice J, Bergan G, et al. A randomized, double-blind, placebo-controlled, 16-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheum. 2014;66(11):S1283–4.

56. Bisson-Vaivre A, Alcaix D, Zarnitsky C, Pueyo L, Daragon A, Lanfant-Weybel K, et al. Efficacy of anti-TNF in patients with spondyloarthritis in absence of any imaging sign. Joint Bone Spine. 2013;80(3):280–6. doi:10.1016/j.jbspin.2012.08.003.

57.•• Ciurea A, Scherer A, Exer P, Bernhard J, Dudler J, Beyeler B, et al. Tumor necrosis factor alpha inhibition in radiographic and nonradiographic axial spondyloarthritis: results from a large observational cohort. Arthritis Rheum. 2013;65(12):3096–106. doi:10.1002/art.38140. **This study from the Swiss Clinical Quality Management (SCQM) Cohort showed that response to anti-TNF treatment is better in the group of patients with radiographic axial SpA than in the group with nonradiographic axial SpA, with the exception of patients with elevated CRP levels at baseline**.

58. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis. 2004;63(6):665–70. doi:10.1136/ard.2003.016386.

59. Davis Jr JC, Van der Heijde DM, Dougados M, Braun J, Cush JJ, Clegg DO, et al. Baseline factors that influence ASAS 20 response in patients with ankylosing spondylitis treated with etanercept. J Rheumatol. 2005;32(9):1751–4.

60. Lord PA, Farragher TM, Lunt M, Watson KD, Symmons DP, Hyrich KL, et al. Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2010;49(3):563–70. doi:10.1093/rheumatology/kep422.

61. Paramarta JE, Baeten D. Spondyloarthritis: from unifying concepts to improved treatment. Rheumatology (Oxford). 2013. doi:10.1093/rheumatology/ket407.

62. van Hoeven L, Luime J, Han H, Vergouwe Y, Weel A. Identifying axial spondyloarthritis in Dutch primary care patients, ages 20–45 years, with chronic low back pain. Arthritis Care Res (Hoboken). 2014;66(3):446–53. doi:10.1002/acr.22180.

63. Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, et al. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, part 1. Ann Rheum Dis. 2014;73(1):101–7. doi:10.1136/annrheumdis-2012-203201.

64. Carette S, Graham D, Little H, Rubenstein J, Rosen P. The natural disease course of ankylosing spondylitis. Arthritis Rheum. 1983;26(2):186–90.

65. Poddubnyy D, Haibel H, Listing J, Marker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum. 2012;64(5):1388–98. doi:10.1002/art.33465.

66. van Tubergen A, Ramiro S, van der Heijde D, Dougados M, Mielants H, Landewe R. Development of new syndesmophytes and bridges in ankylosing spondylitis and their predictors: a longitudinal study. Ann Rheum Dis. 2012;71(4):518–23. doi:10.1136/annrheumdis-2011-200411.

67. Ward MM. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. Arthritis Care Res. 1999;12(4):247–55.