Non-Radiographic Axial Spondyloarthritis

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ABSTRACT: The term non-radiographic axial spondyloarthritis (nrAxSpA) was coined for patients who have a clinical picture of ankylosing spondylitis (AS) but do not exhibit radiographic sacroiliitis. The ASAS classification criteria for nrAxSpA, ensuring the recruitment of homogenous study cohorts, were accepted in 2009, although the respective diagnostic criteria for daily clinical practice have not yet been developed. The clinical diagnosis should be based on the composite of clinical symptoms and signs of the disease, HLA B27 status, and magnetic resonance imaging (MRI) of sacroiliac joints. Notably, a negative MRI or HLA B27 does not exclude the diagnosis in patients with a high clinical suspicion for nrAxSpA. The prevalence of nrAxSpA is similar to that of AS, but the former has a higher female preponderance. The rate of progression of nrAxSpA to the radiographic stage of disease (AS) ranges from 10% to 20% over 2 years. Current treatment strategies for nrAxSpA are the same as for AS and include non-steroidal anti-inflammatory drugs and inhibitors of tumor necrosis factor-alpha. While this review summarizes the current achievements in the field of nrAxSpA, further understanding of the epidemiology and natural history of the disease and, particularly, mechanisms of inflammation and subsequent new bone formation is essential for the development of new treatment strategies for nrAxSpA patients.

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The term non-radiographic axial spondyloarthritis (nrAxSpA) was coined for patients suffering from the early phase of ankylosing spondylitis (AS), where the standard diagnosis, historically based on the presence of sacroiliitis on X-ray images, is impossible due to the absence of radiographic changes. The same patients had been diagnosed earlier by rheumatologists as having "undifferentiated spondyloarthritis" (SpA) or, sometimes, "pre-radiographic AS." The implication of nrAxSpA as an existing entity can be appreciated from the study by Groupe Français d'Etude Génétique des Spondylarthropathies, which unequivocally demonstrated that the frequency of radiographic sacroiliitis increases in parallel with disease duration, while about 60% of patients will require 10 or more years of active disease to demonstrate its radiographic features [1]. These patients, who present with a clinical picture suspicious for AS but have not yet developed radiographic sacroiliitis, would be diagnosed today as having nrAxSpA based on magnetic resonance imaging (MRI) or a composite of clinical manifestations. The success of biologic agents in alleviating clinical symptoms and signs of AS and the anticipation that treating earlier stages of the disease may prevent structural damage and complications led to new studies examining the epidemiology and natural history of the disease and patients' response to treatment. In this review we discuss the most important developments in the field of nrAxSpA.

CLASSIFICATION CRITERIA AND DIAGNOSIS OF nrAxSpA

Classification criteria that ensure recruitment of a homogenous study cohort are essential and a major component of any reliable study. Usually, the patient has already been diagnosed by an expert before being tested whether he or she fulfills the classification criteria. The ASAS (Assessment of SpondyloArthritis International Society) criteria for axial SpA, proposed in 2009, classify patients with a compatible clinical picture as having nrAxSpA with evidence of sacroiliitis on MRI or even without any confirmative imaging for HLA B27-positive individuals [Figure 1] [2]. A major rationale for the development of these new classification criteria was to introduce MRI assessments, based on the accumulating data that MRI of sacroiliac joints can uncover active inflammation in the absence of any detectable radiographic sign of sacroiliitis, as well as predict future development of full-blown AS in some patients with inflammatory back pain [3]. Moreover, regarding the relatively low (~70%)

Figure 1. ASAS (2009) classification criteria for axial spondyloarthritis

In patients with ≥ 3 months back pain and age of onset ≤ 45 years

Sacroiliitis on imaging plus ≥ 1 SpA feature **or** Positive HLA B27 plus ≥ 2 SpA features

SpA features: inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's/colitis, good response to NSAIDS, family history of SpA, HLA-B27, elevated CRP

Sacroiliitis on imaging: active (acute) inflammation on MRI highly suggestive of sacroiliitis or definite radiographic sacroiliitis according to modified New York criteria

sensitivity of MRI for nrAxSpA, as compared to the expert opinion-based gold standard diagnosis [2], the classification of HLA B27-positive patients with normal imaging studies but convincing clinical presentation was also made possible. These ASAS classification criteria define the cohorts of patients with nrAxSpA recruited to the majority of studies reviewed here.

The diagnosis of nrAxSpA in the clinical setting can be challenging. The diagnostic criteria for nrAxSpA, as for most rheumatic diseases, have not yet been developed, while blind adoption of the existing classification criteria for the diagnosis is not advised by the experts [4]. The mechanistic approach of the classification criteria – where the physician has to mark "yes" or "no" on a list of items and decide whether the patient satisfies the criteria based on the number of "yes" answers – may not reflect the complexity and diversity of the whole spectrum of disease presentations. Thus, blinded application of nrAxSpA classification criteria for diagnostic purposes will result in the situation where only "no doubt" cases would be diagnosed, while on the other hand the occasional presence of HLA B27 or non-specific MRI changes may lead to the erroneous diagnosis in individuals with, for example, mechanical back pain or fibromyalgia [4].

An analytical diagnostic approach for early axial SpA, which can be applied successfully in daily practice, was suggested by Rudwaleit et al. in 2004 [5]. According to this algorithm, the combination of inflammatory back pain with at least three other typical SpA features (alternating buttock pain, enthesitis, arthritis, dactylitis, positive family history, good response to non-steroidal anti-inflammatory drugs, acute anterior uveitis, raised acute-phase reactants, HLA B27 association, abnormalities on skeletal imaging), or two of the "high impact" SpA features (uveitis, HLA B27, positive MRI) can lead to a confident diagnosis of axial SpA (≥ 90% probability). Combinations of inflammatory back pain with two other SpA features will still result in a highly probable diagnosis (80–89% probability). Of course, all negative data, as well as the possibility of a competing diagnosis, which are not included in the classification criteria, should always be considered during the diagnostic process in an individual.

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EPIDEMIOLOGY AND NATURAL HISTORY OF nrAxSpA

The prevalence of AS, the "radiographic" stage of axial SpA, has been well studied, with a range of 0.01% in Japan, up to 10% in Haida indigenous Americans in Canada, and 0.3% to 0.9% in the majority of European and American countries, reflecting the frequency of HLA B27 in a given population in the majority of the studies [6]. In contrast, the epidemiology of nrAxSpA is still being learned. A recent retrospective cohort study, based on the analysis of medical records from representative rheumatology practices in the United States, found after extrapolating the data to the national level that the U.S. prevalence of nrAxSpA according to ASAS criteria is 0.35% and similar to that for AS [7]. A previous U.S. study, based on the National Health and Nutrition Examination Survey and combining interviews, physical examinations, conventional radiography and laboratory assessment, showed that the prevalence of nrAxSpA may be as high as 0.4%–0.9%, while the general prevalence of axial SpA was 0.9%–1.4% and that of AS about 0.5% [8]. The latter study, however, used previous Amor and European Spondyloarthropathy Study Group criteria for the classification of SpA.

Of interest, different cohort and pharma-sponsored studies recruiting patients with early SpA (both nrAxSpA and AS) and limited by the pre-trial disease duration, demonstrate various, sometimes opposite ratios of patients with nrAxSpA to those with AS. It seems that the length of disease duration may be the main determining factor of this ratio, with relatively more nrAxSpA patients participating in trials with shorter duration of symptoms and vice versa. To illustrate, the proportion of patients diagnosed with nrAxSpA versus AS in the Berlin early SpA clinic was 67% after ≤ 1 year of symptoms, 53% after 1–3 years of symptoms, and only 39% after 6–9 years of symptoms [9].

The natural history of nrAxSpA, however, may show different patterns of development. Firstly, and according to the aforementioned studies, it has been shown that many patients with nrAxSpA will progress to the radiographic AxSpA, or AS, after years of disease. This radiographic progression can be seen in about 10% of patients over 2 years of follow-up on average, and up to 20% over 2 years among those with elevated C-reactive protein (CRP) or active inflammation on MRI. Baseline radiographic damage, elevated acute-phase reactant levels, cigarette smoking, and male gender can predict future radiographic damage in patients with early SpA [10].

On the other hand, some patients with nrAxSpA will suffer from the disease for decades, and probably for life, without any evidence of radiographic damage [1]. Although there is no clear explanation for this phenomenon, the existence of protective factors against new pathologic bone formation should be questioned. For example, the finding of a higher proportion of females in nrAxSpA cohorts, as compared to AS, as well as previously established data on diminished AS-related radiographic damage in females, suggests that hormonal background may play a role in determining the rate of new bone formation in SpA patients. Further understanding of the mechanisms of new bone formation in AS will shed light on other potential protective factors.

Finally, some patients with nrAxSpA may experience remission. While no study has specifically looked at the rates of spontaneous remission in these patients, the phenomenon is occa-

sionally seen in clinical practice (personal unpublished data). Also, drug-induced, as well as subsequent drug-free, remission in patients with nrAxSpA has been repeatedly reported and is reviewed here.

CLINICAL CHARACTERISTICS OF nrAxSpA

Several cohort studies examined the demographic and clinical features of patients with nrAxSpA in comparison to AS patients, seeking conclusive evidence that both disorders represent a spectrum of the same disease. Notably, every such study, regardless where it was carried out (Europe, North America or Asia), established that cohorts of nrAxSpA patients had much more common than contrasting features with the respective AS cohorts [11-15]. The most important common clinical disease elements were similar levels of pain, clinical disease activity, comorbidities (including uveitis, psoriasis, inflammatory bowel disease), frequency of HLA B27, as well as function and quality of life, according to accepted current outcome measures. The observed dissimilarities between the nrAxSpA and AS cohorts included longer disease duration, higher degree of radiographic damage, and reduced spinal mobility in AS patients.

The clinical diagnosis of nrAxSpA should be based on the composite of clinical, laboratory and imaging signs of the disease, while negative MRI or HLA B27 does not exclude the diagnosis in patients with a high clinical suspicion

Another difference reported by these comparative cohort studies was the higher female prevalence among nrAxSpA compared with AS patients. While well-acknowledged male dominance was still evident in AS cohorts, the percentage of females was about twice as high in nrAxSpA than in AS cohorts in Asian studies [14,15]; moreover, females constituted ≥ 50% of nrAxSpA cohorts in European and North American studies [11-13]. In addition, higher serum levels of CRP and more advanced sacroiliac joint inflammation on MRI in AS patients compared to patients with nrAxSpA have been shown in some but not all studies. The suggested explanation for these dissimilarities is that females, demonstrating lower rates of new bone formation than males, as well as patients with less extensive inflammation (measured by serum CRP or/and MRI) progress more slowly to the radiographic stage, remaining in the nrAxSpA phase of the disease spectrum for longer periods of time [16].

MRI FEATURES OF nrAxSpA

With the recent ASAS criteria, as mentioned before, sacroiliitis detected on MRI became an important alternative to X-rays for classifying patients with SpA [2]. While radiography and computed tomography (CT) demonstrate the advanced, irreversible structural changes of inflammatory sacroiliitis (e.g., erosions and ankylosis), MRI is sensitive for active inflammation (i.e., bone marrow edema) and, therefore, can identify patients at an earlier disease stage when irreversible changes in bone structure are not yet evident (the non-radiographic stage). Therefore, it is accepted today that for early detection of the inflammatory stage of the disease there is no role for radiography or CT and the imaging modality of choice is MRI. MRI findings indicative of inflammatory sacroiliitis are divided into active and structural lesions. Active inflammatory lesions include periarticular bone marrow edema (BME), synovitis and capsulitis [Figure 2], while structural lesions include bone erosions, subchondral sclerosis, fat replacement (also denoted fat metaplasia) and bone bridges [Figure 3]. According to the ASAS definition, diagnosing sacroiliitis on MRI is currently based solely on the active inflammatory lesions in general, and the presence of BME in particular, suggesting inflammatory sacroiliitis in two consecutive MRI slices or in two different sacroiliac quadrants [17]. The presence of structural damage without BME is currently not sufficient, according to ASAS, for a positive diagnosis, although cumulative data suggest that incorporating erosions into the "positive" MRI definition of sacroiliitis improves both its sensitivity and specificity compared to the original ASAS definition. It is crucial to recognize

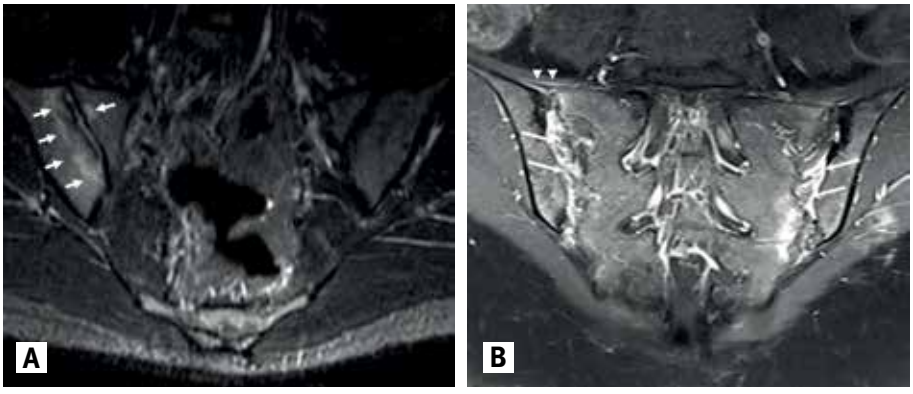

Figure 2. Semi-coronal sequences of the sacroiliac joints of two patients. **[A]** Right periarticular bone marrow edema compatible with sacroiliitis is seen at STIR sequence (short arrows). **[B]** Bilateral enthesitis (long arrows) and capsulitis (arrowheads), demonstrated by T1 weighted sequence after gadolinium injection, are not currently sufficient as a standalone finding for the diagnosis of sacroiliitis

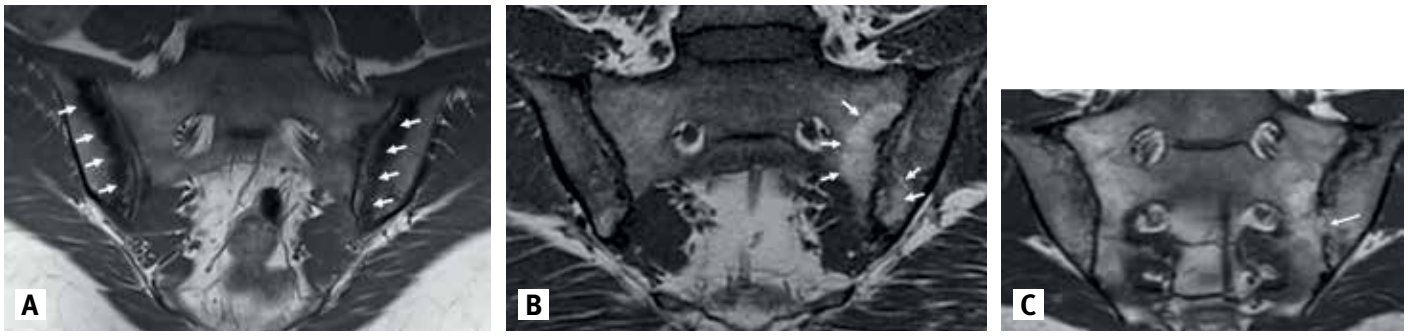

Figure 3. Semi-coronal T1 sequence of the sacroiliac joints of three patients demonstrating **[A]** bilateral bone erosions and subchondral sclerosis (arrows), **[B]** left periarticular fat replacement (arrows), and **[C]** a left bone bridge (arrow)

that some degree of periarticular BME signal can appear in patients with non-specific low back pain and even in the normal population [2], emphasizing the importance of a proficient and expert reading of the MRI images for an accurate diagnosis of inflammatory sacroiliitis. Indeed, when evaluating the sensitivity and specificity of each of the sacroiliac joint MRI lesions, BME had the highest sensitivity (65.1%) for diagnosing AxSpA compared to the other inflammatory and structural lesions but a relative low specificity (74.3%) [18]. In the same study, concomitant evaluation of BME with enthesitis, capsulitis or erosions increased the specificity [18]. Thus, a more global assessment of the sacroiliac joints on MRI was suggested, where all inflammatory and structural lesions are considered when interpreting the MRI of the sacroiliac joints [18]. Using this global assessment approach resulted in higher sensitivity and specificity compared to the ASAS approach and is advocated for clinical purposes [19]. Typical active and structural bone lesions appear on MRI of the spine of patients with AxSpA for which the ASAS group also suggested a definition for positive inflammatory spine [20]. However, the current role of spinal MRI in the diagnosis of patients with AxSpA is not clear and, even more, its additive value when performed together with MRI of the sacroiliac joint has been shown to be relatively minor [21].

When comparing patients with AS to nrAxSpA patients, in addition to the expected more advanced structural disease, the sacroiliac joints have significantly more inflammatory lesions in the radiographic AxSpA patients, irrespective and independent of CRP levels. In addition, patients with radiographic AxSpA have a more advanced spinal disease compared to the nrAxSpA patients. The degree of BME in the sacroiliac joints seems to be affected by tumor necrosis factor-alpha (TNFα) blocking therapy with a very low rate of new-onset BME or fluctuation on MRI during continuous TNFα blocker treatment [22] and was shown to correlate with future radiographic progression [3].

Current treatment strategies for nrAxSpA are the same as for AS and include non-steroidal anti-inflammatory drugs and inhibitors of tumor necrosis factor-alpha

TREATMENT OF nrAxSpA

A list of outcome instruments used in clinical trials examining treatment effects in patients with SpA includes a variety of tools for the measurement of improvement, such as BASDAI-50 (50% improvement in Bath AS Disease activity index), ASAS 20/40 (20% or 40% improvement in ASAS response criteria), or ASAS 5/6 (improvement in at least five of six domains of ASAS response criteria). However, remission has always been the desired target in the management of these patients in real life. Recent trials have demonstrated that adequate pharmacologic interventions in patients with early SpA, including nrAxSpA, can result in a compelling reduction of disease manifestations, defined as ASAS partial remission (ASAS PR) or AS disease activity score inactive disease (ASDAS ID), in a considerable number of patients. Accordingly, the efficacy of the available medical treatments for nrAxSpA is discussed here in light of their capability to induce ASAS PR, defined as a value ≤ 2 (on a 0–10 scale) in pain, patient global assessment, function (as measured by Bath AS Functional Index) and inflammation (as measured by the intensity of morning stiffness by BASDAI questionnaire), or ASDAS ≤ 1.3, which defines the state of inactive disease.

- **Non-steroidal anti-inflammatory drugs (NSAIDs)**

The INFAST trial compared the efficacy of the combined treatment infliximab+naproxene versus placebo+naproxene in early SpA patients with disease duration of less than 3 years. The placebo+naproxene group included 51 patients (33 with AS and 18 with nrAxSpA) with clinically active disease and MRI evidence of inflammation of sacroiliac joints (SIJs) who received naproxen monotherapy (1000 mg/day) for 28 weeks. The number of naproxene-only treated patients with ASAS PR increased steadily and reached > 35% (18/51 patients) by week 28. Only 3/51 patients in this group developed serious adverse events, which included ovarian cyst rupture with anemia, allergic

dermatitis and worsening of AS [23]. NSAIDs were also used to treat the placebo group in another trial which assessed the efficacy of etanercept in nrAxSpA patients with disease duration less than 5 years. More than 17% of 109 patients in this group achieved ASDAS ID state by week 12. Two serious adverse events in NSAIDs-treated patients were observed during this period [24]. In another recent observational study involving 145 patients with nrAxSpA of less than 5 years duration treated "conventionally" with NSAIDs only, 13% of the patients achieved ASDAS ID state during 2 years of follow-up [25]. Notably, despite the low rate of group-specific side effects in the aforementioned and other studies on NSAIDs in SpA, the ability of NSAIDs to alleviate the symptoms and signs of SpA is frequently depreciated, primarily because of the fear of potential side effects. Hopefully, the conclusion of the recent Cochrane Database Systematic Review, stating that NSAID-induced harm may not differ from that of placebo in the short term, will help to re-introduce NSAIDs as a powerful tool for the treatment of SpA, including nrAxSpA [26].

Table 1. Rates of ASAS Partial Remission (ASAS PR) or ASDAS Inactive Disease (ASDAS ID) achieved in major trials involving patients with nrAxSpA

Medicine/ trial	No. of nrAxSpA patients	Mean/ median disease duration	Study duration	ASAS PR rate	ASDAS ID rate	Comparator drug efficacy or group for effect comparison	Ref
Adalimumab	22		12 weeks	22.7%	NA	Placebo: ASAS PR 0%	28
Adalimumab ABILITY 1	91	10 years	12 weeks	16%	24%	Placebo: ASAS PR 5%, ASDAS ID 4%	29
Infliximab (+naproxen)	44 (+61 AS)	1.76 years	28 weeks	61.9%	51.4%	Naproxen: ASAS PR 35% ASDAS ID 19.6%	23
Etanercept EMBARK	106	2.5 years	12 weeks	NA	40%	NSAIDs: ASDAS ID 17.4%	24
Etanercept EMBARK extended	190	2.5 years	48 weeks	~40%	~60%	NA	38
Etanercept ESTHER	20 (+20 AS)	2.6 years	48 weeks	50%	NA	SSZ: ASAS PR 19%	27
Etanercept ESTHER extended	20	2.6 years	1 year	60%	40%	20 AS patients: ASAS PR 40% ASDAS ID 40%	39
Golimumab	98	‹ 5 years	16 weeks	33%	NA	Placebo: ASAS PR 18%	40
Certolizumab pegol	97	6 years	96 weeks	NA	42%	121 AS patients: ASDAS ID 30%	35
All TNFi	54	5.5 years	52 weeks	23.6%	12.2%	239 AS patients: ASAS PR 33.5% ASDAS ID 21.9%	12
All TNFi	62	3 years	24 weeks	53%	NA	259 AS patients: ASAS PR 50%	30

NA = not available, NSAIDs = non-steroidal anti-inflammatory drugs, SSZ = sulfasalazine, TNFi = tumor necrosis factor-alpha inhibitor

- **Sulfasalazine (SSZ)**

SSZ served as a comparator for etanercept in the ESTHER trial. Thirty-six patients with SpA of ≤ 5 years duration (19 patients with AS, 17 patients with nrAxSpA) and active inflammatory lesions of SIJs on MRI were treated with SSZ monotherapy for 48 weeks. Seven of these 36 patients (19%) achieved ASAS PR after 48 weeks of treatment [27]. The results of this study suggested that, contrary to previous beliefs, SSZ treatment can be useful in controlling signs and symptoms of early axial SpA even in patients without peripheral involvement.

- **Tumor necrosis factor-alpha inhibitors (TNFi)**

TNFi have repeatedly been shown to be the most efficacious medicines for the control of clinical manifestations of nrAxSpA [Table 1]. However, the rates of ASAS PR or ASDAS ID in TNFi-treated patients, achieved in the majority of interventional trials or observational studies, vary in the wide range. The factors related to the worse outcome in some of these studies included shorter intervention period [28,29] or longer disease duration before treatment onset [12,29]. For example, the ASAS PR in nrAxSpA patients in an Italian multicenter study was achieved in only 11% of patients by week 12, rising to 53% after a median interval of 6 months [30]. In addition, the suggestion that earlier intervention by TNFi in the course of nrAxSpA can induce a better clinical response has already been proposed and discussed [31]. The presence of BME on the baseline MRI predicted better response to TNFi treatment in several trials [29,30]. On the other hand, up to 40% of patients with an appropriate clinical picture but with no imaging signs of SpA respond to TNFi treatment as well [32]. Of interest, about 20% of 521 patients with inflammatory back pain and no evidence of sacroiliitis on X-ray films from the French DESIR cohort started treatment with a TNFi within the first year of follow-up [33]. A Swiss study showed that as many as 30% of patients with nrAxSpA followed in academic centers are treated with a TNFi [34]. Notably, the achieved clinical effects of TNFi treatment in patients with nrAxSpA are likely to be sustained for long periods [35,36]. According to the data of the Swedish registry, the survival of TNFi was better in nrAxSpA patients, demonstrating acute inflammatory changes on MRI [37]. Whether suppression of the existing BME, as seen on MRI, and prevention of new osteitis by TNFi will inhibit future structural damage have yet to be determined [22].

SUMMARY

Our knowledge in the field of nrAxSpA, an entity formulated less than a decade ago, is expanding progressively. Well-organized and closely followed cohorts of patients with nrAxSpA all over the world continuously provide new information regarding the epidemiology and natural history of the disease, while ASAS and other international study groups are steadily advancing in the research and validation of diagnostic tools,

outcome measures and treatment algorithms. This review summarizes current achievements in the field. More data on the natural history of the disease, its triggers and preventive factors, and, particularly, further understanding of the mechanisms of inflammation and subsequent new bone formation are imperative for the development of new treatment strategies for patients with nrAxSpA patients.

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