CLINICAL INVESTIGATION

New developments in the diagnosis and treatment of axial spondyloarthritis

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Spondyloarthritis (SpA) is an umbrella term for a group of diseases sharing genetic, molecular, immunological, clinical and imaging features. The last few years have witnessed a remarkable progress in the understanding of SpA. Notable advances include the recognition of MRI as a sensitive and specific tool for detecting axial inflammation and the recent development and validation of the Assessment of Spondyloarthritis International Society classification criteria for predominantly axial and predominantly peripheral SpA. This approach has the advantage of better describing the disease, allowing earlier identification and treatment of the non-radiographic forms and potentially leading to improved outcomes. TNF α-blockers, which dramatically improve the clinical symptoms and signs of patients with ankylosing spondylitis, are now being tested in patients with non-radiographic axial SpA, with the first studies providing evidence that patients with the non-radiographic form of the disease also benefit from this treatment in the same order as patients with ankylosing spondylitis. Important advances have been made in clarifying the natural history and pathophysiological mechanisms of axial SpA, which may lead to the discovery of new therapies and innovative treatment strategies in the future.

Keywords: classification • diagnosis • inflammation • MRI • non-steroidal anti-inflammatory drugs • spondylitis • spondyloarthritis • structural damage • treatment • TNF-blockers.

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Spondyloarthritis (SpA) is a term used to describe various diseases with overlapping genetic, molecular, immunological, clinical and imaging features. This group of related diseases (Figure 1) includes psoriatic arthritis, reactive arthritis, arthritis related to inflammatory bowel disease (IBD), arthritis related to anterior uveitis, a subgroup of juvenile idiopathic arthritis, undifferentiated SpA and ankylosing spondylitis (AS) [1–4].

The spectrum of clinical manifestations in SpA includes chronic axial pain (typically, but not always, with inflammatory characteristics), loss of spinal mobility, peripheral arthritis (often asymmetric oligoarthritis involving large joints), enthesitis, dactylitis and extra-articular features such as anterior uveitis, psoriasis and IBD [1–3]. SpA is strongly associated with HLA-B27 variants and clinical manifestations may occur, simultaneously or sequentially, in the same patient or in members of the same family [5].

The high prevalence of AS (up to 1%) and SpA in general (up to 2%) in the Caucasian population [6,7] implies a large economic burden for society [8–12]. The socioeconomic impact of SpA is increased by the fact that SpA usually occurs in active young adults. The disease can have a great impact on health and quality of life in individual patients, and it is associated with substantial sick leave and restrictions while being at work, as well as when performing unpaid tasks [8,12]. However, the natural history of SpA seems to be heterogeneous with several forms from mild to severe disease.

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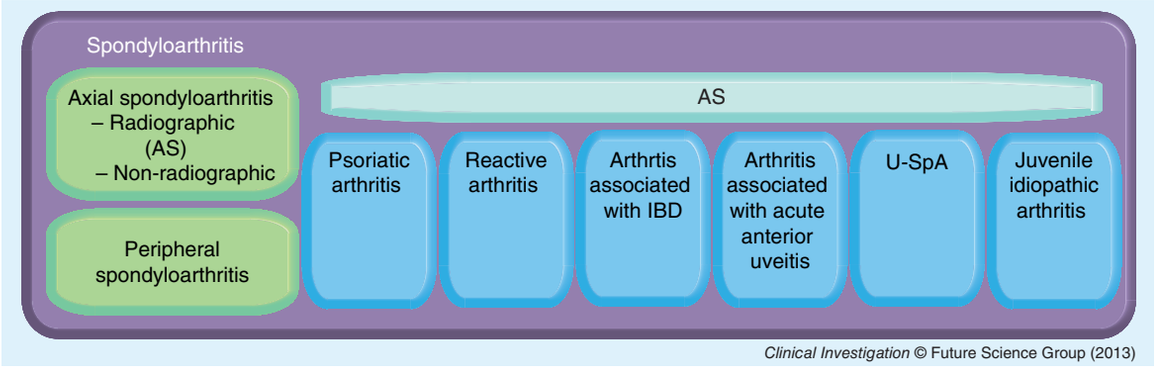

Figure 1. The spondyloarthritis umbrella.
AS: Ankylosing spondylitis; IBD: Inflammatory bowel disease; U-SpA: Undifferentiated spondyloarthritis.

New developments in the diagnosis of axial SpA

Classification criteria for SpA

To classify patients with SpA, various classification criteria have been proposed (Table 1). The Amor and the European Spondyloarthropathy Study Group (ESSG) criteria address the entire group of SpA [13,14]. The modified New York (mNY) criteria are used to classify patients with AS [15]. Recently, the Assessment of Spondyloarthritis International Society (ASAS) has developed new classification criteria for axial SpA (characterized by predominant involvement of the spine and/or sacroiliac joints) [16,17] and peripheral SpA (characterized predominantly by peripheral arthritis, enthesitis, and/or dactylitis) [18].

Classification criteria differ from diagnostic criteria, in that they are used to create homogeneous groups of patients with a classical disease picture, have a high specificity and should give a 'yes or no' answer. By contrast, diagnostic criteria are used to make a diagnosis, are applied to individual patients, have higher sensitivity and allow more flexibility in diagnostic confidence [19]. However, this separation is artificial, since the two, in fact, represent a continuum. The reasoning behind both diagnostic and classification criteria is the same and a diagnosis is, in fact, making a classification in an individual patient [20]. In practice, physicians often use classification criteria as an anchor to support a diagnosis and this has also been the case for the mNY classification criteria for AS, widely used in clinical practice for making this diagnosis. However, the use of the mNY as a diagnostic anchor has contributed to a long delay (from 5 to 10 years) between the first occurrence of symptoms (disease onset) and a diagnosis of AS [4,21].

The reason why the mNY contribute to a long diagnostic delay is because they require the presence of definite sacroiliitis on plain radiographs (based on the presence of several radiographic features, such as erosions, sclerosis, joint space narrowing, pseudo-widening and ankylosis). However, definite radiographic sacroiliitis is a relatively late finding in the majority of patients with axial SpA [19,22,23]. Furthermore, defining reliable morphologic criteria that distinguish in particular grade 1 from grade 2 sacroiliitis (definitions can be found in Table 1), is notably difficult. It is inherently difficult to grade radiographs of the sacroiliac joints, leading to frequent misclassification, and improvements in performance are difficult to achieve even after appropriate training sessions [24]. Thus, the mNY criteria perform well in established disease but lack sensitivity in early disease and are therefore restrictive. Moreover, the mNY criteria were developed in the pre-MRI era and therefore do not recognize the value of MRI in assessing patients suspected of having axial SpA: MRI can visualize sacroiliitis (inflammatory lesions) in patients with normal radiographs of the sacroiliac joints, and has evolved as the most important diagnostic imaging tool in early axial disease [17,25].

The appreciation that inflammation is visible on MRI in patients with an AS clinical phenotype, but without sacroiliitis on plain radiographs [19], was crucial in coining the term 'non-radiographic axial SpA' (nr-axSpA). Indeed, AS is part of the umbrella term 'axial Spa', and can be seen as a late phase of the axial SpA disease spectrum: first, back pain is present (typically with inflammatory clinical characteristics, with or without sacroiliitis on MRI, and without sacroiliitis on radiographs), followed by a stage in which sacroiliitis may be detectable on radiographs, and finally a phase during which syndesmophytes in the spine may occur. However, this sequence of events has to be proven formally and does not likely apply to all patients, as axial SpA is a heterogeneous disease.

In a recent study, the rate of progression from nr-axSpA to AS (i.e., radiographic axial SpA) was estimated to be approximately 12% over 2 years [26]. However, a proportion of patients may never develop radiographic sacroiliitis (although they may develop syndesmophytes, even in the absence of radiographic sacroiliitis; however, this is uncommon). Similarly, a proportion of patients with axial

SpA (including classic AS) may never develop syndesmophytes and may not have MRI sacroiliitis at the time of MRI assessment (including in the preradiographic stage) [27–31]. These patients do all still belong to the same disease spectrum, but with different phenotypes (Figure 2).

This new disease paradigm led the ASAS group to develop new criteria for axial and peripheral SpA [16–18]. The new ASAS classification criteria for axial SpA can help identify patients with axial SpA without radiographic sacroiliitis; therefore at earlier stages of the disease. This is important because the severity of symptoms in this subgroup of patients is similar to AS [29], requiring effective treatment. An accurate and early diagnosis will also prevent unnecessary tests and inappropriate treatments. In addition, if effective and specific treatments are started early in the disease process, they can improve work capability, physical function and health-related quality of life of the patient [32].

Table 1. Published classification criteria for spondyloarthritis[†].

Publication	Definition/entry criterion	Imaging criterion	Clinical criteria	Ref.
Amor criteria for SpA	Sum of points of items must be ≥6; a sum of points ≥5 classifies for probable SpA	Radiographic sacroiliitis[‡] (3 points)	■ Lumbar or dorsal pain during the night, or morning stiffness of lumbar or dorsal spine (1 point) ■ Asymmetric oligoarthritis (2 points) ■ Buttock pain (1 point), if affecting alternately the right or the left buttock (2 points) ■ Dactylitis (2 points) ■ Enthesitis (2 points) ■ Iritis (2 points) ■ Non-gonococcal urethritis or cervicitis accompanying, or within 1 month before, the onset of arthritis (1 point) ■ Acute diarrhea accompanying, or within 1 month before, the onset of arthritis (1 point) ■ Presence or history of psoriasis, balanitis, or IBD (Crohn's/ulcerative colitis; 2 points) ■ Good response to NSAIDs in less than 48 h, or relapse of the pain in less than 48 h if NSAIDs discontinued (2 points) ■ Presence of HLA-B27, or familial history of AS, Reiter syndrome, uveitis, psoriasis, or chronic enterocolopathies (2 points)	[13]
ESSG criteria for SpA	IBP (modified Calin [34]) or synovitis (asymmetric or predominantly in the lower limbs), and ≥1 clinical or radiological criterion	Radiographic sacroiliitis[‡]	■ Buttock pain alternating between right and left gluteal areas ■ Urethritis, cervicitis, or acute diarrhea within 1 month before arthritis ■ IBD ■ Psoriasis ■ Positive family history	[14]
mNY criteria for AS	Imaging criterion plus ≥1 clinical criterion	Radiographic sacroiliitis[‡]	■ Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest ■ Limitation of motion of the lumbar spine in the sagittal and frontal planes ■ Limitation of chest expansion relative to normal values correlated for age and sex	[15]

[†]Please note that the definition of IBP and some SpA features varies between different criteria sets; for details please consult the original publications.
[‡]Defined as radiographic sacroiliitis grade ≥2 bilaterally or grade 3–4 unilaterally: grade 0 = normal; grade 1 = suspicious changes; grade 2 = minimum abnormality (small localized areas with erosion or sclerosis, without alteration in the joint width); grade 3 = unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis); grade 4 = severe abnormality (total ankylosis).
[§]Defined as bone marrow edema (short tau inversion recovery sequence) or osteitis (T1 post-gadolinium sequence) highly suggestive of SpA, clearly present and located in the typical anatomical areas (subchondral or periarticular bone marrow); if there is only one signal (lesion) per MRI slice suggesting active inflammation, the lesion should be present on at least two consecutive slices; if there is more than one signal (lesion) on a single slice, one slice may be sufficient.
AS: Ankylosing spondylitis; ASAS: Assessment of spondyloarthritis international society; CBP: Chronic back pain; ESSG: European Spondyloarthropathy Study Group; IBD: Inflammatory bowel disease; IBP: Inflammatory back pain; mNY: Modified New York; NSAIDs: Non-steroidal anti-inflammatory drugs; SpA: Spondyloarthritis.

Table 1. Published classification criteria for spondyloarthritis (cont.).[†]

Publication	Definition/entry criterion	Imaging criterion	Clinical criteria	Ref.
ASAS criteria for axial SpA	CBP (≥3 months) with an onset <45 years of age and: a) Imaging criterion plus ≥1 the clinical criteria or b) Positive HLA-B27 plus ≥2 other clinical criteria	Radiographic sacroiliitis[‡] or MRI sacroiliitis[§]	■ IBP (ASAS) [137] ■ Arthritis ■ Enthesitis (heel) ■ Uveitis ■ Dactylitis ■ Psoriasis ■ Crohn's/ulcerative colitis ■ Elevated CRP ■ Good response to NSAIDs ■ Family history of SpA ■ HLA-B27	[16,17]
ASAS criteria for peripheral SpA	Peripheral arthritis, enthesitis or dactylitis and: a) Imaging criterion or ≥1 clinical SpA feature from group A or b) ≥ 2 other clinical SpA features from group B	Radiographic sacroiliitis[‡] or MRI sacroiliitis[§]	**Group A:** ■ Uveitis ■ Psoriasis ■ Crohn's/ulcerative colitis ■ Preceding infection ■ HLA-B27 **Group B:** ■ Arthritis ■ Enthesitis ■ Dactylitis ■ IBP ever (ASAS) [137] ■ Family history for SpA	[18]

[†]Please note that the definition of IBP and some SpA features varies between different criteria sets; for details please consult the original publications.
[‡]Defined as radiographic sacroiliitis grade ≥2 bilaterally or grade 3–4 unilaterally: grade 0 = normal; grade 1 = suspicious changes; grade 2 = minimum abnormality (small localized areas with erosion or sclerosis, without alteration in the joint width); grade 3 = unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis); grade 4 = severe abnormality (total ankylosis).
[§]Defined as bone marrow edema (short tau inversion recovery sequence) or osteitis (T1 post-gadolinium sequence) highly suggestive of SpA, clearly present and located in the typical anatomical areas (subchondral or periarticular bone marrow); if there is only one signal (lesion) per MRI slice suggesting active inflammation, the lesion should be present on at least two consecutive slices; if there is more than one signal (lesion) on a single slice, one slice may be sufficient.
AS: Ankylosing spondylitis; ASAS: Assessment of spondyloarthritis international society; CBP: Chronic back pain; ESSG: European Spondyloarthropathy Study Group; IBD: Inflammatory bowel disease; IBP: Inflammatory back pain; mNY: Modified New York; NSAIDs: Non-steroidal anti-inflammatory drugs; SpA: Spondyloarthritis.

Before the ASAS axial SpA criteria were available, only patients with radiographic sacroiliitis could be classified according to the mNY criteria, or the whole group of SpA (without distinguishing a predominantly axial or peripheral phenotype) was addressed by the ESSG and Amor criteria, which were developed in the pre-MRI era. With the new ASAS criteria, two separate classification criteria sets exist for predominantly axial and predominantly peripheral SpA [30,32]. This approach has the additional advantage of better describing the disease and better defining treatment strategies, as they differ between axial and peripheral SpA.

■ The new ASAS classification criteria for axial SpA: a proxy to diagnostic criteria

Important new features of the ASAS axial SpA classification criteria (Table 1) are the new entry criteria and the existence of two arms, with MRI playing the most relevant role in one ('imaging arm') and HLA-B27 in the other ('clinical arm').

The new criteria for axial SpA can be applied in patients with back pain for longer than 3 months with an onset before the age of 45 years. Of note, chronic back pain, not necessarily being inflammatory back pain (IBP), is present as an entry criterion, reflecting the fact that in clinical practice, patients with noninflammatory chronic back pain may represent up to 20–30% of patients with axial SpA, while IBP can be observed in 20–25% of patients with non-inflammatory (mechanical) causes of chronic back pain [25,33,34]. Detailed analysis in the ASAS axial SpA validation study also demonstrated that IBP as an entry criterion did not perform better than chronic back pain [17]. However, the presence of IBP is an important symptom that should prompt further diagnostic tests for axial SpA. Age is also an important factor in the entry criteria, reflecting the fact that complaints associated with

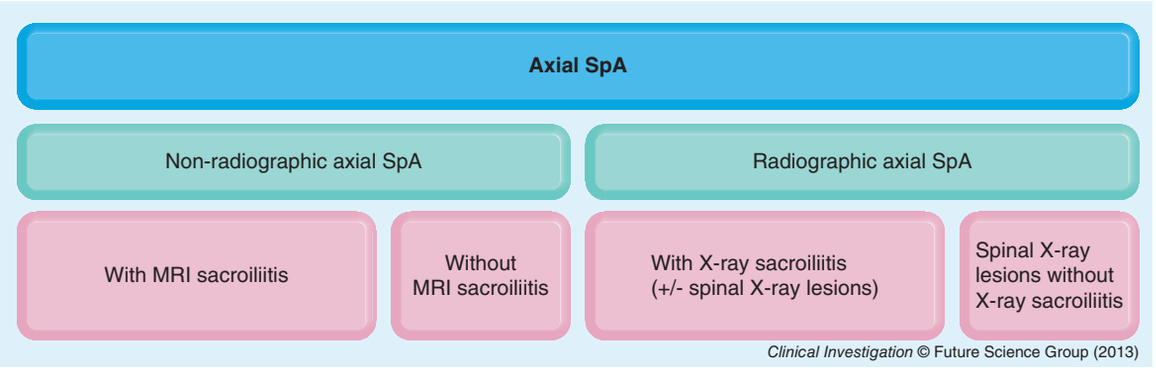

Figure 2. The axial spondyloarthritis disease spectrum. Spinal radiographic lesions are syndesmophytes, bridging of the vertebral bodies, ankylosis of the facet joints.
SpA: Spondyloarthritis.

axial SpA usually start in the third decade of life, and by the age of 45 years, more than 95% of patients are symptomatic [32].

The presence of MRI inflammation, which now plays an important role in the rheumatologist´s judgment to make a diagnosis of axial SpA, is also a prominent factor in the ASAS classification criteria for axial SpA, together with the classical presence of radiographic sacroiliitis. However, not all axial SpA patients have sacroiliitis on imaging (e.g., in the validation study of the ASAS criteria [17], 25% of the patients did not have radiographic or MRI evidence of sacroiliitis), underscoring the fact that in clinical practice the rheumatologist bases his decision also on many other clinical and laboratory features, and that a diagnosis of axial SpA is possible in the absence of sacroiliitis on imaging, including MRI [28]. This is reflected in the HLA-B27 arm of the ASAS axial SpA criteria. HLA-B27 is strongly associated with SpA [35,36] and is estimated to be present in 75–95% of cases of AS and 42–75% of cases of non-radiographic/undifferentiated axial SpA [29,37–42], while in the general population, only 5–10% are HLA-B27 positive [43,44]. HLA-B27 testing can therefore be a very useful test in diagnosing axial SpA, when found in combination with other SpA features [35,36].

Axial SpA is an expert diagnosis based on a clinical picture, including signs, symptoms, family history, imaging and laboratory studies. Expert diagnosis was therefore the gold-standard in the ASAS classification study [18]. Due of the strong association of sacroiliitis with axial SpA, and because of high sensitivity and specificity, if sacroiliitis on imaging is present, only one other SpA feature needs to be present to classify a patient as having axial SpA according to the ASAS criteria, while two additional features are required in the HLA-B27 arm [17].

In the ASAS validation study, the application of the axial SpA criteria resulted in a post-test probability of 89% (imaging arm 97.5% and HLA-B27 arm 86%) and a positive likelihood ratio of 5.3. Among the 649 patients with chronic back pain (for more than 3 months) of unknown origin (no definite diagnosis) that began before 45 years of age included in the study, a diagnosis of axial SpA was made by the rheumatologist in 60.2% of the study population. The ASAS axial SpA criteria had a better sensitivity/specificity balance (82.9/84.4%) than the ESSG (72.4/66.3%), MRI modified ESSG (85.1/65.1%), Amor (69.3/77.9%) and MRI modified Amor (82.9/77.5%) criteria [17]. These data support the idea that the new criteria can be helpful as diagnostic criteria if applied in the appropriate setting, that is, specialized rheumatology clinics. Disease misclassifications are dependent on prevalence of the disease and the criteria are awaiting further testing in settings with a lower prevalence of axial SpA.

■ Definition of a 'positive' MRI

Active inflammatory lesions are best visualized by a short tau inversion recovery sequence (bone edema) or by a T1 postgadolinium sequence (osteitis), while chronic lesions (fatty deposition, erosions, syndesmophytes and ankylosis) are best visualized by a T1-weighted turbo spin-echo sequence [4,45]. Importantly, active sacroiliitis on MRI can predict (at least at the group level) future appearance of sacroiliitis on radiographs [46]. Generally, inflammation starts in the sacroiliac joints, and it often takes 6–8 years before radiographic sacroiliitis is detectable on plain radiographs [19,46]. Therefore, it is important to identify inflammation of the sacroiliac joints on MRI in early axial SpA [25,36].

A definition of sacroiliitis as detected with MRI was developed based on a consensus among radiologists and rheumatologists by the ASAS/Outcome Measures in Rheumatology (OMERACT) MRI study group. An MRI of the sacroiliac joints is considered as 'positive' if the areas of bone marrow edema/osteitis are located at typical sites, that is, if they are in close conjunction with the sacroiliac joints and are 'highly suggestive' of SpA. When only one

bone marrow edema/osteitis lesion is visible on an MRI slice, it should be clearly visible on two consecutive slices; otherwise it is not sufficient for a 'positive' MRI. If there is more than one signal (lesion) on a single slice, one slice is considered sufficient. Enthesitis, capsulitis or synovitis reflect active inflammation as well and are certainly compatible with SpA-related sacroiliitis, yet are not sufficient for a 'positive' MRI if present without concomitant bone marrow edema/osteitis (which is uncommon). Structural lesions are likely to reflect previous inflammation and are visible on MRI, but are currently considered insufficient for the definition of activity on MRI [45].

For diagnostic/classification purposes it is usually sufficient to perform an MRI only of the sacroiliac joints because this is where inflammation generally starts, and lesions rarely occur solely in the spine, as suggested in the ASAS criteria validation study [17,30,45]. For the routine detection of inflammation, the short tau inversion recovery technique (capable of detecting bone edema, reflecting increased water content) is considered sufficient, and gadolinium contrast is not required. Only in cases of doubt (e.g., artefacts) or high suspicion index, should an additional scan after gadolinium (capable of detecting osteitis, reflecting increased perfusion due to inflammation) be considered [45,47,48].

There is, however, evidence that spondylitis may occur prior to or even without sacroiliitis [17,49]. Therefore a definition of a 'positive MRI' for spinal inflammation was recently proposed by the same ASAS/OMERACT MRI study group [50]. A total of six different types of inflammatory lesions (anterior/posterior spondylitis, spondylodiscitis, arthritis of costovertebral joints, arthritis of zygoapophyseal joints and enthesitis of spinal ligaments) and four different types of structural lesions (fatty deposition, erosions, syndesmophytes and ankylosis) are described in the referred article [50]. Based on expert consensus and taking published literature into account [49,51–53], a 'positive' spinal MRI for inflammation was defined as the presence of anterior/posterior spondylitis in ≥3 sites. Therefore we now have a definition of a 'positive' MRI of the spine, but this is not yet incorporated in the definition of a 'positive' MRI required for a diagnosis of axial SpA. Evidence of fatty deposition at several vertebral corners was also found to be suggestive of axial SpA, especially in younger adults. A cut-off of ≥4 sites of fatty deposition was proposed; however more data were considered needed until a formal recommendation can be made.

Imaging of SpA is an area of intense research and the definition of a 'positive' MRI may change in the future, namely regarding the added value (or not) of combining active inflammation and structural lesions in the definition, the number and types of lesions and the potential contribution of spinal lesions in addition to sacroiliac joints' lesions to define a 'positive' MRI. The first steps towards the standardization of morphologic definitions for acute and chronic inflammatory lesions seen on MRI have already been given [45,50,54,55]. Further scrutiny of their specificity and sensitivity is important, namely in comparison to patients with mechanical back disorders. It will also be important to assess the relationship between the different types of inflammatory and chronic lesions, and to what extent they contribute to the new bone formation that can be seen on radiographs of the spine and sacroiliac joints.

New developments in the treatment of axial SpA

■ Updates on the management of axial SpA

The 2010 ASAS/The European League Against Rheumatism recommendations for the management of AS are summarized in Figure 3 [56]. These recommendations refer to AS only because at the time of publication the number of trials addressing the whole axial SpA group was very small. However, the project group highlighted that it can be anticipated that future trials will increasingly target axial SpA, rather than AS, and unanimously agreed that the recommendations should also pertain to patients with nr-axSpA.

Treatment of axial SpA should rely on a multidisciplinary approach and the combination of nonpharmacological and pharmacological treatment modalities. The choice of treatment modality and also the pharmaceutical agent used should be tailored to patients' disease manifestations, such as axial pain and stiffness, enthesitis, peripheral arthritis and extra-articular manifestations.

The basic treatment continues to be patient education, regular exercise and non-steroidal anti-inflammatory drugs (NSAIDs; classical or COX-2 inhibitors). Physiotherapy interventions are more effective than home exercises, with a tendency to be more effective when carried out as a supervised outpatient group [57,58]. TNF-blockers, a major breakthrough in the treatment of axial SpA, are considered a second line treatment for axial SpA. The association of a rehabilitation program or occupational intervention and pharmacological treatment with a TNF-blocker has been demonstrated to be a useful approach [59–61].

The new recommendations emphasize a very limited role for disease-modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine, methotrexate or leflunomide in the management of axial SpA: axial symptoms do not respond to DMARDs and are, therefore, obsolete, while sulfasalazine is moderately effective in patients with concomitant peripheral arthritis. However, it is recognized that in clinical practice methotrexate and sometimes leflunomide are also prescribed to treat patients with peripheral arthritis, but no evidence-based recommendation can presently support this treatment. Analgesics, such as paracetamol and opioid-like drugs, might be considered

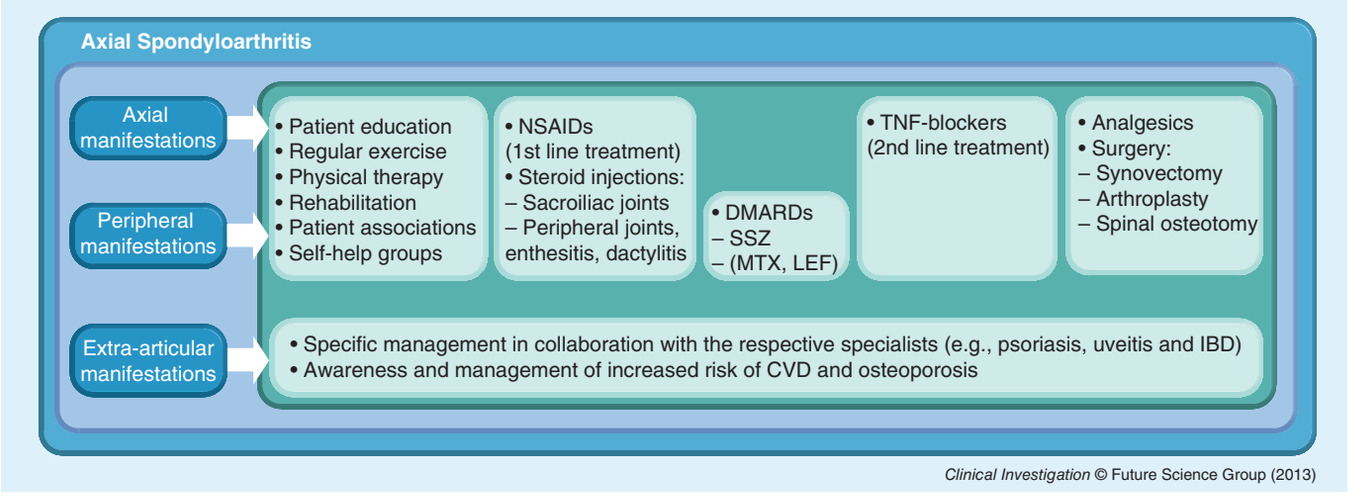

Figure 3. Overview of the Assessment of Spondyloarthritis International Society–European League Against Rheumatism recommendations for the treatment of axial spondyloarthritis.

CVD: Cardiovascular disease; DMARDs: Disease-modifying anti-rheumatic drugs; IBD: Inflammatory bowel disease; LEF: Leflunomide; MTX: Methotrexate; NSAIDs: Non-steroidal anti-inflammatory drugs; SSZ: Sulfasalazine.

for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated. Corticosteroid injections directed to the site of musculoskeletal inflammation should also be considered in case of arthritis or enthesitis. Surgical synovectomy, joint arthroplasty and spinal osteotomy may be considered in selected cases. The decision to operate should be based on symptoms, functional decline and imaging; young age should not be a reason to refrain from joint arthroplasty [56].

The ASAS recommendations to treat patients with TNF-blockers have recently been substantially revised [62], now addressing the whole axial SpA group. TNF-blockers are recommended for patients with NSAID-resistant active axial disease. No recommendation is made regarding individual agent preference, except for the suggestion of the use of monoclonal antibodies when IBD accompanies axial SpA. If the disease manifestations are predominantly axial, no additional treatment with synthetic DMARDs is required before initiation of therapy with a TNF-blocker. It is recommended that patients should have tried at least two different NSAIDs in an optimal anti-inflammatory dose for a total of at least 1 month (unless there is contraindication or intolerance) [63]. Patients with symptomatic peripheral arthritis should also have an insufficient response to at least one local steroid injection (if appropriate) and should normally have had an adequate therapeutic trial of a DMARD (not mandatory), preferably sulfasalazine, while patients with symptomatic enthesitis must have failed appropriate local treatment.

Patients with active axial disease in whom biological therapy is considered should have a Bath AS disease activity index (BASDAI) ≥4 (0–10 scale) for more than 4 weeks. Historically, the BASDAI [64] has been the most widely used clinical disease activity measure in axial SpA, and the BASDAI cut-off of ≥4 is the most common selection criteria for clinical trials with TNF-blockers. However, since the publication of the 2010 ASAS updated recommendations, evidence accumulates that the AS disease activity index (ASDAS) [65–67], a new ASAS and OMERACT-endorsed composite disease activity index recently developed for axial SpA (Table 2) [67–70], with validated disease activity cut-offs (an ASDAS ≥2.1 representing high disease activity) [67], may be a better tool to assess disease activity in patients with axial SpA, as it may better reflect the inflammatory disease processes in this group of patients [71–73]. Furthermore, ASDAS high disease activity (ASDAS ≥2.1) may be a better cut-off than BASDAI elevation (BASDAI ≥4) to select patients for treatment with TNF-blockers [74–76], specifically because it selects a higher number of patients with characteristics predictive of good response to these therapies [74,77]. ASDAS is now being used as an outcome measure in several clinical trials and the cut-off of 2.1 has already been recommended by some rheumatology national societies as an alternative to BASDAI to select patients for treatment with TNF-blockers [78].

Finally, response to treatment should be assessed after at least 12 weeks of continuous treatment with a TNF-blocker and the response criteria is a decrease in BASDAI ≥50% or ≥2 units (0–10 scale) and positive expert opinion. Again, in this regard, the ASDAS response criteria of clinically important improvement (decrease in ASDAS ≥1.1 units) has the potential to replace BASDAI as the preferred response measure in the future owing to the above reasons [67–77].

Table 2. The Ankylosing Spondylitis Disease Activity Score formulae and its cut-offs for disease activity states and response criteria.

ASDAS formulae		ASDAS cut-offs			ASDAS response criteria	
ASDAS-CRP (preferred formula)	ASDAS-ESR (alternative formula)	Inactive disease	Moderate disease activity	High disease activity	Very high disease activity	Clinically important improvement	Major improvement
0.12 × Back pain + 0.06 × Duration of morning stiffness + 0.11 × Patient global + 0.07 × Peripheral pain/swelling + 0.58 × Ln(CRP + 1)	0.08 × Back pain + 0.07 × Duration of morning stiffness + 0.11 × Patient global + 0.09 × Peripheral pain/swelling + 0.29 × √(ESR)	ASDAS < 1.3	1.3 ≤ ASDAS < 2.1	2.1 ≤ ASDAS ≤ 3.5	ASDAS > 3.5	Decrease in ASDAS ≥1.1 units	Decrease in ASDAS ≥ 2.0 units

Back pain, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) question 2: 'How would you describe the overall level of ankylosing spondylitis neck, back or hip pain you have had?' Duration of morning stiffness, BASDAI question 6: 'How long does your morning stiffness last from the time you wake up?' Patient global: 'How active was your spondylitis on average during the last week?' Peripheral pain/swelling, BASDAI question 3: 'How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?' Back pain, patient global, duration of morning stiffness and peripheral pain/swelling are all assessed on a visual analogue scale (from 0 to 10 cm) or on a numerical rating scale (from 0 to 10).
√(ESR): Square root of the erythrocyte sedimentation rate (mm/h); ASDAS: Ankylosing Spondylitis Disease Activity Score; Ln(CRP + 1): Natural logarithm of the CRP (mg/l) + 1.
Data taken from [67,69].

■ TNF-blockers in axial SpA, including nr-axSpA

The efficacy of TNF-blockers (infliximab, etanercept, adalimumab and golimumab) has been clearly demonstrated in several placebo-controlled trials in NSAID-refractory patients with AS. Published efficacy and safety data also include registries and observational studies. A trial with certolizumab is currently ongoing [201] and the first pharmacokinetic, efficacy and overall safety trial with a biosimilar product (CT-P13) to infliximab was recently presented in abstract format [79].

The effect of TNF-blockers on pain, stiffness, physical function and fatigue can be seen as early as 2 weeks after the start of treatment [80–83]. Other sustained benefits include reduced acute phase reactants, improvement in synovial histopathology, reduction in MRI spinal inflammation, improvements in spinal mobility, quality of life, social participation and work productivity and reduction in sick leave.

TNF-blockers are effective in both axial and peripheral manifestations and across all demographic subgroups and disease severity levels, including patients with complete spinal ankylosis. Several observational studies have shown the benefit of switching to a second or even a third TNF-blocker [84–89]. Switching after TNF-blocker failure is especially successful in cases of secondary ('loss of response') rather than primary failures ('absence of initial response').

It is now clear that patients with AS and those with nr-axSpA have comparable clinical manifestations and burden of disease [29], requiring treatment irrespective of the presence of radiographic sacroiliitis. Therefore clinical trials in patients with nr-axSpA fulfill an unmet medical need. There have been four clinical trials (summarized in Table 3) investigating the effect of TNF-blockers in patients with nr-axSpA [90–93], although only the last trial prospectively recruited patients fulfilling the ASAS axial SpA classification criteria [93]. Other TNF-blocker trials recruiting patients with nr-axSpA are ongoing [201–206].

In the first trial, adalimumab demonstrated good clinical efficacy and safety in patients with axial SpA without radiographically defined sacroiliitis [90]. In the second study, infliximab was an effective therapy in reducing clinical and imaging evidence of disease activity in patients with MRI-determined early axial SpA; all the patients in this trial were also HLA-B27 positive and approximately 12% had AS [91]. In the third study (the ESTHER trial), etanercept-treated patients with early axial SpA and active inflammatory lesions detected by whole-body MRI had significantly better improvement in clinical and MRI inflammatory activity compared with patients treated with sulfasalazine [92]. Interestingly, all patients in this study retrospectively fulfilled the ASAS classification criteria for axial SpA (49% with nr-axSpA and 51% with AS). The fourth published study was the

first randomized placebo-controlled clinical trial to prospectively recruit patients using the ASAS axial SpA classification criteria [93]. Importantly, AS patients and patients with psoriasis were excluded from this trial and only nr-axSpA patients were included. Adalimumab treatment resulted in effective control of disease activity, decreased

Table 3. Clinical trials of TNF-blockers in non-radiographic axial spondyloarthritis.

	Haibel *et al.* [90]	Barkham *et al.* [91]	Song *et al.* [92]	Sieper *et al.* [93]
Study Design	12-week placebo-controlled study followed by an open extension up to week 52	16-week placebo-controlled study	48-week open-label study	12-week placebo-controlled study followed by an open extension up to week 156
Inclusion criteria	Axial SpA without radiographic sacroiliitis, based on the presence of CBP (>3 months), symptom onset <50 years, and ≥3 of the following six criteria, including ≥2 of the first three: 1) IBP (modified Calin [34]); 2) HLA–B27 positivity; 3) active MRI of the SIJ or spine; 4) history of a good response to NSAIDs; 5) presence (current or past) of ≥1 extra spinal manifestations; 6) family history of SpA	Axial SpA with IBP (modified Calin [34]) for the previous 3 months to 3 years, HLA–B27 positivity and MRI evidence of sacroiliitis	Axial SpA based on the presence of CBP (>3 months), symptom onset <45 years, and active inflammatory lesions on whole-body MRI in either the SIJ or the spine plus three out of the following criteria: 1) IBP (modified Calin [34]); 2) HLA-B27 positivity; 3) history of a good response to NSAIDs; 4) presence (current or past) of ≥1 extraspinal manifestations; 5) family history of SpA[†]	ASAS criteria for axial SpA, patients fulfilling mNY criteria for AS were excluded
Active disease definition	BASDAI ≥4 despite treatment with NSAIDs	At least two of the following: BASDAI ≥4, a pain score ≥4 (10 cm VAS) or early morning stiffness ≥45 min	BASDAI ≥4 and total back pain ≥4 (10 cm VAS) despite treatment with NSAIDs	BASDAI ≥4, total back pain ≥4 (10 cm VAS) and inadequate response, intolerance or contraindication to NSAIDs
Number of patients	46 (22 Adalimumab vs 24 Placebo)	40 (20 Infliximab vs 20 Placebo)	76 (40 Etanercept vs 36 Sulfasalazine)	185 (91 Adalimumab vs 94 Placebo)
Mean symptom duration (years)	7.5	1.3	2.9	10.1
HLA–B27 positive (%)	67	100	82	78
MRI positive	65% (inflammatory lesions in the SIJ/spine diagnosed by consensus opinion of local rheumatologist and radiologist)	100% (inflammatory lesions in the SIJ diagnosed by local radiologists)[‡]	100% (inflammatory lesions on whole-body MRI in the SIJ/spine diagnosed by local radiologists)	48% (inflammatory lesions in the SIJ diagnosed by the local radiologist/rheumatologist)
HLA–B27 positive and MRI negative (%)	31	0	0	50
nr-axSpA/AS (%)	100/0	88/12[§]	49/51	100/0

[†]Retrospectively, all patients fulfilled the ASAS classification criteria for axial SpA.

[‡]When blinded paired scoring of the scans was performed after the study, three patients (all in the placebo group) had a baseline MRI Leeds score of zero.

[§]Only 34/40 patients had baseline radiographic SIJ assessment.

AS: Ankylosing spondylitis; ASAS: Assessment of Spondyloarthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CBP: Chronic back pain; IBP: Inflammatory back pain; mNY: modified New York; nr-axSpA: Non-radiographic axial spondyloarthritis; NSAIDs: Non-steroidal anti-inflammatory drugs; PR: Partial remission; SIJ: Sacroiliac joints; SpA: Spondyloarthritis; SPARCC: Spondyloarthritis Research Consortium of Canada; VAS: Visual analogue scale.

inflammation and improved quality of life compared with placebo, leading to the first European Medicines Agency TNF-blocker approval for the treatment of adults with severe axial SpA who do not have radiographic evidence of structural damage. This represents a significant step forward in the disease management of patients with axial SpA. Overall, these four studies provide evidence that patients with nr-axSpA also benefit from TNF-blocker treatment, and that this benefit may be at least as great as in patients with AS [90–93].

Prediction of response to TNF-blockers

Several studies have tried to identify predictors of response to TNF-blockers. Predictors of response to therapy may enable improved patient selection, outcomes and resource utilization. The populations and study design used in these studies have been heterogeneous (placebo-controlled randomized trials, open-label extension studies and registers) and the studied response criteria have been variable (ASAS, BASDAI and ASDAS response criteria). Consistent predicting variables of better response to therapy have included younger age [90,93–95], the closely related and overlapping factor shorter disease duration [95,96], increased baseline CRP [77,90,94–96], a good response to treatment in the first 3–6 months [97], and less consistently HLA-B27 positivity, better baseline functional status, absence of enthesitis and the presence of MRI axial inflammation at baseline [77,90,94–96].

Recently, in a study using data from 635 AS patients that participated in two TNF-blocker-trials, a matrix model that provides a potential basis for patient selection for this type of therapy was proposed [77]. Several response criteria were evaluated in this study and, for example, patients with enthesitis, age over 40 years, HLA-B27 negative and with high disability levels, had a 3% probability of achieving ASDAS inactive disease. In comparison, in younger patients (≤40 years) without enthesitis, HLA-B27 positive and with better functional status, this probability increased to 53%. Since the predictive value of single parameters is not strong enough to predict treatment response in the individual patient, such models are potentially useful in supporting treatment decisions with TNF-blockers in daily clinical practice.

Structural damage & TNF-blockers

Structural damage in axial SpA is characterized by excessive bone formation, with syndesmophytes as the typical lesion. Radiographs are still considered the gold-standard for assessment of syndesmophytes in axial SpA [98]. Axial SpA may lead to syndesmophyte formation and spinal fusion in a substantial proportion of patients. These processes can lead to impaired spinal mobility, which in turn decreases the patient's ability to perform daily activities and may severely impair quality of life [99,100]. Therefore, preventing progression of structural damage of the spine is an important goal in the treatment of axial SpA.

The processes underlying new bone formation are insufficiently understood. Bone proliferation may reflect a pathologically enhanced repair response of bone [98,101], and a causal relationship between MRI inflammation and syndesmophyte formation is hypothesized. However, despite the strong anti-inflammatory effect of TNF blockers, including at the MRI level [102,103], these agents do not influence new bone formation [104–106].

Three studies have shown that MRI inflammation in a vertebral corner/unit (VC/VU) slightly increases the likelihood of finding a new syndesmophyte in the same VC/VU 2 years later [107–109]. However, the majority of syndesmophytes developed in VC/VUs without any sign of inflammation on MRI, suggesting that the relationship between MRI inflammation and syndesmophyte formation is not straightforward. Recently it was also postulated that syndesmophytes are more likely to develop at those corners in which inflammation resolves than at those where inflammation persists [108,110]. As syndesmophytes grow slowly, longer study periods would help to clarify the magnitude of the effect of inflammation in predicting new bone formation.

The subtle association between MRI activity and new syndesmophytes is in conflict with the absence of an effect of TNF-blockers on structural damage [104–106]. It has been proposed that osteoproliferation can be explained by the intermittent nature of the inflammation in axial SpA. In an early disease phase, mechanical or other triggers might cause tissue inflammation, and TNF would simultaneously drive destruction and inhibit remodeling by the Wnt pathway by upregulating DKK-1. On downregulation of TNF in a later phase, the brake on Wnt-mediated remodeling would be released and the early erosions would trigger reactive osteoproliferation [101,111]. In such a scenario, early treatment initiation (before repair processes are switched on) may prevent the anabolic response that leads to syndesmophyte formation. It is hypothesized that focal fat lesions at vertebral corners on MRI represent a postinflammatory phase between osteitis on MRI, and sclerotic bone formation on radiographs [112]. However, other authors have suggested that the same initiating triggers might also directly activate stromal cells and induce an inflammation-independent pathway of endochondral bone formation, in which bone morphogenic proteins are thought to play a key role [113].

If inflammation is indeed the principal trigger of repair responses, a strong case can be made for early and aggressive anti-inflammatory treatment. Conversely, if inflammation and repair are independent pathways triggered by common factors, specific therapies targeting stromal pathways may be needed to prevent new bone formation in axial SpA.

Table 3. Clinical trials of TNF-blockers in non-radiographic axial spondyloarthritis (cont.).

	Haibel *et al.* [90]	Barkham *et al.* [91]	Song *et al.* [92]	Sieper *et al.* [93]
Clinical response, active group vs placebo	Week 12: ASAS 20: 68 vs 25% (p = 0.007); ASAS 40: 55 vs 13% (p = 0.004); ASAS PR: 23 vs 0% (p = 0.019)	Week 16: ASAS 20: not reported; ASAS 40: 61 vs 18% (p = 0.009); ASAS PR: 56 vs 13% (p = 0.009)	Week 16: ASAS 20: 85 vs 42% (p = 0.001); ASAS 40: 70 vs 31% (p = 0.001); ASAS PR: 50 vs 19% (p = 0.006)	Week 12: ASAS 20: 52 vs 31% (p = 0.004); ASAS 40: 36 vs 15% (p < 0.001); ASAS PR: 16 vs 5% (p = 0.01)
MRI inflammation response, active group vs placebo	Not formally assessed using an MRI activity scoring system. Baseline MRI activity not associated with clinical response	Week 16 (median change, Leeds MRI scoring system) [138]: SIJ: -2.0 vs 0 (p = 0.033)	Week 48 (mean change, modified Berlin scoring system)[47]: SIJ: -5.4 vs -1.9 (p = 0.02) Spine: -1.3 vs -0.1 (p = 0.03)	Week 12 (mean change, SPARCC MRI scoring system) [139,140]: SIJ: -3.2 vs -0.6 (p = 0.003); Spine: -1.8 vs -0.2 (p = 0.001)

†Retrospectively, all patients fulfilled the ASAS classification criteria for axial SpA.

‡When blinded paired scoring of the scans was performed after the study, three patients (all in the placebo group) had a baseline MRI Leeds score of zero.

§Only 34/40 patients had baseline radiographic SIJ assessment.

AS: Ankylosing spondylitis; ASAS: Assessment of Spondyloarthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CBP: Chronic back pain; IBP: Inflammatory back pain; mNY: modified New York; nr-axSpA: Non-radiographic axial spondyloarthritis; NSAIDs: Non-steroidal anti-inflammatory drugs; PR: Partial remission; SIJ: Sacroiliac joints; SpA: Spondyloarthritis; SPARCC: Spondyloarthritis Research Consortium of Canada; VAS: Visual analogue scale.

■ NSAIDs, acute phase reactants, smoking & radiographic progression

Until very recently only two studies existed that suggest the potential benefit of NSAIDs in preventing radiographic progression. The first study dates from 1976 and suggested that phenylbutazone (an NSAID that is not used anymore) could retard spinal bone formation in patients with AS [114]. However, this was a very small (40 patients) retrospective study with many limitations and potential biases. The second study was a 2-year randomized clinical trial, published in 2005, comparing the strategies of long-term continuous and on-demand use of NSAIDs, with respect to their influence on radiographic progression [115]. Interestingly, this study demonstrated that a strategy of continuous treatment reduces radiographic progression (mean radiographic progression was 0.4 ± 1.7 modified Stoke AS Spinal Score [mSASSS]) points in the continuous treatment group and 1.5 ± 2.5 in the on-demand group; p = 0.002), despite a similar effect of both strategies on signs and symptoms (pain, inflammation, spinal mobility). This observation provided a strong indication that NSAIDs may retard structural damage in AS patients but confirmation of these results was required [115]. A third study was recently published in abstract format, comparing 20 patients with AS on anti-TNF therapy who continued their NSAIDs with 20 patients with AS on biological therapy in whom NSAIDs had been discontinued [116]. After 2 years, there was a trend towards more radiographic progression in the anti-TNF only group (3.05 ± 6.2 vs 0.2 ± 3.4 mSASSS units;p = 0.08). However this was a very small non-randomized study requiring further validation.

Recently, two studies provided important insights into the potential disease-modifying effect of NSAIDs. The first study came from the German SpA Inception Cohort and demonstrated that patients with a high NSAID intake (NSAID index ≥ 50) over 2 years (calculated using the ASAS recommendations for collecting, analyzing and reporting NSAID intake in clinical trials/epidemiological studies [117], index range 0–100, 0 representing no NSAID intake at all, and 100 representing a daily NSAID intake in a dose equivalent to diclofenac 150 mg, over the period of interest) had less new bone formation in the spine (odds ratio: 0.15; 95% CI: 0.02–0.96; p = 0.045), for the outcome mSASSS change ≥ 2 units over 2 years) than patients with low NSAID intake (NSAID index <50) over this period [118]. Interestingly, this protective effect was nearly exclusively seen in patients with elevated CRP levels over time and with baseline syndesmophytes, the strongest risk factors for the growth of new syndesmophytes. However, in the nr-axSpA subgroup this effect could not be shown [118].

The second study was a *post hoc* analysis of the above mentioned 2005 NSAID trial [119], and provided evidence that the progression-inhibitory effects of continuous use of NSAIDs, in comparison with NSAID use on-demand, is more pronounced in patients with elevated CRP, erythrocyte sedimentation rate (ESR), ASDAS-CRP or ASDAS-ESR values over time. This effect was entirely dependent on acute phase reactants as a reflection

of inflammation, since it was not seen with BASDAI, a fully patient-oriented disease activity measure.

In conclusion, patients with elevated acute phase reactants seem to benefit most from treatment with NSAIDs an observation that may lead to an improved benefit-to-risk ratio of these drugs. However, other factors have to be taken into account when prescribing NSAIDs to patients with axial SpA, and the final decision to treat or not with NSAIDs and which treatment regimen to use should be an individualized decision, based on the symptomatic state of the patient and the required dose to achieve disease activity control, the patient-safety profile (e.g., age, concomitant medication and cardiovascular, gastrointestinal and renal co-morbidities) and the risk of structural damage progression.

At present, the most robust predictor of spinal structural progression is the presence of syndesmophytes at baseline [31]. The most important factors influencing radiological progression in axial SpA are still to be identified and several less consistent independent associations have been reported: smoking [120], high serum levels of CRP [120], ESR [119,120] and MMP3 [121] and low serum levels of sclerostin [122] have been identified as independent predictors of radiographic progression, while high functional levels of dickkopf-1 may protect against syndesmophyte formation [123]. In a recent report, the strongest predictor of progression of radiographic sacroiliitis was an elevated baseline serum CRP level (odds ratio = 3.65; 95% CI: 1.19–11.15) for nr-axSpA and 5.08 (95% CI: 1.02–25.38) for AS, indicating an important role of inflammation for progression of radiographic damage in the sacroiliac joints [26].

However, as discussed above, TNF-blockers, which have very good efficacy on clinical disease activity, acute-phase reactants and inflammation visible on MRI, do not reduce the rate of osteoproliferation [104–106]. This is an intriguing finding and suggests that there are inflammation-independent mechanisms driving new bone formation that are sensitive to the effects of NSAIDs, the inhibitory effect on bone metabolism of which seems related to the inhibition of the bone anabolic response driven by prostaglandins [124,125]. These findings raise the question whether NSAIDs, which not only act on inflammation but also suppress bone formation by interfering with osteoblast differentiation, should be combined with TNF-blockers, which are potent inhibitors of axial inflammation, in order to inhibit the process of syndesmophyte formation, especially if this treatment strategy is used early in the disease process. Studies addressing these questions in more detail are currently underway.

The recent identification of smoking as an independent risk factor for structural progression is a finding that also deserves to be highlighted [120]. In a recent study, smoking was found to have an effect on damage progression (odds ratio: 2.41; 95% CI: 1.01–5.76) for worsening of the mSASSS by ≥2 units over 2 years. The other two factors identified as independent predictors of radiographic progression in this study were elevated levels of acute phase reactants (CRP and ESR) and the presence of syndesmophytes at baseline. For example, in non-smoking patients without baseline syndesmophytes and a normal baseline CRP level, the risk of radiographic spinal progression was only 4%, while in smoking patients with baseline syndesmophytes and an elevated baseline CRP level, the risk of progression increased to 55% [120]. Interestingly, in a recent large cross-sectional study, a clear adverse effect of smoking was also reported in 647 patients with early IBP and suspected axial SpA [126]. In this study, smoking was independently associated with earlier onset of IBP, higher disease activity, increased axial inflammation and structural damage on MRI, increased structural damage on spinal radiographs (mSASSS), worse functional status and worse quality of life. Taking into account that smoking is a potentially modifiable lifestyle factor, axial SpA patients who smoke should be informed by the rheumatologist about these facts and should be strongly advised to quit this habit, as there seem to be disease-specific benefits that go beyond those described for the general population. The benefits of quitting smoking begin as soon as an individual stops, and there are evaluated programs to help give up smoking [127].

Other therapies

The success of other therapies in axial SpA has been limited. Most studies have been performed in patients with advanced disease or patients who have not responded to TNF-blockers.

Rituximab, a monoclonal antibody to CD20 (targeting B cells) has been tried in a pilot 24-week open-label trial enrolling 20 patients with active AS (ten patients naive to TNF-blockers and ten patients with an inadequate response to TNF-blockers) [128]. The response seen in the subgroup of patients naive to TNF-blockers came close to classical response rates in an AS TNF-blockers drug trials, with ASAS 20, ASAS 40, ASAS partial remission and BASDAI50 responses reached by 50, 40, 30 and 50% of the patients, respectively. Recently, a 1-year follow-up report of this study was published [129]. Patients regarded as responders (defined as an ASAS 20 response on at least two consecutive visits out of a total of four visits: weeks 12, 16, 20 and 24) were offered to be followed up and to receive a second course of rituximab in case of flare. Nine patients were considered responders (six naive to TNF-blockers and three TNF-blocker failures). Interestingly, all nine patients (45% of the initially treated patients) demonstrated a good clinical response at the end of the first year, with five flared patients (56%)

having received a second course of rituximab. Based on these results, a larger controlled study evaluating the role of a B cell directed therapy in active axial SpA may be justified.

Abatacept, an inhibitor of T-cell co-stimulation, was tested in a pilot 24-week open-label trial enrolling 30 patients with active AS (15 patients naive to TNF-blockers and 15 patients with an inadequate response to TNF-blockers) [130]. This study failed to show a relevant response to abatacept, a finding supported by a recent small study in seven axial SpA patients refractory to TNF-blockers [131].

Two randomized, double-blind, placebo-controlled trials investigating the effect of monoclonal antibodies against the IL-6 receptor (tocilizumab and sarilumab) in patients with AS were recently presented and published in abstract format [132,133]. In the tocilizumab trial, 102 NSAID inadequate responders and anti-TNF naive patients were randomized into two groups (51 patients in each treatment arm) [132]. In the sarilumab trial, 301 NSAID-inadequate responders or intolerant patients were randomized into six groups (one placebo group and five different treatment regimen groups) [133]. In both studies, the primary end point (ASAS 20 response) was not met, which means that these targeted treatments do not seem to play a role in the treatment of AS.

Secukinumab, a human monoclonal antibody to IL-17A, was recently investigated in a small Phase II clinical trial in AS. This IL-17A inhibitor looked promising with an ASAS 20 response at week 6 achieved in 61% (14 out of 23) of the AS patients receiving secukinumab as compared with 17% of the patients receiving placebo (1 out of 6) [134]. These data suggest that secukinumab may be useful for the treatment of active AS and thereby warrants larger long-term safety and efficacy studies; these studies are ongoing [207,208].

Ustekinumab, a human monoclonal antibody that binds with high affinity to the shared p40 subunit of human IL-12 and IL-23, showed promising results in psoriatic arthritis [135] and is currently being investigated in a 28-week, prospective, open-label, proof-of-concept study in patients with active AS [209].

Finally, apremilast, a novel, orally available small molecule that specifically inhibits phosphodiesterase-4, an intracellular enzyme that modulates the expression of a network of pro- and anti-inflammatory mediators, was recently investigated in a small pilot study (19 patients on placebo, 17 on apremilast) [136]. A trend towards improvement was observed in active AS patients treated with apremilast and this drug is currently being evaluated in a larger randomized, double-blind, placebo-controlled clinical trial [210].

Future perspective

While a lot of knowledge has been obtained regarding the clinical and biological efficacy of TNF-blockers in axial SpA, there is still an important gap: 'can these agents somehow inhibit osteoproliferation if started very early in the course of the disease or in combination with other drugs, particularly NSAIDs?' Studies addressing this question are ongoing or in a planning phase. Surprisingly, little data are available about the use of DMARDs in axial SpA and additional systematic studies of these agents are also needed.

It is yet to be determined if the BASDAI cut-off ≥4 is an appropriate cut-off to recommend initiation of therapy with TNF-blockers, and if objective evidence of active disease, either increased CRP or evidence or inflammation on MRI, should be used to select patients for therapy with TNF-blockers. In this regard, ASDAS, the new disease activity index for patients with axial SpA, has the advantage of providing combined information on objective and subjective measures and it has been shown to better reflect the spinal inflammatory disease process in axial SpA than BASDAI.

Future MRI research in axial SpA should focus on differential diagnostics and prognostic significance of MRI lesions in large and diverse cohorts of patients (particularly in early/non-radiographic axial SpA), on the assessment of whether adding MRI to routine care improves clinical and radiographic outcomes in patients with axial SpA, and on the clarification of prognostic significance of MRI lesions, with regards to radiographic progression and long-term outcomes.

The recognition of key mediators of molecular regulation of bone formation and resorption in axial SpA (e.g., DKK-1, bone morphogenic proteins, sclerostin and Wnt proteins) may lead to the discovery of inhibitors of new bone formation. In principle, specific drug therapies selectively targeting the anabolic pathways involved in new bone formation seem promising from a theoretical point of view. However, targets allowing dissecting physiological bone formation from new bone formation remain to be identified.

Finding alternative therapies for patients with axial SpA who do not respond (or lose their clinical response), do not tolerate or have contra-indication to treatment with NSAIDs and TNF-blockers, is still important. Targeting of the IL-12/23/17 immune pathways seems a promising approach.

Axial SpA is an exciting research field that is continually making rapid advances. The increasing interest of the scientific community and the new discoveries introduced at a rapid pace allow us to be optimistic regarding future improved treatment, and better treatment outcomes for patients with axial SpA.

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Executive summary

- Spondyloarthritis (SpA) is an umbrella term for a group of diseases sharing genetic, molecular, immunological, clinical and imaging features.
- The Assessment of Spondyloarthritis international Society (ASAS) group has developed new classification criteria for axial SpA (characterized by predominant involvement of the spine and/or sacroiliac joints) and peripheral SpA (characterized predominantly by peripheral arthritis, enthesitis, and/or dactylitis).
- MRI can detect axial inflammation and has become an important tool in the diagnosis, management, monitoring and prognosis of patients with axial SpA.
- Definitions of a 'positive' MRI for spinal and sacroiliac joint inflammation have been developed by the ASAS/Outcome Measures in Rheumatology MRI study group.
- The 2010 ASAS/The European League Against Rheumatism recommendations for the management of ankylosing spondylitis and the 2010 update of the ASAS recommendations to treat patients with TNF-blockers have recently been published.
- Clinical trials in patients with non-radiographic axial SpA (nr-axSpA) are an unmet medical need of which the new criteria for axial SpA allow investigation.
- The first randomized placebo-controlled clinical trial with a TNF-blocker prospectively recruiting patients with nr-axSpA according to the ASAS criteria has just been published, leading to the first TNF-blocker approval for the treatment of patients with nr-axSpA.
- It is hypothesized that rapid control of inflammation with TNF-blockers in the early phase of disease could prevent structural damage. However, other authors have suggested that the triggering of new bone formation may be completely or partially independent of inflammation.
- Non-steroidal anti-inflammatory drugs (NSAIDs) may have a disease-modifying effect in ankylosing spondylitis. Patients with elevated acute phase reactants seem to benefit most from treatment with NSAIDs, an observation that may lead to an improved benefit-to-risk ratio of these drugs.
- Studies assessing the structural effect of combining TNF-blockers and NSAIDs, especially in early disease phases, are warranted.
- Smoking is a new independent risk factor for structural progression in axial SpA.
- Important advances have been made in clarifying the natural history and pathophysiological mechanisms of axial SpA, which may lead to the discovery of new therapies and innovative treatment strategies in the future.

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