Axial spondyloarthritis

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Axial spondyloarthritis manifests as a chronic inflammatory disease primarily affecting the sacroiliac joints and spine. Although chronic back pain and spinal stiffness are typical initial symptoms, peripheral (ie, enthesitis, arthritis, and dactylitis) and extra-musculoskeletal (ie, uveitis, inflammatory bowel disease, and psoriasis) manifestations are also common. Timely and accurate diagnosis is challenging and relies on identifying a clinical pattern with a combination of clinical, laboratory (HLA-B27 positivity), and imaging findings (eg, structural damage on pelvic radiographs and bone marrow oedema on MRI of the sacroiliac joints). The Assessment in SpondyloArthritis international Society classification criteria for axial spondyloarthritis are widely used for research and have contributed to a better understanding of the gestalt of axial spondyloarthritis. Persistent disease activity, assessed mainly by the Axial Spondyloarthritis Disease Activity Score, leads to irreversible structural damage and functional impairment. Management involves non-pharmacological (eg, education, smoking cessation, exercise, physiotherapy) and pharmacological therapy. Non-steroidal anti-inflammatory drugs remain first line pharmacotherapy, while tumour necrosis factor, IL-17, and Janus kinase inhibitors are considered second-line therapies. Future advances are expected to increase disease awareness, facilitate early and accurate diagnosis, optimise disease management, and enhance overall quality of life in patients with axial spondyloarthritis.

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Introduction

Axial spondyloarthritis is a chronic rheumatological disease that primarily affects the sacroiliac joints and the spine, but often also involves the peripheral skeleton and other organs.[1,2] Axial spondyloarthritis places a considerable burden on patients and their families, and health-care systems. Disease onset occurs typically within a period characterised by considerable activity in occupational, social, and economic spheres.[3] Research indicates that two thirds of actively employed individuals with axial spondyloarthritis encounter work-related issues, leading to considerable societal costs.[4,5]

Definite structural damage on pelvic radiographs (ie, radiographic sacroiliitis) is the main feature of the modified New York classification criteria (mNY),[6] which has been used for decades to describe the disease historically referred to as ankylosing spondylitis. The term ankylosing spondylitis describes the process of bone fusion and subsequent typical forward-bending spinal deformity (ankylosis) driven by pathological new bone formation (ie, structural damage), which is often a late finding. Therefore, the ankylosing spondylitis-phenotype is a result of considerable diagnosis delay and adverse outcomes.

The discovery that inflammation of the sacroiliac joints can be detected by MRI and represents an early stage of the disease was a major step forward in the early recognition of the disease,[7] and led to the development of the Assessment in SpondyloArthritis international Society (ASAS) classification criteria for axial spondyloarthritis.[8] These criteria capture both patients with (radiographic axial spondyloarthritis) and without (non-radiographic axial spondyloarthritis) definite radiographic damage in the sacroiliac joints. Several studies have shown that patients with radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis have similar clinical presentation and disease burden, which supports the idea that both are part of the same disease spectrum.[9] Recent data have also shown that almost all patients fulfilling the ASAS criteria based on damage on pelvic radiographs (radiographic axial spondyloarthritis) also fulfil the mNY classification criteria (ankylosing spondylitis).[10]

Based on this evidence, the ASAS has recently published a consensus statement about the nomenclature of the disease.[11] It was agreed that the terms radiographic axial spondyloarthritis and ankylosing spondylitis are equivalent and can therefore be used interchangeably, but with preference for radiographic axial spondyloarthritis. In addition, there was agreement that the distinction between radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis is only relevant for research and that axial spondyloarthritis is the overall term of the disease.

Epidemiology

Axial spondyloarthritis typically emerges during the third decade of life. There is male predominance in

Search strategy and selection criteria

Data for this Seminar were identified by searches of MEDLINE, PubMed, and the references from relevant articles using the search terms "axial spondyloarthritis" or "ankylosing spondylitis", and "pathogenesis" or "diagnosis" or "classification" or "treatment" or "management" or "burden". Any type of article (eg, observational studies, randomised controlled trials, and reviews) published in English until April 2024 was included. We largely selected publications from the past 3 years considering the relevance for clinical practice and international scope of the studies but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by the search strategy and selected those we judged as relevant.

radiographic axial spondyloarthritis (male to female ratio ~2–3:1), and an equal sex distribution among patients with non-radiographic axial spondyloarthritis. The proportion of patients with non-radiographic axial spondyloarthritis is increasing as a consequence of earlier recognition, largely driven by the more frequent use of MRI.[12] Estimates of the prevalence of axial spondyloarthritis vary between 0·3% and 1·4% and are highly influenced by the background prevalence of HLA-B27, its major genetic marker.[13]

Populations with high background prevalence of HLA-B27 have higher rates of axial spondyloarthritis. In contrast, axial spondyloarthritis was uncommon in geographical regions where HLA-B27 prevalence is low. Most studies report an incidence rate of approximately 7 cases per 100 000 persons per year. However, most incidence data come from the USA and northern European countries and might not necessarily represent other parts of the world. There is a need for population studies across different regions and ethnicities of the world to analyse the prevalence of HLA-B27 positivity.

Pathogenesis

Axial spondyloarthritis occurs in individuals with a genetic susceptibility (hereditability greater than 90%). However, most of the genetic predisposition remains unidentified. Only 20% of the genetic predisposition of axial spondyloarthritis is attributable to MHC genes.[13] Two important non-MHC genetic loci associated with an increased risk of axial spondyloarthritis are the endoplasmic reticulum aminopeptidase-1 (ERAP-1) and the interleukin-23 (IL-23) receptor.[14,15] Recently, the cluster of differentiation 74 (CD74), which is involved in the assembly of MHC class II molecules and preventing premature binding of these molecules to peptides, is suggested to be involved in the pathogenesis of axial spondyloarthritis.[16]

Synovial membrane pathology is mainly a secondary process in axial spondyloarthritis and is influenced by signals from the entheses and from the subchondral bone.[17] Entheses are load-bearing structures (ie, tendon, ligament, joint capsule, or fascia) responsible for transmitting mechanical forces from muscles to bones. Blood vessels connect peri-entheseal bone marrow to the enthesis and an interplay between these two structures has been suggested in the pathogenesis of axial spondyloarthritis.[18] In people with genetic-predisposition, local immune cells might be more susceptible to activation by mechanical and microbial triggers (figure 1).[17] In fact, mechanical (over)load has been linked with the onset and progression of axial spondyloarthritis.[19–21] In addition, damage to the skin by psoriasis and intestinal barriers by gut inflammation facilitate the exposure to pathogens. One typical example is (spondylo)arthritis reactive to infections. However, it is important to recognise that exposure to pathogens does not always result in clinically apparent infections but can still trigger an aberrant (ie, chronic) immune response.[22]

The sequence of events remains unclear, but entheseal or bone inflammation, bone destruction, and new bone formation are thought to be key processes in the pathophysiology of axial spondyloarthritis. Subchondral bone marrow oedema visible on MRI is present in biopsy specimens early in the disease course and reflects active inflammation.[23,24] Bone marrow oedema is then replaced by a granulation tissue containing adipocytes.[25] On MRI, fatty lesions are believed to represent this repair tissue, which can either erode the subchondral bone plate or form new bone.[25,26] Bone destruction driven by the contact between osteoblasts and osteoclasts prevails with continued inflammation, while bone formation occurs when inflammation subsides and in the absence of osteoclasts.[27] In axial spondyloarthritis, inflammation is thought to fluctuate, which allows repair and an anabolic response driven by bone morphogenic proteins and Wnt proteins.[17] Several studies show that inflammation leads to subsequent new bone development.[27–35] However, whether fatty lesions mediate this effect remains unclear. Vertebral corners with bone marrow oedema, followed by fatty lesions, have a higher risk of new syndesmophytes

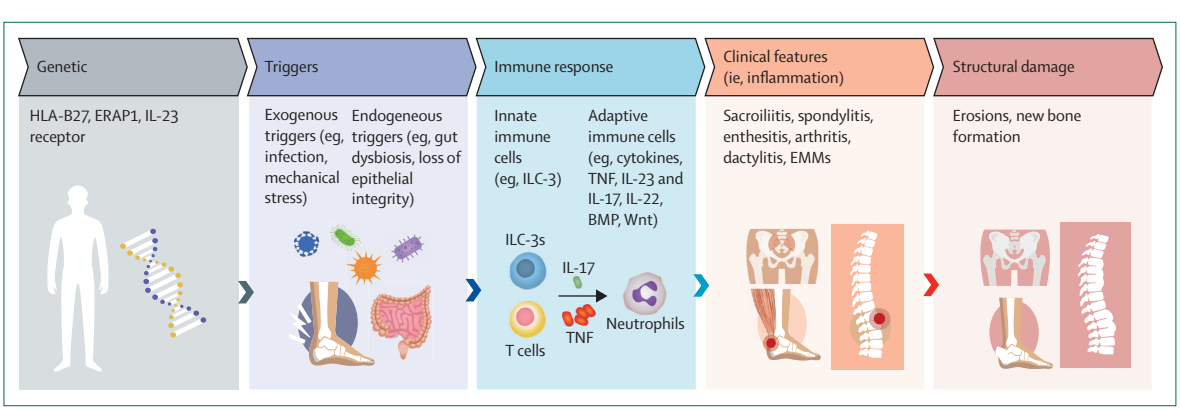

Figure 1: **Pathogenesis of axial spondyloarthritis**
ERAP1=endoplasmic reticulum aminopeptidase-1. IL-23=interleukin-23. TNF=tumour necrosis factor. BMP=bone morphogenic protein. EMM=extra-musculoskeletal manifestation.

than vertebral corners with either lesion separately.[30] However, the complete sequence of lesions is infrequent and recent analyses did not show that fatty lesions are necessary for the transition between bone marrow oedema and new bone formation in radiographic axial spondyloarthritis.[36] Moreover, most new syndesmophytes develop in sites without preceding bone marrow oedema or fatty lesions.

Tumour necrosis factor (TNF) and IL-23 or IL-17 are major proinflammatory cytokine pathways in axial spondyloarthritis,[17] and their central role in pathogenesis is supported by the efficacy of TNF-inhibitors and IL-17-inhibitors in controlling symptoms of the disease.[37] Both TNF and IL-17 induce a down-regulation of osteoblast function when osteoblasts and osteoclasts interact. In the absence of osteoclasts (eg, in axial spondyloarthritis), these cytokines lead to bone formation,[38] suggesting that their inhibition can interfere with disease progression. Recently, Janus kinase (JAK; a family of molecules involved in communicating signals from outside the cell to the nucleus) inhibitors have also proved effective in axial spondyloarthritis, but not IL-23-inhibitors.[39,40] IL-17 is primarily produced by T helper 17 (TH17) cells in response to IL-23 secretion. The inefficacy to IL-23i in axial spondyloarthritis suggests, however, an uncoupling between the two cytokines. In fact, IL-17 secretion might occur independently of IL-23 in type 3 innate lymphoid cells.[40]

Diagnosis

Diagnosing axial spondyloarthritis involves recognising the clinical pattern (ie, the gestalt) of the disease, considering the presence and absence of features, and exploring alternative diagnoses. Early diagnosis allows early treatment aimed at reducing the disease burden and improving long-term prognosis.[41,42] Recent data have shown that approximately one third of patients with chronic back pain (≥3 months) of unknown origin and with 2 years or less duration can confidently be diagnosed as axial spondyloarthritis by rheumatologists.[43] However, discerning the spondyloarthritis pattern from (more common) similarly presenting conditions (eg, degenerative spine disease, diffuse idiopathic skeletal hyperostosis, or chronic widespread pain syndromes) can sometimes be challenging.[44] No gold-standard diagnostic test exists, but diagnostic algorithms can provide guidance.[45]

Diagnostic algorithms can be applied to a patient with a suspicion of axial spondyloarthritis to calculate the disease probability considering all features that are present and those that are absent. Each feature's ability to discriminate between axial spondyloarthritis and no axial spondyloarthritis can be expressed as a positive (LR+) and a negative (LR–) likelihood ratio, but the knowledge of the pretest probability is essential for their application. A recent meta-analysis provides an update on the diagnostic performance of each spondyloarthritis feature.[46] The higher the feature's LR+, the more likely a diagnosis of axial spondyloarthritis if that feature is present. However, the lower the feature's LR–, the less likely is the diagnosis of axial spondyloarthritis if the feature is absent. The LR+ of present features and the LR– of absent features can be multiplied to provide the overall probability of axial spondyloarthritis.[47] These calculations can be translated into a diagnostic algorithm, which assumes the patient comes from a population with a 5% prevalence of axial spondyloarthritis (ie, patients with chronic back pain in general practice).[48] Spondyloarthritis features are recognised by history-taking, physical examination, and laboratory and imaging tests.

Clinical features

Chronic back pain, frequently accompanied by morning stiffness, is the most common manifestation of axial spondyloarthritis, and is typically the first symptom of the disease. Pain and stiffness usually involve the lower spine and buttocks and have an insidious onset and inflammatory characteristics, relieved with activity or non-steroidal anti-inflammatory drugs (NSAIDs) and worsened by rest.[49] Around 70% of patients have inflammatory back pain and diseases other than axial spondyloarthritis might present with this feature. Recent data suggest that inflammatory back pain has an LR+ of 1·7 (ie, lower than initially thought at around 3·0) and an LR– of 0·3.[46] These values suggest that inflammatory back pain is useful for referring patients with the suspicion of axial spondyloarthritis to the rheumatologist, but does not add much diagnostic utility thereafter. Physical examination at early stages of the disease might be anodyne in patients presenting only with axial manifestations, while in advanced stages, impaired spinal mobility is frequently observed.[50]

Peripheral features may manifest, with arthritis and enthesitis being the most common.[51] While a prevalence of peripheral manifestations of 30–40% were previously reported, a recent study revealed axial and peripheral manifestations coincide in a higher proportion of patients (66%) with axial spondyloarthritis.[52] Peripheral arthritis (ie, swollen and painful joints) is usually an asymmetrical mono or oligoarthritis involving predominantly the lower limbs. Peripheral enthesitis manifests with pain or tenderness and most commonly affects the insertion of the Achilles tendon and the plantar fascia. In addition, axial enthesitis (eg, at the insertion of the anterior longitudinal ligament) and synovitis of the axial joints can also occur, causing chest and back pain. Dactylitis (so-called sausage digit) is an infrequent feature, affecting less than 10% of patients.[51] Dactylitis manifests as swelling of a finger or toe due to a combination of synovitis, tenosynovitis, and enthesitis.

Extra-musculoskeletal manifestations—ie, uveitis, inflammatory bowel disease, and psoriasis—can also occur in axial spondyloarthritis. Uveitis is associated with

HLA-B27 positivity,[53] and is the most frequent extra-musculoskeletal manifestation, occurring in approximately one quarter of the patients,[51] typically presenting as unilateral acute anterior uveitis. Psoriasis (in 10% of patients) and inflammatory bowel disease (in 5–10% of patients), including ulcerative colitis and Crohn's disease, are less frequent.[51,54] In severe cases, patients might have constitutional symptoms. Involvement of the heart (eg, aortic valve insufficiency), lung (eg, restrictive lung disease), and kidney (eg, IgA nephropathy) can also occur.

Peripheral features and extra-musculoskeletal manifestations are specific for axial spondyloarthritis (LR+ range: 1·9–5·2), but are less common than axial complaints (all with an LR– close to 1·0),[46] meaning that these features are helpful to identify the disease when present, but their absence does not necessarily exclude an axial spondyloarthritis diagnosis. Clinicians should also keep in mind that in some patients, spondyloarthritis features that are absent at presentation could occur later.

Laboratory features

A few laboratory tests are available for the diagnosis of axial spondyloarthritis. HLA-B27 is positive in 70–90% of patients. Although considered a typical marker of the disease, it should be noted that a positive test for HLA-B27 has a diagnostic value lower than what was initially thought (LR+ 3·1 instead of 9·0),[46] but also depends on the referral strategy (eg, higher in those strategies including HLA-B27), geographical region (eg, lower value in Latin America where its prevalence is lower), and pre-test probability. Family history of axial spondyloarthritis is closely related with HLA-B27; as such, its diagnostic value is low when the HLA-B27 status is already known.[55] Recently, testing for IgG4 antibodies against CD74 together with HLA-B27 has been shown to yield a better diagnostic performance than HLA-B27 alone in a population with low background prevalence for HLA-B27.[56] However, the role of these antibodies in diagnosing axial spondyloarthritis is yet to be defined. Inflammation can be quantified by measuring the levels of the C reactive protein (CRP) or the erythrocyte sedimentation rate (ESR). However, up to 60% of patients with axial spondyloarthritis have normal acute phase reactants despite having symptoms.[57]

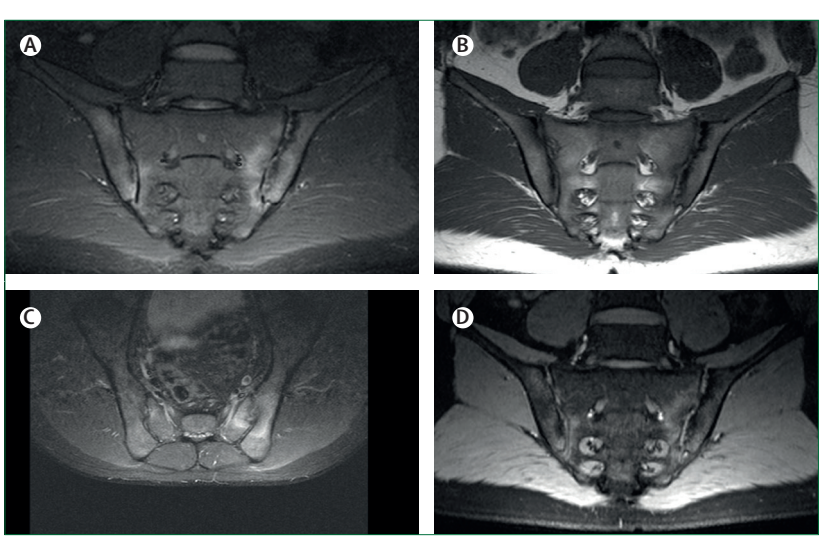

Figure 2: **Examples of images according to the ASAS-SPARTAN proposed image acquisition protocol**
(A) Semi-coronal orientation, STIR sequence. (B) Semi-coronal orientation, T1-weighted sequence. (C) Semi-axial orientation, STIR sequence. (D) Semi-coronal orientation, VIBE sequence.[60] ASAS=Assessment in SpondyloArthritis international Society. STIR=short tau inversion recovery. VIBE=volumetric interpolated breath-hold examination.

Imaging

Conventional radiography of the sacroiliac joints is typically the first imaging modality used to identify their involvement, mostly because of feasibility and accessibility. Typical findings include, sclerosis, erosions, and loss of joint space. The mNY grading system is used to quantify structural damage in the sacroiliac joints with definite structural changes (ie, radiographic sacroiliitis) defined as bilateral grade 2 or higher or unilateral grade 3 or higher.[6] However, aside from radiation exposure, this method has other major limitations. Damage in the sacroiliac joints only becomes visible in pelvic radiographs several years after the start of the symptoms.[58] Furthermore, the interpretation of radiographs of the sacroiliac joints can be particularly difficult, even for experienced readers.[59]

MRI of the sacroiliac joints is recommended if the diagnosis cannot be made based on clinical features and conventional radiographs, but clinical suspicion remains high. MRI should be performed according to the standardised MRI image acquisition protocol for diagnostic ascertainment of sacroiliitis; this should include at least four sequences with imaging in two planes and optimally visualised inflammation, structural damage, and the bone–cartilage interface: (1) semi-coronal oblique T1-weighted (ie, for fatty lesions, erosions, and ankylosis), (2) semi-coronal short tau inversion recovery (STIR) or another T2-weighted sequence with suppressed fat signal for bone marrow oedema, (3) semi-coronal cartilage (erosion sensitive) sequence (eg, 3D-gradient eco or volumetric interpolated breath-hold examination [VIBE]), and (4) a second T2-weighted semi-axial sequence with suppressed fat signal and also for bone marrow oedema (figure 2).[60] ASAS defines active sacroiliitis on MRI as the presence of bone marrow oedema in the subchondral bone that is highly suggestive of spondyloarthritis.[61] The presence of bone marrow oedema on MRI of the sacroiliac joints fulfilling the ASAS definition increases the likelihood of a diagnosis of axial spondyloarthritis, especially if structural changes are also present (eg, erosions, sclerosis, and fatty lesions). However, clinicians should bear in mind that bone marrow oedema can also occur in patients with non-specific back pain, patients with osteitis condensans, healthy individuals, post-partum

women, and recreational runners and athletes (although deep or extensive lesions are mostly found in patients with axial spondyloarthritis; figure 3).[7,62] Too much reliance on positive imaging, especially in the absence of other spondyloarthritis features, can easily lead to overdiagnosis and overtreatment.[48] Likewise, the absence of inflammation on MRI does not, per se, rule out axial spondyloarthritis.[63] A few studies recently evaluated the use of artificial intelligence (deep learning algorithms) to detect sacroiliitis on imaging exams.[64,65] These findings need validation but suggest artificial intelligence could help clinicians who are inexperienced in interpreting imaging to identify changes in the sacroiliac joints indicative of axial spondyloarthritis.

MRI of the spine alone has limited value for diagnosing axial spondyloarthritis.[66] Also, abnormalities on spine radiographs do not always occur and when they do, it is often too late in the disease course to be of use in early diagnosis. Other imaging modalities, such as scintigraphy, ultrasonography of the sacroiliac joints, and PET scans are not recommended for the diagnosis of axial spondyloarthritis.[67] A low-dose CT scan of the spine is more sensitive than conventional radiographs in detecting structural changes;[68] however, its role for the diagnosis of axial spondyloarthritis is yet to be defined. The ASAS has recently issued recommendations for requesting and reporting imaging examinations in patients with suspected axial spondyloarthritis, which can help clinicians when requesting and interpreting imaging tests.[69]

Structural lesions, such as joint surface erosion and ankylosis, are important factors for differential diagnosis. CT scanning is generally considered the standard to evaluate these lesions. Nonetheless, recent advances in MRI allow for direct bone imaging and the reconstruction of CT-like images that can provide similar information—so called bone-MRI—enhancing the ability of MRI to detect and measure structural lesions.[70]

Diagnostic delay

Despite the availability of tools for early diagnosis and the recommendation that the axial spondyloarthritis diagnosis should be made within 3 months since the onset of symptoms,[71] major diagnostic delay remains, which is larger in women (mean 8·8 years) than in men (6·5 years).[72] There are sex differences in disease presentation that might, at least in part, explain the larger gap in women (table). Male patients are more likely to be HLA-B27 positive, a feature associated with imaging abnormalities typical of radiographic axial spondyloarthritis and with a higher likelihood of acute anterior uveitis.[74] Female patients, on the other hand, are less likely to have imaging abnormalities and be positive for HLA-B27.[75] A lower prevalence of HLA-B27 is associated with peripheral features and extra-musculoskeletal manifestations (especially psoriasis) in axial spondyloarthritis.[76–78] These differences and physician bias might render the recognition of the spondyloarthritis-pattern in women more difficult. Moreover, excessive reliance on the detection of radiographic changes, a lack of awareness of the disease, and wrong referrals to other health-care providers other than rheumatologists[79] can lead to further delays in diagnosis in primary care. The ASAS-endorsed recommendations for early referral of patients with a suspicion of axial spondyloarthritis can help in such a setting.[80]

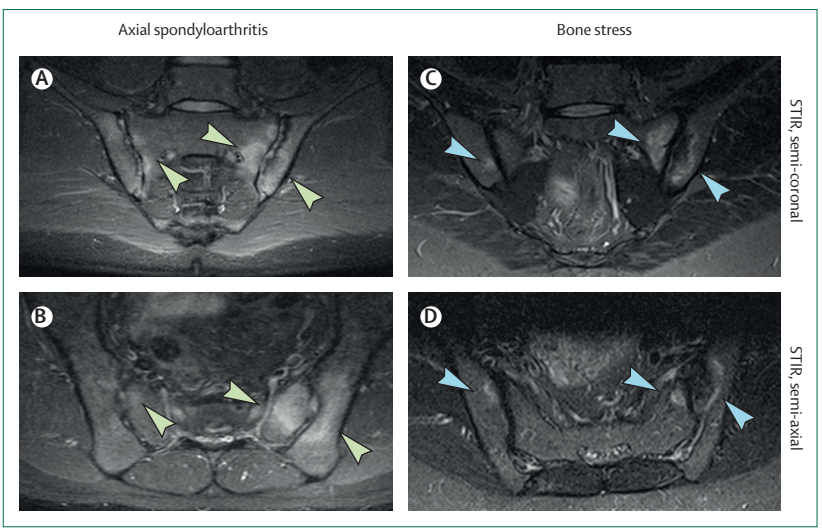

Figure 3: **Imaging findings of bone marrow oedema related to axial spondyloarthritis and bone stress**
MRI (ie, STIR sequences, in semi-coronal [A and C] and in semi-axial orientation [B and D]) of sacroiliac joints. (A, B) Typical for axial spondyloarthritis is the large extent and intensity of the bone marrow oedema (green arrows), here found bilateraly, both at the sacral and the iliac bone and in the middle part of the joint, where also the cartilage is located anatomically. (C, D) Typical for non-axial spondyloarthritis suggestive bone marrow oedema (ie, bone stress) is shown as the smaller extent and lower intensity signal (blue arrows), which is especially located in the upper or ventral part of the joint (here also at the sacral and iliac bones) where anatomically less or no cartilage is located. STIR=short tau inversion recovery.

	Female	Male
Demographic	Longer diagnostic delay	Younger age at diagnosis
Disease phenotype	More peripheral manifestations (ie, arthritis and enthesitis)	More pure axial disease
Genetic	Less associated with HLA-B27	Higher proportion are HLA-B27 positive
Clinical	Higher disease activity (ie, with ASDAS, BASDAI, and PGA); more functional impairment, fatigue, pain, and sleep disturbances	Higher level of C-reactive protein; higher levels of inflammatory cellular markers (ie, IL-23, IL-17A, etc)
Comorbidities	Higher frequency of concomitant diagnosis of depression and fibromyalgia	Higher frequency of cardiovascular risk factors (ie, hypertension, dyslipidaemia, renal impairment, and ischaemic heart disease)
Damage visible on radiograph	Less radiographic damage (ie, non-radiographic axial spondyloarthritis); lower radiographic progression	More radiographic damage (ie, radiographic axial spondyloarthritis); higher radiographic progression
Response to treatment	Lower	Higher

ASDAS=Axial Spondyloarthritis Disease Activity Score. BASDAI=Bath Ankylosing Spondylitis Disease Activity Index.

Table: **Demographic and disease characteristics of axial spondyloarthritis in female and male patients,[73] based on observational studies drawn from registries and cohorts**

Classification criteria

Classification should serve a completely different purpose than diagnosis and never substitute it. While diagnosis involves pattern recognition and clinical reasoning, classification criteria aim at recruiting a homogeneous population for studies, and therefore should be used in patients previously diagnosed with axial spondyloarthritis. Currently, the ASAS classification criteria for axial spondyloarthritis are used for most research studies.[8,81] The criteria are intended for patients experiencing chronic back pain with an onset before age 45 years. The criteria consist of two main entry groups: the imaging group (ie, the presence of sacroiliitis on radiographs or MRI) and the clinical group (ie, the presence of HLA-B27). To be classified as axial spondyloarthritis, patients should additionally have at least one or two, in case of the clinical group, typical characteristics of spondyloarthritis (often referred as spondyloarthritis features): inflammatory back pain, arthritis, enthesitis, dactylitis, acute anterior uveitis, psoriasis, inflammatory bowel disease, a good response to NSAIDs, family history of spondyloarthritis, HLA-B27 presence, or elevated CRP levels.

Research studies have shown that the ASAS criteria for axial spondyloarthritis perform well, with an overall sensitivity of 82% and specificity of 89%.[82] Since their development, the criteria have facilitated their inclusion in trials of patients covering the full spectrum of axial spondyloarthritis, leading to the approval of new drugs. However, concerns have been raised about both the development and misuse of these criteria, particularly regarding their tendency to over-diagnose the disease.[83] In this sense, it is emphasised that classification criteria should be applied to patients who have been previously diagnosed based on clinical reasoning. Moreover, some experts argue that all features are given the same importance despite their differing diagnostic value, which was mainly driven by implementation. Hence, the ASAS in collaboration with the Spondyloarthritis Research and Treatment Network decided to conduct a large prospective study—the ASAS Classification of Axial Spondyloarthritis Inception Cohort—aiming to validate the performance of the current ASAS classification criteria in a combined worldwide cohort. Further details and the current status of this study is available online.[84]

Monitoring

The assessment of axial spondyloarthritis is relevant for understanding the disease status and effect, while guiding appropriate treatment strategies. Since the disease affects deep anatomical structures, assessing it by physical examination is insufficient. Thus, most validated axial spondyloarthritis tools rely on laboratory testing, imaging, or patient-reported outcomes.[85] The choice of the tool depends on the disease domain to be examined and whether it is in a clinical practice or research setting.

Monitoring axial spondyloarthritis should consider all manifestations and focus on core domains identified by experts and patients as the most significant.[86] For clinical trials, the instruments to assess each core domain were recently updated in the ASAS-OMERACT (Outcome Measures in Rheumatology) core set for axial spondyloarthritis (figure 4).[87] Furthermore, the ASAS clinical response criteria (ie, ASAS20, ASAS40, ASAS5/6, and ASAS partial remission) are frequently used as outcomes.[88] While the instruments for the ASAS-OMERACT core set were specifically selected for trials, they also reflect what patients and rheumatologists prioritise, and can guide clinical practice. Nevertheless, in

Mandatory instruments for all trials

Domain	Disease activity	Pain	Morning stiffness	Fatigue	Physical function	Overall functioning and health
Instrument	ASDAS Patient global assessment of disease activity (NRS)	NRS total back pain (BASDAI Q2)	Severity and duration of stiffness (BASDAI [Q5+Q6]/2)	NRS fatigue (BASDAI Q1)	BASFI	ASAS-HI

Additional mandatory instruments for disease-modifying drugs trials

Domain	Disease activity	Extra-musculoskeletal manifestations	Peripheral manifestations	Structural damage
Instrument	SPARCC MRI activity of the sacroiliac joints* SPARCC MRI activity of the spine*	Acute anterior uveitis†‡ Psoriasis†§ Inflammatory bowel disease†¶	44 swollen joint count MASES Dactylitis count (including active fingers or toes)	mSASSS*

Figure 4: **Instruments for the ASAS core domain set for axial spondyloarthritis**
ASAS=Assessment of SpondyloArthritis international Society. ASAS-HI=ASAS Health Index. ASDAS=Axial Spondyloarthritis Disease Activity Score. BASDAI=Bath Ankylosing Spondylitis Disease Activity Index. BASFI=Bath Ankylosing Spondylitis Functional Index. MASES=Maastricht Ankylosing Spondylitis Enthesitis Score. mSASSS=modified Stoke Ankylosing Spondylitis Spinal Score.[87] NRS=numerical rate scale. Q=question from BASDAI. SPARCC=Spondyloarthritis Research Consortium of Canada. *Needs to be assessed at least once in a disease-modifying drug programme. †According to ASAS recommendations: diagnosis has never been made, was known at the preceding visit, or has been made since the last visit. ‡In case of diagnosis: the number of episodes since the last visit and corresponding treatment. §In case of diagnosis: percentage of skin area with psoriasis and treatment: yes or no. ¶In case of diagnosis: subtype and treatment: yes or no.

this setting, the absence of resources can make it challenging to regularly monitor the disease.[89] This issue can be addressed by using digital solutions (eg, ASAS app).

For assessing disease activity in clinical settings, composite indices are preferred,[85] with the recommended tool being the Axial Spondyloarthritis Disease Activity Score (ASDAS).[11] ASDAS involves four questions answered by the patient regarding axial pain, peripheral pain-inflammation, morning stiffness duration, and global disease activity, along with CRP value in mg per L (ie, using the value of 2 mg per L if less than the threshold or <2 mg per L), or alternatively, with ESR in mmHg (referred as ASDAS-ESR). With ASDAS, clinicians can classify disease activity as inactive (>=0·6 and <1·3), low (>=1·3 and <2·1), high (>=2·1 and <=3·5), and very high (>3·5).[90] Clinically important improvement is considered if there is a decrease of 1·1 units or higher, with a decrease of 2·0 or higher indicating major improvement. A disease flare is defined as an increase in ASDAS of 0·9 or higher.[91] Furthermore, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is also available.[92] Compared with BASDAI, the ASDAS has superior psychometric properties and is therefore preferred.[87] Additionally, when there is uncertainty regarding the source of complaints, MRI can help to establish whether inflammation is present, aiding decision making. Nevertheless, routine use of MRI to monitor is not advised as its additional value remains to be clarified.[67] For research studies, various scores have been developed to quantify inflammation in the sacroiliac joints and spine, frequently used to evaluate treatment response.[87]

It is typical for axial spondyloarthritis to affect physical function and spinal mobility. The Bath Ankylosing Spondylitis Functional Index, consisting of ten questions, is recommended to establish physical function, with scores ranging from 0 (good) to 10 (poor).[93] The Bath Ankylosing Spondylitis Metrology Index is usually used to assess mobility impairment, which covers several measurements of the axial skeleton.

To evaluate overall functioning and quality of life, the ASAS Health Index has been formulated. This index, freely available in most languages, includes 17 items addressing functional limitations in daily activities.[94] The smallest detectable change has been defined as 3 units. According to ASAS Health Index, overall health and functioning can be classified as good (≤5·0), moderate (>5–<12), and poor (≥12).[95]

The laboratory tests commonly used to monitor disease activity are CRP and ESR. However, both are elevated in only 40% of patients with axial spondyloarthritis and thus, by themselves, are only useful in a few cases.[57]

For assessing structural damage, conventional radiography of the sacroiliac joints and spine is used, but there is no consensus for monitoring this in clinical practice.[67] For research purposes, the modified Stoke Ankylosing Spondylitis Spinal Score on spinal radiographs is used, ranging from 0–72.[87] Initial findings of low-dose CT of the spine show a promising increase in sensitivity to change, but further studies need to corroborate these findings.[36]

Management

The primary goal to manage axial spondyloarthritis is to maximise health-related quality of life with the control of symptoms and inflammation, prevention of progressive structural damage, and preservation or normalisation of function and social participation.[96–98] As stated on the ASAS-EULAR (European Alliance of Associations for Rheumatology) management recommendations, it is crucial that decisions are made collaboratively between patients and rheumatologists, with a personalised approach considering patient characteristics and disease manifestations, and incorporating both non-pharmacological and pharmacological therapies. Non-pharmacological interventions are recommended throughout the course of the disease.[39] Patients should be educated about axial spondyloarthritis and self-management and encouraged to stop smoking and to exercise on a regular basis; in addition, considering physiotherapy is also recommended.

The pharmacological options for treating axial spondyloarthritis have considerably increased in the past few years (figure 5). First line treatment typically involves NSAIDs up to the maximum dose. Both traditional NSAIDs and selective inhibitors of cyclooxygenase-2 (COX-2) are effective.[39] However, considerations such as drug pharmacokinetics, coexisting conditions (ie, comorbidities), pregnancy, and potential adverse effects should be carefully considered. For patients who respond well to NSAIDs, continuous use is preferred if needed to control axial spondyloarthritis symptoms. If treatment response is inadequate, switching to a second NSAID is recommended, but whether switching between traditional NSAIDs and COX-2 inhibitors or transitioning to a second NSAID of the same class is more effective remains unclear.[99]

The second line of treatment for axial manifestations involves biological disease-modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs, which should be considered in case of persistently high disease activity (ASDAS score ≥2·1) despite use of two different NSAIDs over a total period of 4 weeks.[96] Additionally, patients should exhibit at least one of the following three characteristics: elevated CRP levels, inflammation on MRI of the sacroiliac joints, or radiographic sacroiliitis. Currently, two classes of biological DMARDs (ie, TNF and IL-17 inhibitors) and one class of targeted synthetic DMARDs (ie, JAK inhibitor) are available.[37,39] Examples of TNF inhibitors for axial spondyloarthritis include fusion proteins (ie, etanercept)[100,101] and monoclonal antibodies (ie, adalimumab,[102,103] certolizumab pegol,[104] golimumab,[105,106] and infliximab).[107] Among the IL-17 inhibitors,

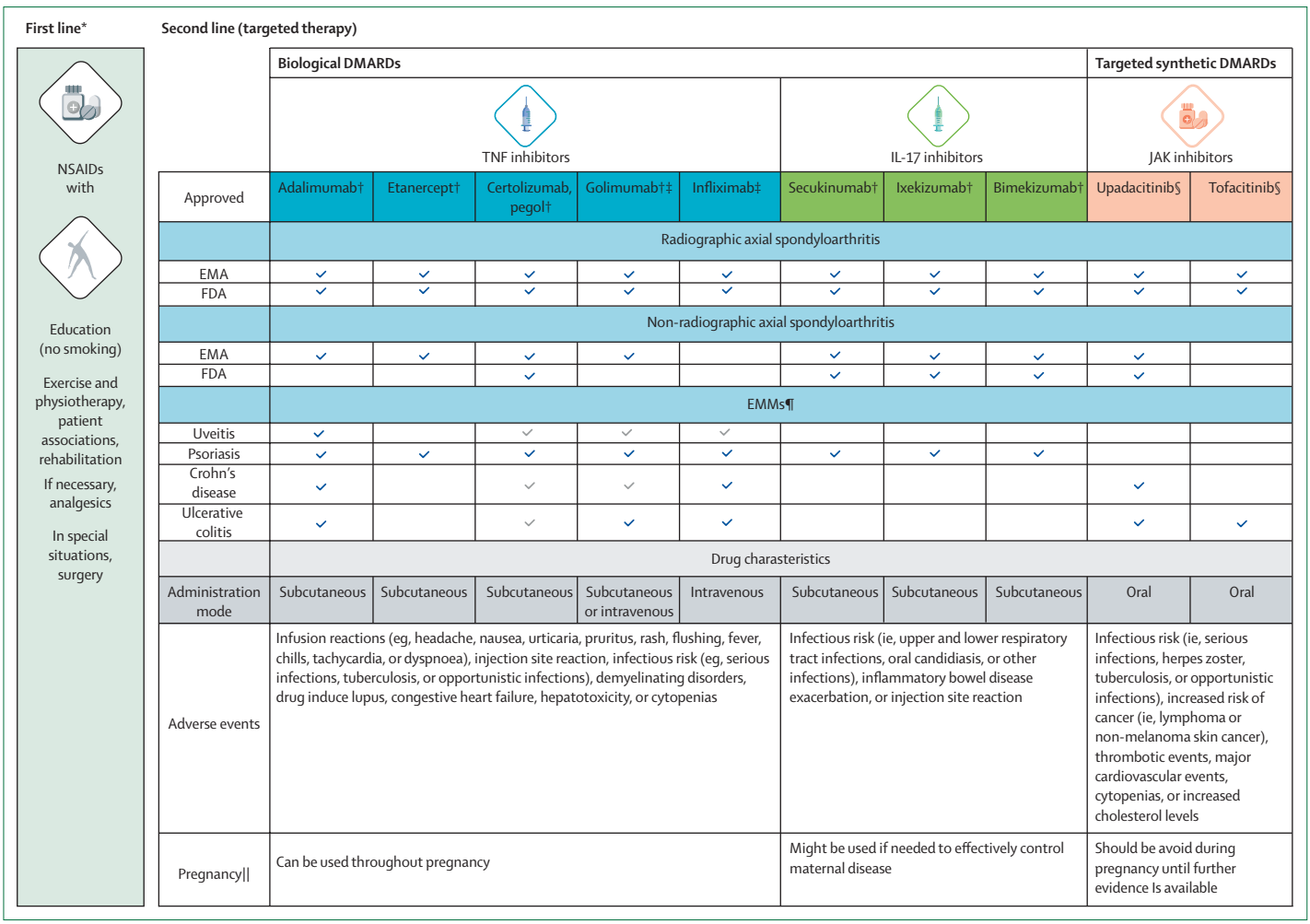

Figure 5: **Recommendations to manage axial spondyloarthritis[96]**

Adverse events: TNF inhibitors—infusion reactions (ie, headache, nausea, urticaria, pruritus, rash, flushing, fever, chills, tachycardia, and dyspnoea), injection site reaction, infectious risk (ie, serious infections, tuberculosis, and opportunistic infections), demyelinating disorders, drug induce lupus, congestive heart failure, hepatotoxicity; cytopenias; IL-17 inhibitors—infectious risk (ie, upper and lower respiratory tract infections, oral candidiasis; other infections), inflammatory bowel disease exacerbation, injection site reaction; JAK inhibitors—infectious risk (ie, serious infections, herpes zoster, tuberculosis, and opportunistic infections); increased risk of cancer (ie, lymphoma and non-melanoma skin cancer), thrombotic events (ie, deep vein thrombosis, pulmonary embolism, and arterial thrombosis), major cardiovascular events (ie, myocardial infarction and stroke), cytopenias, and increased cholesterol levels. For pregnancy, individual drug effectiveness and transplacental transfer should be taken into consideration. NSAIDs should only be used intermittently and stopped after 28 weeks of gestation. Non-selective NSAIDs with a short half-life are preferred. All TNF inhibitors can be used throughout pregnancy. IL-17 inhibitors can be used if needed to effectively control maternal disease. JAK inhibitors should be avoided during pregnancy until further evidence is available. DMARD=disease modifying anti-rheumatic drug. EMA=European Medicines Agency. EMM=extra-musculoskeletal manifestation. FDA=US Food and Drug Administration. IL-17=interleukin-17. NSAID=non-steroideal antiinflammatory drug. TNF=tumour necrosis factor. *For peripheral manifestations, local steroids or conventional synthetic DMARDs (ie, sulfasalazine or methotrexate). †Subcutaneous delivery. ‡Intravenous delivery. §Oral administration. ¶Drug effectiveness for the EMM. Symbol in blue when approved by EU or FDA for indication per se. ||Individual drug effectiveness and transplacental transfer should be taken into consideration. NSAIDs should be used only intermittently and stopped after 28 weeks of gestation. Non-selective NSAIDs with a short half-life are preferred.

secukinumab[108,109] and ixekizumab[110–112] (both IL-17A inhibitors), and bimekizumab[113] (a dual IL-17A and IL-17F inhibitor) are available. All biological DMARDs except infliximab (mainly intravenous) are for subcutaneous administration. All biological DMARDs are approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for radiographic axial spondyloarthritis. For non-radiographic axial spondyloarthritis, certolizumab is the only TNF inhibitor approved by the FDA, while adalimumab, etanercept, and golimumab are only approved by the EMA; infliximab, on the other hand, is not approved by any regulatory agency for non-radiographic axial spondyloarthritis due to insufficient data. All three IL-17 inhibitors are approved by the EMA and FDA for non-radiographic axial spondyloarthritis. JAK inhibitors for axial spondyloarthritis include upadaticitib[114,115] and tofacitinib.[116] Contrary to biological DMARDs, JAK inhibitors can be administrated orally. Both JAK inhibitors are approved by the EMA and FDA for radiographic axial spondyloarthritis, but for non-radiographic axial spondyloarthritis; only upadacitinib is

approved by both regulatory agencies. Another JAK inhibitor filgotinib[117] has shown efficacy for radiographic axial spondyloarthritis in a phase 2 study and is under further investigation.

All the different classes of drugs (ie, TNF, IL-17, and JAK inhibitors) have shown efficacy in relieving the symptoms and signs of axial spondyloarthritis with a favourable safety profile.[37,39,118–120] In the absence of head-to-head trials, it is difficult to prioritise any of these inhibitors in terms of efficacy on axial disease. However, due to the longer experience, current practice is to initiate treatment with a TNF or IL-17A inhibitor.[96] The frequency of serious infections, malignancies, and cardiovascular events in randomised controlled trials of patients with axial spondyloarthritis treated with TNF, IL-17, or JAK inhibitor was observed to be low.[37] Based on data in rheumatoid arthritis studies, the EMA's safety committee recommended measures to minimise the risk of serious side-effects associated with JAK inhibitors, including cardiovascular conditions, blood clots, cancer, and serious infections.[121] Additionally, in the case of concomitant uveitis or inflammatory bowel disease, a monoclonal antibody TNF inhibitor is recommended, while in patients with considerable psoriasis, an IL-17 inhibitor might be preferred.[96] The efficacy of JAK inhibitor to treat extra-musculoskeletal manifestations in axial spondyloarthritis is still to be established, but JAK inhibitors have shown efficacy in inflammatory bowel disease, leading to the approval of upadacitinib for both ulcerative colitis[122] and Crohn's disease,[123] and tofacitinib for ulcerative colitis.[124] Considerations about reproduction and pregnancy can also influence treatment decisions (figure 5). As such, EULAR has recently updated the points for patients and health-care providers to consider on use of antirheumatic drugs in reproduction, pregnancy, and lactation.[125]

If the first biological or targeted synthetic DMARD is ineffective, switching to a second DMARD is recommended, either a TNF, IL-17, or JAK inhibitor. However, the evidence in terms of the efficacy of a specific drug class after non-response is scarce. Currently, there is no preferred strategy between switching or cycling of these treatments, and further evidence is required to establish the optimal strategy.[96]

Other types of biological DMARDs have not shown efficacy in axial spondyloarthritis. Also, there is no evidence supporting the efficacy of conventional synthetic DMARDs, such as methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine in improving axial manifestations, and therefore, their use is not recommended in patients with purely axial disease.[96] Sulfasalazine might be considered in patients with peripheral arthritis. Local glucocorticoid injections in peripheral, or rarely in sacroiliac joints, might also be considered, but the long-term use of glucocorticoids in axial spondyloarthritis is not recommended.[96]

Around 60–65% of patients have a clinical response and show low disease activity following the first biological or targeted synthetic DMARD.[37,39] Specific characteristics, such as male sex, no smoking, shorter disease duration, and objective inflammation are associated with better response.[37] If disease remission is sustained, tapering a biological DMARD can be considered to minimise side-effects and costs. The primary factor of success is a longer duration of remission before dose reduction. Discontinuation of drugs is not recommended as this usually results in flares.[126] However, if discontinuation is temporarily necessary for reasons such as surgery or pregnancy, achieving a similar response after restarting is possible.

Most patients show a clinical response or low disease activity, but sustained remission occurs only in less than one third in clinical practice.[127,128] Further data needs to clarify whether this target is nowadays unattainable or if it can be reached by implementing specific measures. Currently, there are no robust data to conclude that early treatment leads to better outcomes.[41,42] However, available data stem from studies that define early disease heterogeneously and is mainly restricted to patients with less than 5 years of symptom duration. The first step to clarify a potential window of opportunity is to standardise the definition of early axial spondyloarthritis for research.[129] Recently, the ASAS-SPEAR project has set this definition as 2 years of less of axial symptom duration.[130] To further investigate whether there is a window of opportunity, it is crucial to identify patients at an early stage of the disease, by decreasing the current unacceptable diagnostic delay. Furthermore, in addition to reasons related to the disease itself, several factors other than biological non-response (eg, chronic pain syndrome, concomitant degenerative disease, etc) might explain the absence or partial response to treatment in axial spondyloarthritis, which makes the disease more difficult to manage in a subgroup of patients. To focus on characterising these patients, identifying mechanisms beyond refractory disease and conducting intervention trials, the ASAS is developing a consensus definition of difficult-to-manage axial spondyloarthritis.

The effect of different therapies on the progression of structural damage remains controversial. Initial studies suggested that continuous administration of NSAIDs could slow progression of structural damage, particularly in patients with syndesmophytes and raised CRP levels.[131] However, subsequent trials have not confirmed these findings.[132,133] On the other hand, pivotal studies with TNF inhibitors initially did not show the inhibition of structural damage, although later research suggested they might exert a protective effect, mainly after long-term treatment, by controlling disease activity.[134–136] Recently, the first head-to-head trial with TNF and IL-17A inhibitors has indicated that only a few patients experience progression in the short term, with no difference between both classes.[137] It is possible that future causal inference

analyses of observational studies will help to clarify whether disease modification is possible in axial spondyloarthritis.[138]

Research agenda

Considerable unmet needs require attention.[139] The future research agenda is to improve diagnostic tools and strategies to facilitate timely and accurate diagnosis of axial spondyloarthritis, including raising disease awareness and refining novel diagnostic tests,[140] such as the so-called bone MRI or low-dose CT,[70] or specific biomarkers identified by omics.[140] Early disease identification could elucidate the benefits of early intervention and the existence of a window of opportunity. Additionally, a deeper understanding of differences between subgroups (eg, geographical and sex) is necessary.[141–143] Efforts are required to implement the regular use of standardised monitoring instruments[89] and to integrate devices for disease management. The benefits of incorporating MRI into routine clinical practice for monitoring remains to be clarified.[71]

Implementating current recommendations for axial spondyloarthritis management is crucial.[96] Further research is needed to clarify whether the target set nowadays is a chimera or a reality. Developing new drugs for non-responsive patients is necessary.[140] Additionally, there is a need to characterise and develop a consensus definition of difficult to manage axial spondyloarthritis, as well as identifying response predictors to drugs and defining optimal individualised strategies. In this sense, scientific data from head-to-head and strategic trials are warranted.[87]

More data on the potential use of artificial intelligence for different purposes, such as diagnostic support, characterisation of disease phenotypes, personalised treatment, and prediction of disease progression and prognosis are expected to become available in the future.

By addressing these research priorities, future advances are expected to facilitate a timely and accurate diagnosis, optimise disease management, and implement quality standards to enhance overall quality of health and care services in patients with axial spondyloarthritis.

Contributors

All authors were involved in drafting the article or revising it critically for important intellectual content. All authors reviewed the published evidence and approved the final version of the manuscript.

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