Axial spondyloarthritis

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ABSTRACT

Axial spondyloarthritis (axSpA) encompasses both radiographic and non-radiographic axSpA. It is a chronic inflammatory disease with a predilection for involving the axial skeleton. The most common presenting symptoms are chronic back pain and spinal stiffness but peripheral and extra-musculoskeletal manifestations occur also frequently. The diagnosis of axSpA relies on the recognition of a clinical pattern of the disease, based on clinical, laboratory and imaging features. The Assessment in SpondyloArthritis international Society classification criteria for axSpA are valid and well implemented for research purposes. Sustained disease activity, measured by validated tools such as the Ankylosing Spondylitis Disease Activity Score, leads to irreversible structural damage and poor functioning and therefore should be abrogated. As part of the management algorithm, non-steroidal anti-inflammatory drugs remain as the first line of pharmacological treatment besides physiotherapy. As a second line, tumour necrosis factor inhibitor and interleukin-17 inhibitor are available but recently Janus kinase inhibitors have also shown efficacy in improving symptoms of the disease.

INTRODUCTION

Spondyloarthritis (SpA) is a chronic inflammatory disease that either involves predominantly the axial (ie, the sacroiliac joints (SIJ) and the spine; axial SpA (axSpA)) or the peripheral skeleton (ie, joints of the limbs; peripheral SpA (pSpA)).[1] The prototype of axSpA is radiographic axSpA (r-axSpA), also known as ankylosing spondylitis and historically described according to the modified New York classification criteria (mNY).[2] The hallmark feature of r-axSpA is commonly referred to as 'radiographic sacroiliitis'. The term, however, is misplaced because sacroiliitis implies inflammation, but only structural damage, rather than inflammation, is visible on radiographs.

By the time that structural abnormalities become apparent on pelvic radiographs, patients typically had already symptoms, such as pain, for several years. Efforts to reduce the diagnostic delay of axSpA led to the recognition of patients presenting with a clinical phenotype similar to r-axSpA except for the absence of definite damage visible on pelvic radiographs. Unlike radiographs, MRI allows direct visualisation of inflammation.[3] In the mid-1990s, MRI demonstrated that these patients have inflammation on the SIJ often predating radiographic damage for years.[4]

This evidence led the Assessment in SpondyloArthritis international Society (ASAS) to coin the term 'axial spondyloarthritis' to refer to the entire spectrum of the disease, covering both patients who have already developed definite radiographic damage in the SIJ (r-axSpA) and patients without such damage

(non-radiographic axSpA (nr-axSpA)).[5][6] Patients with nr-axSpA represent early forms of axSpA, in a disease continuum, in which some, but not all, eventually progress to r-axSpA. For the purpose of diagnosis, in clinical practice, the distinction between r-axSpA and nr-axSpA is less relevant, and preference should be given to the term axSpA to refer to all patients.[7]

EPIDEMIOLOGY

AxSpA usually starts in the third decade of life with a male to female ratio of 2:1 for r-axSpA, and with an equal sex distribution among patients with nr-axSpA. The percentage of patients with nr-axSpA is increasing over time, which is partly due to its better recognition[8] (figure 1).

Most data on the prevalence of axSpA pertain to r-axSpA with a prevalence ranging widely from 0.1% to 1.4%. Differences in study design can explain some variability; however, it is well-known that the prevalence of the disease is highly affected by the background prevalence of the human leucocyte antigen (HLA)-B27, its major genetic association.[9]

Populations with high background prevalence of HLA-B27 show higher rates of axSpA, such as in Northern Europe and among the native peoples of the circumpolar arctic and subarctic regions of Eurasia and North America.[10] In contrast, the near absence of axSpA in southern Africa and the low rates in Japan is linked to low HLA-B27 prevalence. AxSpA prevalence (including both r-axSpA and nr-axSpA) varies between 0.3% and 1.4%,[11][12] and the estimates for the entire group of SpA (including axSpA and pSpA) from 0.3% to 1.9%, making it at least as prevalent as rheumatoid arthritis.[13]

PATHOGENESIS

The primary pathophysiology in axSpA occurs in the entheses and in the subchondral bone.[14][15] Although synovitis may also occur, it is a secondary process originating from signals in the enthesis.[14] Entheseal and bone pathology occurs in individuals with a specific genetic background. Genetic studies estimate a heritability greater than 90%. The most important genetic risk factor is HLA-B27, but other major histocompatibility complex (MHC) variants are also involved.[16] Two non-MHC genetic loci have also been associated with axSpA, the endoplasmic reticulum aminopeptidase (ERAP) and the interleukin-23 (IL-23) receptor.[17] Polymorphisms on these loci have functional consequences and associate with disease manifestations.[18][19] Of note, ERAP1 associates with axSpA only in HLA-B27-positive cases, indicating the relevance of peptide presentation by HLA-B27.[20]
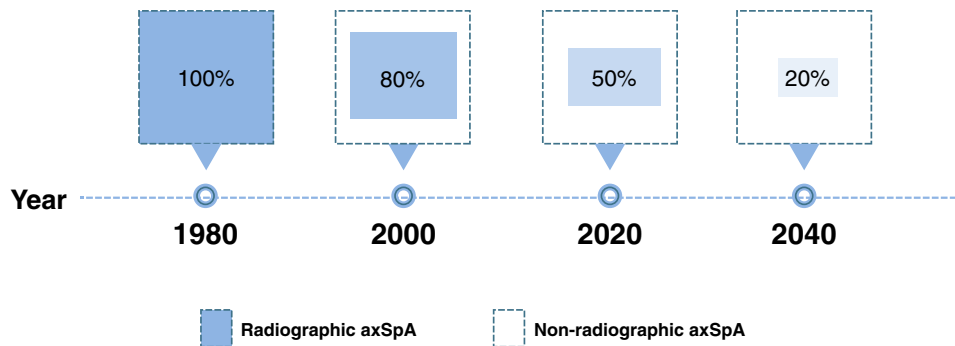
Figure 1 Distribution of axial spondyloarthitis subtypes over time. The graph represents an estimation of the prevalence ratio between non-radiographic and radiographic axial spondyloarthritis, showing the estimated percentage of patients with radiographic axial spondyloarthritis for each period at the time of diagnosis. Adapted from Benavent *et al*. Clin Rheumatol. 2021 Feb;40(2):501–512. axSpA, axial spondyloarthritis.

Entheses are load-bearing structures with a specific immune microenvironment that, in susceptible individuals, may be activated by mechanical and microbial triggers.[14] There is increasing evidence of the importance of mechanical stress in the onset and progression of axSpA.[21 22] In addition, damage to the skin, induced by psoriasis, and to the intestinal mucosa by inflammatory bowel disease (IBD), facilitate exposure to pathogens. This mechanism may happen even in asymptomatic patients. In fact, subclinical gut inflammation has been linked to earlier disease onset and worse prognosis.[23] Dysbiosis is thought to be of relevance in the link between the intestine and SpA pathogenesis[15] (figure 2).

Axial inflammation, bone destruction and new bone formation are key events in the pathophysiology of axSpA. Even though, it is yet to be fully clarified the mechanisms that govern their interplay, several studies using bone biopsies, animal models and imaging had already yielded important insights. Subchondral bone marrow oedema (BME) visible on MRI is the earliest detectable change in biopsy specimens.[24 25] BME is then replaced by an inflammatory granulation tissue, containing also adipocytes and fat vacuoles, that erodes the subchondral bone plate, but also has bone-forming capabilities.[26] Fatty lesions on MRI are thought to be the imaging translation of this repair tissue.[27]

Thus, inflammation can lead either to bone destruction or to bone formation. One hypothesis defends that bone destruction, driven by the contact between osteoblasts and osteoclasts (by receptor activator of NF-κB–receptor activator of NF-κB ligand interactions), prevails with sustained inflammation, while bone formation implies that inflammation subsides and the absence of osteoclasts.[28] In axSpA, inflammation is thought to fluctuate, which allows repair and an anabolic response driven by bone morphogenic proteins and Wnt proteins.[14] Several clinical studies corroborate the observation that inflammation leads to subsequent new bone in axSpA.[28–35] Whether or not a repair mechanism (fatty lesions) mediate this effect, remains an open question.[36]

Tumour necrosis factor (TNF)-α and IL-23/IL-17 are, thus far, identified as the major pro-inflammatory cytokine pathways in axSpA.[14] The pivotal role of TNF-α in the pathogenesis of axSpA is supported by the success of TNF inhibitors (TNFi) in controlling the symptoms of the disease,[37] More recently, IL-17-inhibitors (IL-17i) have also proved effective in axSpA, but not IL-23-inhibitors (IL-23i).[38] These results offer important clues on the role of the IL-23/IL-17 pathway in SpA. IL-17 is produced by T helper 17 (TH17) cells in response to IL-23, in a later stage of their differentiation. The inefficacy to IL-23i in controlling axial manifestations suggests, however, an uncoupling between the two cytokines. The fact that IL-17 secretion might take place in the absence of IL-23 and that cell types other than TH17, such as the type 3 innate lymphoid cells, produce IL-17 independently of IL-23 supports this claim.[38]

Both TNF-α and IL-17 induce bone destruction and cause a downregulation of osteoblast function when osteoblasts and osteoclasts interact. In absence of osteoclasts, as in axSpA, however, these cytokines lead to bone formation,[39] suggesting their inhibition can, potentially, interfere with the disease progression.

CLINICAL, LABORATORY AND IMAGING FEATURES

The most common, and often presenting, symptom of axSpA is chronic (lasting >3 months) almost daily back pain (CBP),
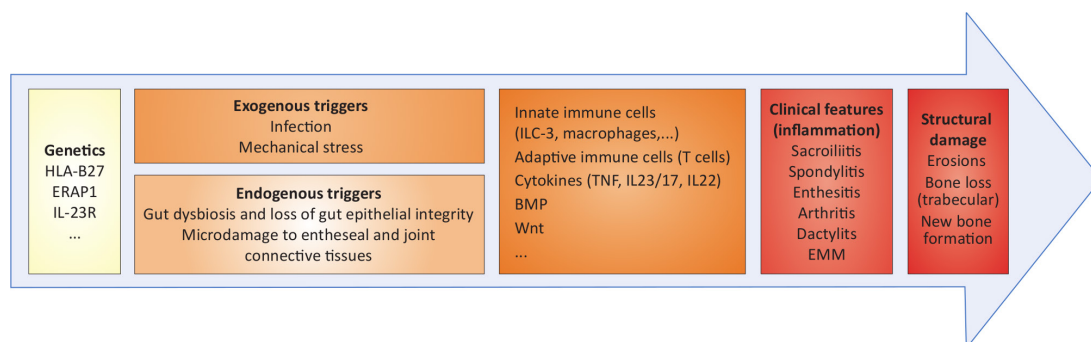

Figure 2 Pathogenesis scheme for axial spondyloarthritis. A schematic presentation of the various aspects that play a role in the pathogenesis of axial SpA. BMP, bone morphogenetic protein; EMM, extra-musculoskeletal manifestation; ERAP, endoplasmic reticulum aminopetidase; HLA, human leucocyte antigen; IL, interleukin; ILC, innate lymphoid cell; SpA, spondyloarthritis; TNF, tumour necrosis factor.

which is frequently accompanied by morning stiffness. Pain and stiffness usually involve the lower spine and the buttocks, but any level of the spine can be affected. CBP in axSpA typically has an insidious onset and has inflammatory characteristics: it is worse in the second part of the night and in the morning, it is relieved with activity and worsened by rest and usually improved by non-steroidal anti-inflammatory drugs (NSAIDs). Several criteria have been proposed to define inflammatory back pain (IBP).[40 41] Though typical, not all axSpA patients have IBP. In fact, up to one third of patients present with mechanical back pain,[42] also diseases other than axSpA may present with IBP.[43] In axSpA, axial inflammation (synovitis and enthesitis) leads to irreversible structural damage and both can limit the mobility of the spine.[44] However, limited spine mobility is usually a late disease manifestation and, although a characteristic feature of axSpA, it may also occur in patients with CBP from diseases other than axSpA.[45]

In addition to CBP, patients with axSpA can present peripheral manifestations. Arthritis and enthesitis are the most common peripheral manifestations in axSpA, each occurring in approximately 30% of the patients.[46] Peripheral arthritis, presenting as a swollen and painful joint, is usually an asymmetrical monoarthritis/oligoarthritis, and involves predominantly the lower extremities. Peripheral enthesitis usually manifests with pain, stiffness and/or tenderness. The most common affected entheses are at the insertion of the Achilles tendon and the plantar fascia. However, axial enthesitis (eg, at the insertion of the anterior longitudinal ligament) together with synovitis of the axial joints (costovertebral, costosternal and manubriosternal joints), can also be involved causing chest/back pain. Dactylitis (sausage digit), which is a swelling of a finger or toe as the consequence of a combination of synovitis, tenosynovitis and enthesitis is a typical feature of axSpA but it occurs in <10% of the patients.[46]

Patients with axSpA may present concomitant extra-musculoskeletal manifestations (EMMs), that is, uveitis, IBD and psoriasis. Uveitis is associated with HLA-B27 positivity,[47] and is the most frequent EMM, occurring in approximately 25% of the patients.[46] Uveitis presents typically as unilateral acute anterior uveitis (AAU), and frequently alternates from one eye to the other. Psoriasis (10%) and IBD (5%–10%), including both ulcerative colitis and Crohn's disease, are less frequent EMM of axSpA.[46 48] In severe cases, patients might present with constitutional symptoms, such as low-grade fever and weight loss. Heart (eg, aortic valve insufficiency), lung (restrictive lung disease) and kidney (eg, IgA nephropathy) involvement can also occur in axSpA.

Different laboratory and imaging features are found in axSpA. The presence of HLA-B27, tested in peripheral blood samples, is positive in 70%–90% of patients. 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 axSpA have symptoms despite normal acute phase reactants.[49] Inflammatory lesions of the axial skeleton can be seen with MRI of the SIJ and the spine. The ASAS group define active sacroiliitis as the presence of BME on MRI in subchondral bone highly suggestive of SpA.[50] On the MRI of the spine, the presence of ≥5 corner inflammatory lesions discriminates well between axSpA and no axSpA.[51] Radiographs can detect structural abnormalities (sclerosis, erosions, joint space narrowing/widening or ankylosis) that occur in the SIJ and in the spine. The mNY grading system is traditionally used to quantify structural damage in the SIJ,[2] with a score of 0 (normal), 1 (suspicious changes), 2 (minimal abnormalities), 3 (unequivocal abnormalities) and 4 (total ankylosis) given to each joint. Definite structural changes

(radiographic 'sacroiliitis') are defined as bilateral grade ≥2 or unilateral grade ≥3. Structural lesions can also be seen with MRI both in SIJ and in the spine (eg, erosions, sclerosis and fatty lesions). Definitions of each lesion have been published.[52 53]

There are gender differences in the presentation of axSpA. Male patients are more likely to be HLA-B27 positive,[54] a feature associated with imaging abnormalities typical of r-axSpA and with a higher likelihood of AAU.[47 55] Female patients, on the other hand, are less likely to show inflammation and structural damage on imaging studies, and to be positive for HLA-B27.[54] A lower prevalence of HLA-B27 is associated with a higher likelihood of peripheral features and EMM (especially psoriasis) in axSpA.[56–59]

DIAGNOSIS

The diagnosis of axSpA relies on recognising the pattern (the 'Gestalt') of axSpA, taking into account all features that are present, as well as those that are absent and considering alternative diagnoses. SpA features are identified during the history taking (eg, family history, back pain characteristics, response to NSAIDs, history of enthesitis/arthritis/dactylitis or EMMs), physical examination (eg, arthritis) and in laboratory (eg, CRP and HLA-B27) and imaging (eg, MRI-SIJ) exams. Early diagnosis allows early treatment aiming at reducing the disease burden and improving long-term prognosis. However, the SpA-pattern is sometimes difficult to recognise, especially in early disease and in absence of objective findings leading to uncertainty. In clinical practice, clinicians may use diagnostic algorithms for guidance[42] (figure 3).

Diagnostic algorithms are based on probability rules. The probability of the disease is calculated considering each feature's ability to discriminate between axSpA and no axSpA. Positive and negative likelihood ratios (LR+ and LR−) are easy ways to quantify diagnostic value (table 1).

The higher the LR+ the more likely a diagnosis of axSpA if the feature is positive. Conversely, the lower the LR− the less likely the diagnosis if the feature is negative. The LR+ of present features and the LR− of absent features are multiplied to get the LR-product.[60] Clinicians may follow the diagram in figure 2 to guide their diagnostic reasoning. Importantly, the diagram assumes that the patient comes from a population with a 5% prevalence of axSpA (ie, patients with CBP in general practice).[4]

It should be kept in mind that some features, especially peripheral features and EMM, absent at presentation may occur later on.[58] On the other hand, a negative MRI of the SIJ for the presence of BME is unlikely to become positive within 1 year.[61] Thus, usually repeating the scan does not help in the diagnosis. Also, important to note that the diagnostic value of family history of axSpA is low when the HLA-B27 status is already known.[62] Moreover, IBP is an important feature for referring patients with suspicion of axSpA to the rheumatologist but does not add much diagnostic utility thereafter.[63]

Conventional radiography of the SIJ is usually used as the first imaging modality to identify the involvement of SIJ, mostly because of feasibility reasons. However, on top of the exposure to radiation, this method has major limitations. Damage in the SIJ only becomes visible in pelvic radiographs several years after the start of the symptoms.[64] In addition, the interpretation of radiographs of the SIJ is often challenging even among experienced readers.[65] MRI of the SIJ is recommended if the diagnosis cannot be made based on clinical features and conventional radiographs, but yet the clinical suspicion of axSpA remains high (figure 4).
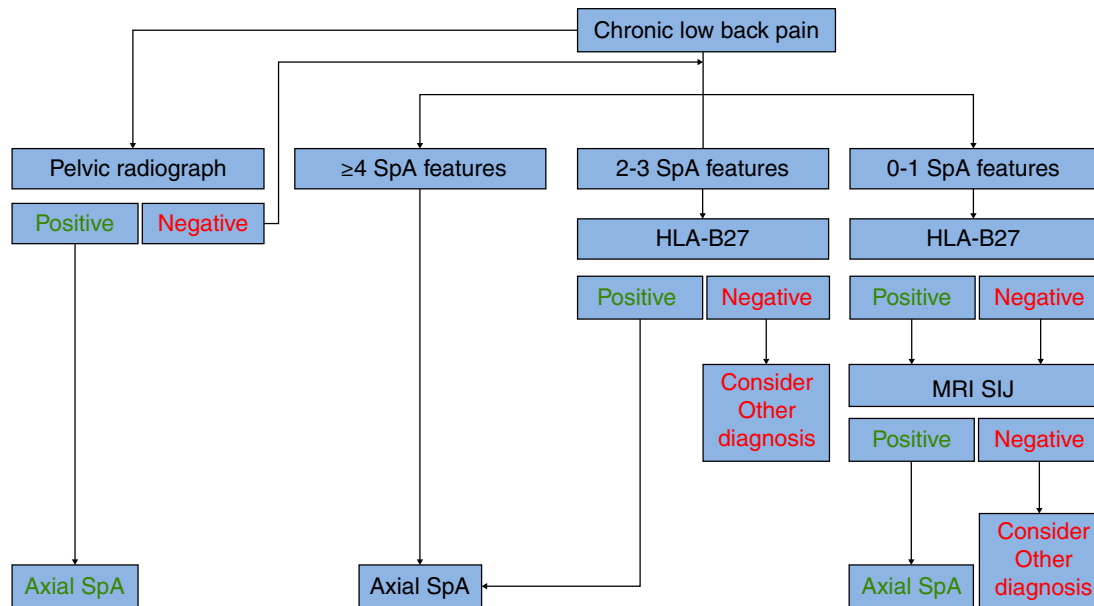
Figure 3 ASAS adaptation of the Berlin algorithm. ASAS, Assessment in SpondyloArthritis international Society; HLA, human leucocyte antigen; SIJ, sacroiliac joints; SpA, spondyloarthritis. SpA features: inflammatory back pain, alternating buttock pain, good response to non-steroidal anti-inflammatory drugs, peripheral arthritis, enthesis, dactylitis, psoriasis, inflammatory bowel disease, uveitis, elevated acute phase reactants, preceding infection, family history. Adapted from van den Berg *et al*.[42]

The presence of BME on MRI of the SIJ fulfilling the ASAS definition increases the likelihood of a diagnosis of axSpA, especially if structural changes are also present. However, clinicians should bear in mind that BME is less specific for axSpA than initially thought.[66] BME can also occur in patients with non-specific back pain, osteitis condensans, healthy individuals, post-partum women, recreational runners and athletes (although deep (extensive) lesions are exclusively found in axSpA patients).[3 67]

Too much reliance on positive imaging findings can easily lead to overdiagnosis and overtreatment.[68] Likewise, the absence of inflammation on MRI does not, per se, rules out axSpA. Recent data suggest that in addition to the 'classical' axSpA phenotype, dominated by imaging findings, some axSpA patients, mostly women, have a high likelihood of peripheral features co-occurring with CBP but without axial imaging findings.[69]

MRI of the spine has little diagnostic value on its own, and there is conflicting data on the value of combining MRI of the spine with SIJ for diagnosis.[70] 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 skeletal scintigraphy, ultrasonography of the SIJ and positron emission tomography are not recommended for the diagnosis of axSpA.[71] The role of (low-dose) CT for diagnosis is yet to be defined.

A major delay of 5–7 years remains between the start of CBP and the diagnosis of axSpA. Despite a similar age of onset,
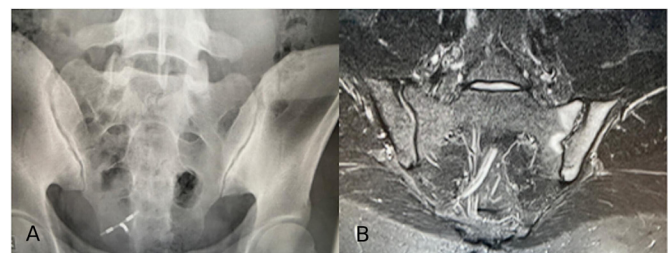
Table 1 Diagnostic value of SpA features

SpA feature	LR+	LR−
Inflammatory back pain*	3.1*	0.33
Heel enthesitis	3.4	0.71†
Peripheral arthritis	4.0	0.67†
Dactylitis	4.5	0.85†
Acute anterior uveitis	7.3	0.80†
Psoriasis	2.5	0.94†
IBD	4.0	0.97†
Positive family history	6.4‡	0.72
Good response to NSAIDs	5.1	0.27
Raised acute-phase reactants (CRP/ESR)	2.5	0.63
HLA-B27	9.0§	0.11
Sacroiliitis on MRI	9.0¶	0.11
Radiographic 'sacroiliitis' grade ≥3	20**	0.61

Adapted from Rudwaleit *et al*.[60]
*If the patient is referred based on the presence of IBP: LR+=1.4–1.7.
†Ignore if negative for the calculation of the LR− product (feature may develop later).
‡Lower if HLA-B27 status is known.
§Applies to European Caucasians, may differ in other ethnic groups.
¶LR varies with different definitions.
**Best estimation (poor reliability should be taken into account).
CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; IBP, inflammatory back pain; LR−, negative likelihood ratio (LR−=(1−sensitivity)/specificity); LR+, positive likelihood ratio (LR+=sensitivity/1−specificity); LR, likelihood ratio; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis.

Figure 4 Imaging findings in non-radiographic axial spondyloarthritis. Clinical case: a female patient, 40 years old, complaining of back pain during the last 6 months with inflammatory characteristics (worsening with rest improving with exercise and awaking at second half of night) and morning stiffness of 1 hour. (A) On the pelvis radiograph, no changes are observed; (B) on MRI (fat suppressed sequence) of sacroiliac joints, deep bone marrow oedema suggestive of axial spondyloarthritis on the left sacroiliac bone (both at the sacral margin and iliac bone) is shown.

the diagnostic delay is larger in women (mean 8.8 years) than in men (6.5 years).[72] Differences in disease presentation, as described above, and physician bias may render the recognition of the SpA-pattern in women more difficult.[57 73] In addition, in both genders, too much reliance on the presence of radiographic changes can further delay the diagnosis of axSpA among patients with CBP in primary care. Several referral strategies have been proposed over the years.[74] More recently, ASAS has endorsed a screening method for early referral.[75] Patients with CBP starting before 45 years of age should be referred to the rheumatologist if ≥1 SpA feature (see next section) is present. The method is flexible to local conditions, such as limited availability of imaging and HLA-B27 typing (which are not mandatory) and can therefore be applied widely.

CLASSIFICATION CRITERIA

Given the limitations of the existing classification criteria in including earlier stages of the disease, the ASAS axSpA criteria were established in 2009 and later implemented in most studies.[5 6 76] The ASAS axSpA criteria are applicable to the entire spectrum of the disease (nr-axSpA and r-axSpA) and incorporate MRI of the SIJ.[50] The criteria are meant to be applied in patients with CBP and an onset before age 45 years old and have a diagnosis of axSpA. They have two possible entry arms: the 'imaging arm' (presence of sacroiliitis on radiography or MRI) and the 'clinical arm' (presence of HLA-B27). To classify as axSpA, patients must additionally have at least one (or two, in case of the clinical arm) typical characteristics of SpA, so-called SpA features: IBP, arthritis, enthesitis, dactylitis, uveitis, IBD, psoriasis, good response to NSAIDs, family history of SpA, presence of HLA-B27 and elevated CRP. Their implementation allowed the inclusion in clinical trials of patients covering the entire spectrum of the disease, especially those at an earlier stage, thus representing one of the major advances in the last decade.[77] These criteria have shown to perform well against the rheumatologist's diagnosis, with an overall sensitivity of 82% and specificity of 89%.[78]

However, the ASAS classification criteria for axSpA are not without criticism. They may lead to overdiagnosis in case they are misused for making a diagnosis. But this is a conceptual error, because similar to all classification criteria, the ASAS criteria should not be used to diagnose patients but to classify patients already diagnosed with axSpA (as described above) in order to be included in a study.[79] On the other hand, some experts argue that all features are given the same weight despite not having the same value (LR+ and LR−).[80] The main reason for assigning them the same weight was simplicity, favouring implementation. Nevertheless, ASAS in collaboration with SPondyloArthritis Research and Treatment Network is currently conducting a large prospective study, which will re-evaluate the criteria in an international cohort to provide further insight.

MONITORING

Numerous tools are now available to monitor axSpA. As the disease affects deep anatomical structures, it is difficult to make a proper assessment by physical examination. Therefore, most of the tools used in axSpA are based on laboratory or imaging findings and patient-reported outcomes.[81 82] Multiple patient-reported outcomes have been developed and validated to determine the disease status and impact. The use of one or

the other depends on the disease domain to be explored and the setting (ie, clinical practice or research).[83]

To assess disease activity in clinical practice, the use of composite indices is preferred.[84] Currently, it is recommended to use the Ankylosing Spondylitis Disease Activity Score (ASDAS), which consists of four questions answered by the patient (axial pain, peripheral pain-inflammation, morning stiffness duration and global disease activity) and CRP value in mg/L (using 2 if below the threshold or <2 mg/L).[85–87] According to ASDAS, clinicians may classify disease activity as inactive (<1.3), low activity (<2.1), high activity (<3.5) and very high activity (>3.5).[86] In addition, clinically important improvement is considered if a decrease between two assessments of at least 1.1 is achieved, and major improvement if the decrease is 2.0. A flare of the disease is defined as an increase in the ASDAS ≥0.9 compared with the previous assessment.[88] Additionally, the Bath Ankylosing Spondylitis Disease Activity Index is also available as a valid alternative, preferably in combination with CRP. This is an older index composed of six questions that assesses the first three items of the ASDAS plus fatigue, enthesitis and severity of morning stiffness, ranging between 0 (no disease activity) and 10 (very high disease activity).[83] In the past, this index has been used extensively, however, the ASDAS has shown better psychometric properties and it is currently recommended as the preferred index in clinical practice.[89] For clinical trials, the instruments to assess disease activity recommended within the ASAS-Outcome Measures in Rheumatology (OMERACT) core set are usually employed.[76] Additionally, the ASAS clinical response criteria (ASAS20, ASAS40, ASAS5/6, ASAS partial remission) are commonly used in recent trials.[90] The ASAS-OMERACT core set already exists for at least two decades and is currently in an update process.[91]

It is common for axSpA to affect physical function and spinal mobility. To assess physical function, the Bath Ankylosing Spondylitis Functional Index is recommended, an index composed of 10 questions, with a total score between 0 (good physical function) and 10 (poor physical function).[92] To determine mobility impairment, usually the Bath Ankylosing Spondylitis Metrology Index is employed that encompasses several measurements of the axial skeleton.[82 93] Recently, the ASAS Health Index has been developed and validated to assess overall functioning and quality of life in patients with axSpA. This index, freely available in 15 languages, encloses 17 items addressing functional limitation in daily activities. A lower score indicates a better health status.[94]

The CRP and the ESR are the used laboratory parameters to monitor activity in axSpA. These parameters are raised in only 40% of patients with axSpA and therefore, per se, they are only useful in a minority of patients to monitor disease activity.[49] As mentioned, MRI can detect inflammatory signs in the SIJs and spine. However, their routine use in clinical practice to monitor axSpA is not recommended, as its additional value compared with more feasible tools remains to be elucidated.[71] For research studies, different scores have been developed to quantify inflammation in the SIJ and in the spine, which are frequently used to evaluate treatment response.[95–97]

If disease activity persists, it results in irreversible structural damage.[31 44] The recommended tool for evaluating damage is conventional radiography of the SIJ and spine, but there is no consensus on how to use it for monitoring in clinical practice.[71] For research, the modified Stoke Ankylosing Spondylitis Spinal Score is employed for most studies, with a total score ranging from 0 to 72.[3] First results of scoring low-dose CT
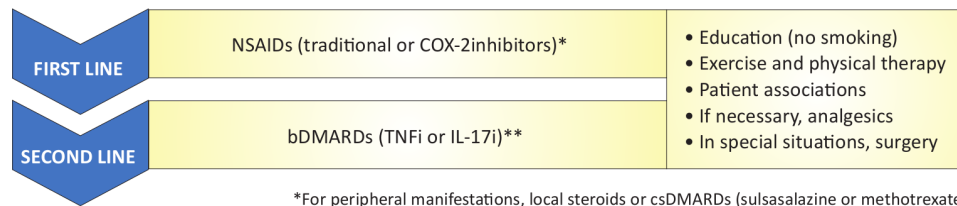
Figure 5 Recommendations to manage axial spondyloarthritis. bDMARDs, biolgical disease-modifying anti-rheumatic drugs; COX-2, cyclooxygenase-2; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; IL-17i, IL-17 inhibitors; JAKi, Janus kinase inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; r-axSpA, radiographic axial spondyloarthritis; TNFi, tumour necrosis factor inhibitors; tNSAIDs, traditional non-steroidal anti-inflammatory drugs; tsDMARDs, targeted synthetic disease-modifying anti-rheumatic drugs Adapted from van der Heijde et al.[101]

scans of the spine show a promising increase in sensitivity to change.

BURDEN OF THE DISEASE

Axial SpA usually begins in the third decade of life, which is a very active period in occupational, social and economic spheres.[98] Two thirds of active employed population with axSpA have work-related issues, leading to substantial direct and indirect costs to the society.[99] As a consequence, axSpA is associated with a high burden of the disease, which is comparable in patients with r-axSpA and nr-axSpA.[100] Older age, lower level of education, longer disease duration, higher disease activity (objective signs of inflammation), reduced physical functioning and employment in more physically demanding jobs are the major determinants of disease burden in axSpA.[22 29–31]

MANAGEMENT

The primary goal of treatment is to maximise health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage and preservation/normalisation of function and social participation.[101 102] Treatment should be guided through tight control according to a specific target, usually aiming at achieving sustained remission and, if not possible, low disease activity, employing the ASDAS as preferred instrument.[89] Importantly, the treatment in axSpA should be based on shared decisions between patients and rheumatologists and includes non-pharmacological and pharmacological therapies (figure 5).

Non-pharmacological therapies such as physical exercise and physiotherapy are recommended throughout the disease course.[101] Recent evidence has evaluated the paradoxical effect of exercise in axSpA.[103] On one hand, physical exercise is the cornerstone of treatment as it reduces disease activity and improves spinal function and quality of life. On the other hand,

mechanical stress could contribute to inflammation and new bone formation at the entheseal and articular sites.[21] Further studies should address this possible paradox, but for the moment it is advisable to encourage patients to regular exercise.

Different types of pharmacological treatment are available for treating axial manifestations of axSpA ((figure 6)).

The first line are NSAIDs. Both traditional NSAIDs and cyclooxygenase-2 (COX-2)-selective inhibitors in full dose are efficacious in reducing the symptoms and signs of the disease.[104] However, drug pharmacokinetics, concomitant manifestations, comorbidities, pregnancy and potential adverse effects must be taken into account.[105 106] In patients with concomitant IBD in remission, the use of COX-2 inhibitors for a maximum period of 2 weeks may be preferred over traditional NSAIDs.[107] Usually, clinical response to full-dose NSAID is observed within 2 weeks. In case of insufficient response after this period, a second NSAID is recommended. To date, there is insufficient evidence to conclude whether switching between traditional NSAIDs and COX-2 inhibitors is more effective than treatment with a second NSAID of the same class.[108] A recent study suggested that switching NSAID classes may be more effective but further studies are needed to confirm these data.[109]

Biological disease-modifying antirheumatic drugs (bDMARD) are indicated as second-line treatment for axial manifestations. Currently, there are two classes of bDMARDs available: TNFi and IL-17i. bDMARDs are indicated if the target is not achieved after 4 weeks receiving at least two different NSAIDs.[110] In addition, patients must have at least one of the following three characteristics to be eligible: an elevated CRP value, inflammation on MRI or radiographic evidence of sacroiliitis.[101] TNFi for axSpA are classified into fusion protein (etanercept[111 112]) and monoclonal antibodies (adalimumab,[113 114] certolizumab pegol,[115] golimumab[116 117] and infliximab[118]). Among the IL-17i, secukinumab[119 120] and ixekizumab[121–123] are available. All bDMARDs except infliximab (intravenous) are for subcutaneous
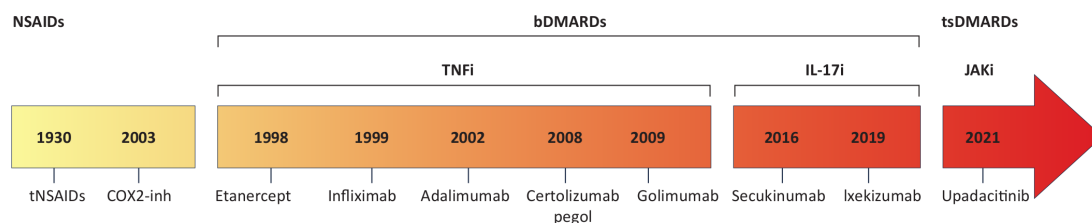

Figure 6 Evolution of pharmacological drugs available to treat axial spondyloarthritis. The figure shows the date (year) for first time approval of a new type of drug by regulatory agencies (European Medicines Agency or Food and Drug Administration) for radiographic axial spondyloarthritis. bDMARDs, biolgical disease-modifying anti-rheumatic drugs; COX2-inh: cyclooxygenase-2 inhibitor; IL-17i, IL-17 inhibitors; JAKi, Janus kinase inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitors; tNSAIDs, traditional non-steroidal anti-inflammatory drugs; tsDMARDs: targeted synthetic disease-modifying anti-rheumatic drugs.

DIAGNOSIS	TREATMENT	MANAGEMENT
< 3 days	At least every 6 months	< 2 months from diagnosis
QS1. Referral (suspicion of axSpA)	**QS4. Monitoring** (ASDAS, alt: BASDAI and CRP)	**QS7. Education and self-management** (utilities, treatment options and healthy lifestyle)
< 3 weeks		< 2 working days
QS2. Time to specialist (rheumatologist and health professionals)	**QS5. Disease control** (treatment escalation, target: remission/LDA)	**QS8. Rapid access** (if flare or drug side effect)
< 2 months		
QS3. Assessment (history taken, lab, imaging)	**QS6. Non-pharma treatment** (information on regular exercise)	**QS9. Annual review** (clinical symptoms, disease severity, comorbidities)

Figure 7 ASAS quality standards to improve the quality of health and care services for patients with axial spondyloarthritis. Adapted from Kiltz *et al*.[147] ASAS, Assessment in SpondyloArthritis international Society; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein; LDL, low disease activity.

administration. Overall, their efficacy in r-axSpA and nr-axSpA is comparable. All above-mentioned bDMARDs are approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) for r-axSpA. For nr-axSpA, certolizumab is the only TNFi approved by FDA and EMA, while adalimumab, etanercept and golimumab are only approved by the EMA; infliximab is not approved by any regulator due to lack of data. Secukinumab and ixekizumab are approved for nr-axSpA by both agencies. Another IL-17i under investigation is bimekizumab.[124] Both TNFi and IL-17i relief symptoms and signs of the disease, with a good safety profile, but no evidence of superiority of one over the other is available. However, given the greater experience with TNFi, current practice is to start with a TNFi. Furthermore, in case of concomitant uveitis or IBD, a monoclonal antibody TNFi is recommended.[101]

Other bDMARDs are not effective in treating patients with axSpA. These treatments include abatacept,[125 126] IL-6 inhibitors[127 128] and IL-12/IL-23 inhibitors.[129] In patients with previous TNFi exposure, rituximab does not seem to be effective either. Similarly, there is also no evidence that conventional synthetic DMARDs such as methotrexate, sulfasalazine, leflunomide or hydroxychloroquine are effective for improving axial manifestations and therefore their use is not indicated in patients with purely axial disease.[108] Sulfasalazine may be considered in patients with peripheral arthritis. Local injection of glucocorticoids in peripheral (or more rarely in SIJ) may be considered too but the use of long-term treatment with glucocorticoids is not recommended for axSpA.

Recently, targeted synthetic DMARDs (tsDMARDs) against Janus kinase inhibitor (JAKi) have shown to improve axial manifestations in patients with r-axSpA. An advantage of these new therapies is that they are orally administrated. Upadacitinib has been recently approved as the first JAKi for patients with r-axSpA but no data on nr-axSpA are available yet.[130] Other tsDMARDs including tofacitinib[131] and filgotinib[132] have shown to be efficacious in phase II studies. Further approval for new JAKi and for nr-axSpA are expected.

Approximately 60% to 65% of patients achieve clinical response after a first bDMARD.[133] Some characteristics (male sex, no smoking, shorter disease duration, elevated CRP and inflammatory lesions on MRI) are associated with a better response (evidence available only for TNFi).[37] It is therefore advisable to

encourage patients to stop smoking.[101] If the clinical response is sustained over time, tapering bDMARD (evidence available only for TNFi) can be considered to minimise side effects and costs. Tapering may be successful but stopping usually result in flares in a large proportion of patients.[134] The main factor determining the success of tapering is longer time in remission or low disease activity prior to dose reduction. However, discontinuation of bDMARDs is not recommended, as this leads to disease flare in most patients.[135] Nevertheless, if for any reason, such as surgery or pregnancy, discontinuation is temporarily required, evidence supports that the likelihood of achieving a similar response after restarting is very high.[136]

In case the first bDMARD fails, it is recommended to switch to a second bDMARD, either TNFi or IL-17i. No strategy (switching target or cycling) is preferred but so far, most studies included patients who switched either from a first TNFi to a second/third TNFi or from a TNFi to an IL-17i.[119 122 137] Further evidence is required to determine which is the best strategy. In addition, the place of JAKi in the management algorithm needs to be defined.

The effect of different therapies on structural damage progression (assessed by spinal radiographs) in axSpA is controversial. Initial studies showed that continuous administration of NSAIDs could slow the progression of structural damage, especially in patients with syndesmophytes and elevated CRP.[138 139] However, another trial has not confirmed these data.[140] With TNFi, the opposite was true: pivotal studies did not show inhibition of structural damage while later studies suggest they might have a protective effect, mainly after long-term treatment by controlling disease activity.[141–143] But this remains an open question.[144] Finally, recent trials with TNFi and IL-17i have shown that only a minority of patients progress in the short term.[119 122] However, to date, there is no head-to-head study to compare the results between the different drugs. Future studies are expected to clarify the effect of the different therapies on the progression of structural damage. But in the meantime, causal inference analysis using observational data may contribute to a better understanding of whether disease modification is possible in axSpA.[145]

Finally, when managing patients with axSpA, it is relevant to consider the ASAS Quality Standards.[146] These comprehend an initial and thereafter annual review of all aspects of the disease.

This includes assessment of the patients in terms of current disease management, and any further support they may need in the future, in order to maximise health, participation in society and life satisfaction. Focus should not only be on clinical symptoms and severity of disease but also on comorbidities such as cardiovascular risk management or osteoporosis, employment, psychological factors and lifestyle including physical activity. Ideally, this review is performed by a multidisciplinary team under the supervision of a rheumatologist (figure 7).

RESEARCH AGENDA

In recent years, enormous advances in the understanding and management of axSpA occurred but still relevant unmet needs are to be resolved.[147] In the future, further efforts should be made in identifying the disease at an early stage. This starts with increasing the awareness of primary care physicians and other specialists treating patients with CBP. The optimisation of the use of imaging and other biomarkers for early diagnosis is likely to also play a role. A better understanding of the overlap and differences between axSpA and other phenotypes of SpA such as pSpA and psoriatic arthritis should be clarified.

Efforts to further improve the standardisation of instruments to monitor the disease and treatment response are required. In clinical practice, the implementation of more recent developed instruments such as the ASDAS is needed. In addition, the employment of mobile devices to manage the disease should be explored. For research, the updated ASAS-OMERACT core set will consider the new advances.

The development of new drugs against known and new targets is also required to successfully treat those patients who fail to current available drugs. In this sense, the management recommendations should be updated in order to incorporate new drugs, especially JAKi.

SEARCH STRATEGY AND SELECTION CRITERIA

Data for this review were identified by searches of MEDLINE, PubMed and references from relevant articles using the search terms "spondyloarthritis" or "ankylosing spondylitis", and "pathogenesis" or "diagnosis" or "classification" or "treatment" or "management" or "burden" or "work". Articles published in English until February 2021 were included. We largely selected publications in the past 4 years, 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 relevant.

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REFERENCES

1 Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017;390:73–84.
2 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361–8.
3 Maksymowych WP. The role of imaging in the diagnosis and management of axial spondyloarthritis. *Nat Rev Rheumatol* 2019;15:657–72.
4 Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum* 2005;52:1000–8.
5 Rudwaleit M, Landewé R, van der Heijde D, *et al*. The development of assessment of spondyloarthritis International Society classification criteria for axial spondyloarthritis (Part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770–6.
6 Rudwaleit M, van der Heijde D, Landewé R, *et al*. The development of assessment of spondyloarthritis International Society classification criteria for axial spondyloarthritis (Part II): validation and final selection. *Ann Rheum Dis* 2009;68:777–83.
7 Deodhar A, Reveille JD, van den Bosch F, *et al*. The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the assessment of spondyloarthritis International Society in response to the US food and drug administration's comments and concerns. *Arthritis Rheumatol* 2014;66:2649–56.
8 Sieper J, van der Heijde D. Review: Nonradiographic axial spondyloarthritis: new definition of an old disease? *Arthritis Rheum* 2013;65:543–51.
9 Brown MA. Human leucocyte antigen-B27 and ankylosing spondylitis. *Intern Med J* 2007;37:739–40.
10 Stolwijk C, van Onna M, Boonen A, *et al*. Global prevalence of spondyloarthritis: a systematic review and meta-regression analysis. *Arthritis Care Res* 2016;68:1320–31.
11 Bakland G, Alsing R, Singh K, *et al*. Assessment of spondyloarthritis International Society criteria for axial spondyloarthritis in chronic back pain patients with a high prevalence of HLA-B27. *Arthritis Care Res* 2013;65:448–53.
12 Costantino F, Talpin A, Said-Nahal R, *et al*. Prevalence of spondyloarthritis in reference to HLA-B27 in the French population: results of the GAZEL cohort. *Ann Rheum Dis* 2015;74:689–93.
13 Branco JC, Rodrigues AM, Gouveia N, *et al*. Prevalence of rheumatic and musculoskeletal diseases and their impact on health-related quality of life, physical function and mental health in Portugal: results from EpiReumaPt- a national health survey. *RMD Open* 2016;2:e000166.
14 Schett G, Lories RJ, D'Agostino M-A, *et al*. Enthesitis: from pathophysiology to treatment. *Nat Rev Rheumatol* 2017;13:731–41.
15 Watad A, Bridgewood C, Russell T, *et al*. The early phases of ankylosing spondylitis: emerging insights from clinical and basic science. *Front Immunol* 2018;9:2668.
16 Ellinghaus D, Jostins L, Spain SL, *et al*. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. *Nat Genet* 2016;48:510–8.
17 International Genetics of Ankylosing Spondylitis Consortium (IGAS), Cortes A, Hadler J, *et al*. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet* 2013;45:730–8.
18 Ruyssen-Witrand A, Luxembourger C, Cantagrel A, *et al*. Association between IL23R and ERAP1 polymorphisms and sacroiliac or spinal MRI inflammation in spondyloarthritis: DESIR cohort data. *Arthritis Res Ther* 2019;21:22.
19 Roberts AR, Vecellio M, Chen L, *et al*. An ankylosing spondylitis-associated genetic variant in the IL23R-IL12RB2 intergenic region modulates enhancer activity and is associated with increased Th1-cell differentiation. *Ann Rheum Dis* 2016;75:2150–6.
20 Evans DM, Spencer CCA, Pointon JJ, *et al*. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. *Nat Genet* 2011;43:761–7.
21 Ansell RC, Shuto T, Busquets-Perez N, *et al*. The role of biomechanical factors in ankylosing spondylitis: the patient's perspective. *Reumatismo* 2015;67:91–6.
22 Ramiro S, Landewé R, van Tubergen A, *et al*. Lifestyle factors may modify the effect of disease activity on radiographic progression in patients with ankylosing spondylitis: a longitudinal analysis. *RMD Open* 2015;1:e000153.
23 Van Praet L, Van den Bosch FE, Jacques P, *et al*. Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. *Ann Rheum Dis* 2013;72:414–7.
24 François RJ, Neure L, Sieper J, *et al*. Immunohistological examination of open sacroiliac biopsies of patients with ankylosing spondylitis: detection of tumour necrosis factor alpha in two patients with early disease and transforming growth factor beta in three more advanced cases. *Ann Rheum Dis* 2006;65:713–20.

25 Bollow M, Fischer T, Reisshauer H, *et al*. Quantitative analyses of sacroiliac biopsies in spondyloarthropathies: T cells and macrophages predominate in early and active sacroiliitis- cellularity correlates with the degree of enhancement detected by magnetic resonance imaging. *Ann Rheum Dis* 2000;59:135–40.

26 Poddubnyy D, Sieper J. Mechanism of new bone formation in axial spondyloarthritis. *Curr Rheumatol Rep* 2017;19:55.

27 Baraliakos X, Boehm H, Bahrami R, *et al*. What constitutes the fat signal detected by MRI in the spine of patients with ankylosing spondylitis? A prospective study based on biopsies obtained during planned spinal osteotomy to correct hyperkyphosis or spinal stenosis. *Ann Rheum Dis* 2019;78:1220–5.

28 van der Heijde D, Machado P, Braun J, *et al*. Mri inflammation at the vertebral unit only marginally predicts new syndesmophyte formation: a multilevel analysis in patients with ankylosing spondylitis. *Ann Rheum Dis* 2012;71:369–73.

29 Poddubnyy D, Protopopov M, Haibel H, *et al*. High disease activity according to the ankylosing spondylitis disease activity score is associated with accelerated radiographic spinal progression in patients with early axial spondyloarthritis: results from the German spondyloarthritis inception cohort. *Ann Rheum Dis* 2016;75:2114–8.

30 Poddubnyy D, Rudwaleit M, Haibel H, *et al*. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011;70:1369–74.

31 Ramiro S, van der Heijde D, van Tubergen A, *et al*. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. *Ann Rheum Dis* 2014;73:1455–61.

32 Dougados M, Sepriano A, Molto A, *et al*. Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort. *Ann Rheum Dis* 2017;76:1823–8.

33 Maksymowych WP, Chiowchanwisawakit P, Clare T, *et al*. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. *Arthritis Rheum* 2009;60:93–102.

34 Baraliakos X, Heldmann F, Callhoff J, *et al*. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? a long-term observational study using MRI and conventional radiography. *Ann Rheum Dis* 2014;73:1819–25.

35 Sepriano A, Ramiro S, Landewé R, *et al*. Is active sacroiliitis on MRI associated with radiographic damage in axial spondyloarthritis? real-life data from the ASAS and DESIR cohorts. *Rheumatology* 2019;58:798–802.

36 Machado PM, Baraliakos X, van der Heijde D, *et al*. Mri vertebral corner inflammation followed by fat deposition is the strongest contributor to the development of new bone at the same vertebral corner: a multilevel longitudinal analysis in patients with ankylosing spondylitis. *Ann Rheum Dis* 2016;75:1486–93.

37 Callhoff J, Sieper J, Weiß A, *et al*. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. *Ann Rheum Dis* 2015;74:1241–8.

38 Sieper J, Poddubnyy D, Miossec P. The IL-23-IL-17 pathway as a therapeutic target in axial spondyloarthritis. *Nat Rev Rheumatol* 2019;15:747–57.

39 Gravallese EM, Schett G. Effects of the IL-23-IL-17 pathway on bone in spondyloarthritis. *Nat Rev Rheumatol* 2018;14:631–40.

40 Rudwaleit M, Metter A, Listing J, *et al*. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006;54:569–78.

41 Sieper J, van der Heijde D, Landewé R, *et al*. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the assessment of spondyloarthritis International Society (ASAS). *Ann Rheum Dis* 2009;68:784–8.

42 van den Berg R, de Hooge M, Rudwaleit M, *et al*. ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis* 2013;72:1646–53.

43 Wang R, Crowson CS, Wright K, *et al*. Clinical evolution in patients with new-onset inflammatory back pain: a population-based cohort study. *Arthritis Rheumatol* 2018;70:1049–55.

44 Machado P, Landewé R, Braun J, *et al*. A stratified model for health outcomes in ankylosing spondylitis. *Ann Rheum Dis* 2011;70:1758–64.

45 Fongen C, Dagfinrud H, Berg IJ, *et al*. Frequency of impaired spinal mobility in patients with chronic back pain compared to patients with early axial spondyloarthritis. *J Rheumatol* 2018;45:1643–50.

46 de Winter JJ, van Mens LJ, van der Heijde D, *et al*. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis Res Ther* 2016;18:196.

47 Rademacher J, Poddubnyy D, Pleyer U. Uveitis in spondyloarthritis. *Ther Adv Musculoskelet Dis* 2020;12:1759720X20951733.

48 Stolwijk C, van Tubergen A, Castillo-Ortiz JD, *et al*. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:65–73.

49 Spoorenberg A, van der Heijde D, de Klerk E, *et al*. Relative value of erythrocyte sedimentation rate and C-reactive protein in assessment of disease activity in ankylosing spondylitis. *J Rheumatol* 1999;26:980–4.

50 Lambert RGW, Bakker PAC, van der Heijde D, *et al*. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI Working group. *Ann Rheum Dis* 2016;75:1958–63.

51 de Hooge M, van den Berg R, Navarro-Compán V, *et al*. Patients with chronic back pain of short duration from the space cohort: which MRI structural lesions in the sacroiliac joints and inflammatory and structural lesions in the spine are most specific for axial spondyloarthritis? *Ann Rheum Dis* 2016;75:1308–14.

52 Weber U, Lambert RGW, Østergaard M, *et al*. The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. *Arthritis Rheum* 2010;62:3048–58.

53 Maksymowych WP, Lambert RG, Østergaard M, *et al*. MRI lesions in the sacroiliac joints of patients with spondyloarthritis: an update of definitions and validation by the ASAS MRI Working group. *Ann Rheum Dis* 2019;78:1550–8.

54 Ortolan A, van Lunteren M, Ramiro S, *et al*. Are gender-specific approaches needed in diagnosing early axial spondyloarthritis? data from the spondyloarthritis caught early cohort. *Arthritis Res Ther* 2018;20:218.

55 Coates LC, Baraliakos X, Blanco FJ, *et al*. The phenotype of axial spondyloarthritis: is it dependent on HLA-B27 status? *Arthritis Care Res* 2021;73:856–60.

56 Arévalo M, Gratacós Masmitjà J, Moreno M, *et al*. Influence of HLA-B27 on the ankylosing spondylitis phenotype: results from the REGISPONSER database. *Arthritis Res Ther* 2018;20:221.

57 Rusman T, van Bentum RE, van der Horst-Bruinsma IE. Sex and gender differences in axial spondyloarthritis: myths and truths. *Rheumatology* 2020;59:iv38–46.

58 López-Medina C, Dougados M, Ruyssen-Witrand A, *et al*. Evaluation of concomitant peripheral arthritis in patients with recent onset axial spondyloarthritis: 5-year results from the DESIR cohort. *Arthritis Res Ther* 2019;21:139.

59 López-Medina C, Moltó A, Dougados M. Peripheral manifestations in spondyloarthritis and their effect: an ancillary analysis of the ASAS-COMOSPA study. *J Rheumatol* 2020;47:211–7.

60 Rudwaleit M, Feldtkeller E, Sieper J. Easy assessment of axial spondyloarthritis (early ankylosing spondylitis) at the bedside. *Ann Rheum Dis* 2006;65:1251–2.

61 Bakker PAC, Ramiro S, Ez-Zaitouni Z, *et al*. Is it useful to repeat magnetic resonance imaging of the Sacroiliac joints after three months or one year in the diagnosis of patients with chronic back pain and suspected axial spondyloarthritis? *Arthritis Rheumatol* 2019;71:382–91.

62 van Lunteren M, van der Heijde D, Sepriano A, *et al*. Is a positive family history of spondyloarthritis relevant for diagnosing axial spondyloarthritis once HLA-B27 status is known? *Rheumatology* 2019;58:1649–54.

63 de Hooge M, van Gaalen FA, Renson T, *et al*. Low specificity but high sensitivity of inflammatory back pain criteria in rheumatology settings in Europe: confirmation of findings from a German cohort study. *Ann Rheum Dis* 2019;78:1605–6.

64 Feldtkeller E, Khan MA, van der Heijde D, *et al*. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003;23:61–6.

65 van den Berg R, Lenczner G, Feydy A, *et al*. Agreement between clinical practice and trained central reading in reading of sacroiliac joints on plain pelvic radiographs. results from the DESIR cohort. *Arthritis Rheumatol* 2014;66:2403–11.

66 Lukas C, Cyteval C, Dougados M, *et al*. MRI for diagnosis of axial spondyloarthritis: major advance with critical limitations 'Not everything that glisters is gold (standard)'. *RMD Open* 2018;4:e000586.

67 de Winter J, de Hooge M, van de Sande M, *et al*. Magnetic resonance imaging of the Sacroiliac joints indicating sacroiliitis according to the assessment of spondyloarthritis International Society definition in healthy individuals, runners, and women with postpartum back pain. *Arthritis Rheumatol* 2018;70:1042–8.

68 Landewé RBM. Overdiagnosis and overtreatment in rheumatology: a little caution is in order. *Ann Rheum Dis* 2018;77:1394–6.

69 Sepriano A, Ramiro S, van der Heijde D, *et al*. What is axial spondyloarthritis? A latent class and transition analysis in the space and DESIR cohorts. *Ann Rheum Dis* 2020;79:324–31.

70 Jones A, Bray TJP, Mandl P, *et al*. Performance of magnetic resonance imaging in the diagnosis of axial spondyloarthritis: a systematic literature review. *Rheumatology* 2019;58:1955–65.

71 Mandl P, Navarro-Compán V, Terslev L, *et al*. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Ann Rheum Dis* 2015;74:1327–39.

72 Jovaní V, Blasco-Blasco M, Ruiz-Cantero MT, *et al*. Understanding how the diagnostic delay of spondyloarthritis differs between women and men: a systematic review and Metaanalysis. *J Rheumatol* 2017;44:174–83.

73 Garrido-Cumbrera M, Poddubnyy D, Gossec L, *et al*. Gender differences in patient journey to diagnosis and disease outcomes: results from the European map of axial spondyloarthritis (EMAS). *Clin Rheumatol* 2021;40:2753-2761.

74 Abawi O, van den Berg R, van der Heijde D, *et al*. Evaluation of multiple referral strategies for axial spondyloarthritis in the spondyloarthritis caught early (space) cohort. *RMD Open* 2017;3:e000389.

75 Poddubnyy D, van Tubergen A, Landewé R, et al. Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. *Ann Rheum Dis* 2015;74:1483–7.

76 Bautista-Molano W, Navarro-Compán V, Landewé RBM, et al. How well are the ASAS/OMERACT core outcome sets for ankylosing spondylitis implemented in randomized clinical trials? A systematic literature review. *Clin Rheumatol* 2014;33:1313–22.

77 Navarro-Compán V. An update on diagnosis and classification of axial spondyloarthritis. *Curr Rheumatol Rep* 2019;21:39.

78 Sepriano A, Rubio R, Ramiro S, et al. Performance of the ASAS classification criteria for axial and peripheral spondyloarthritis: a systematic literature review and meta-analysis. *Ann Rheum Dis* 2017;76:886–90.

79 Landewé RB, van der Heijde DM. Why caps criteria are not diagnostic criteria? *Ann Rheum Dis* 2017;76:e7.

80 Dubreuil M, Deodhar AA. Axial spondyloarthritis classification criteria: the debate continues. *Curr Opin Rheumatol* 2017;29:317–22.

81 Landewé R, van Tubergen A. Clinical tools to assess and monitor spondyloarthritis. *Curr Rheumatol Rep* 2015;17:47.

82 Sieper J, Rudwaleit M, Baraliakos X, et al. The assessment of spondyloarthritis International Society (ASAS) Handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68 Suppl 2:ii1–44.

83 Ogdie A, Duarte-García A, Hwang M, et al. Measuring outcomes in axial spondyloarthritis. *Arthritis Care Res* 2020;72 Suppl 10:47–71.

84 Landewé RBM, van der Heijde D. Use of multidimensional composite scores in rheumatology: parsimony versus subtlety. *Ann Rheum Dis* 2021;80:280–5.

85 Lukas C, Landewé R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:18–24.

86 Machado PM, Landewé R, Heijde Dvander, et al. Ankylosing spondylitis disease activity score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis* 2018;77:1539–40.

87 Machado P, Navarro-Compán V, Landewé R, et al. Calculating the ankylosing spondylitis disease activity score if the conventional C-reactive protein level is below the limit of detection or if high-sensitivity C-reactive protein is used: an analysis in the DESIR cohort. *Arthritis Rheumatol* 2015;67:408–13.

88 Molto A, Gossec L, Meghnathi B, et al. An Assessment in SpondyloArthritis International Society (ASAS)-endorsed definition of clinically important worsening in axial spondyloarthritis based on ASDAS. *Ann Rheum Dis* 2018;77:124–7.

89 Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international Task force. *Ann Rheum Dis* 2018;77:3–17.

90 van der Heijde D, Calin A, Dougados M, et al. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. progress report of the ASAS Working Group. assessments in ankylosing spondylitis. *J Rheumatol* 1999;26:951–4.

91 Navarro-Compán V, Boel A, Boonen A, et al. The ASAS-OMERACT core domain set for axial spondyloarthritis. *Semin Arthritis Rheum* 2021. doi:10.1016/j.semarthrit.2021.07.021. [Epub ahead of print: 01 Aug 2021].

92 Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath ankylosing spondylitis functional index. *J Rheumatol* 1994;21:2281–5.

93 Ramiro S, van Tubergen A, Stolwijk C, et al. Reference intervals of spinal mobility measures in normal individuals: the mobility study. *Ann Rheum Dis* 2015;74:1218–24.

94 Kiltz U, van der Heijde D, Boonen A, et al. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. *Ann Rheum Dis* 2015;74:830–5.

95 Lukas C, Braun J, van der Heijde D, et al. Scoring inflammatory activity of the spine by magnetic resonance imaging in ankylosing spondylitis: a multireader experiment. *J Rheumatol* 2007;34:862–70.

96 Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005;53:502–9.

97 Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005;53:703–9.

98 Garrido-Cumbrera M, Poddubnyy D, Gossec L, et al. The European map of axial spondyloarthritis: capturing the patient Perspective-an analysis of 2846 patients across 13 countries. *Curr Rheumatol Rep* 2019;21:19.

99 Garrido-Cumbrera M, Bundy C, Navarro-Compán V, et al. Patient-Reported impact of axial spondyloarthritis on working life: results from the EMAS survey. *Arthritis Care Res* 2020. doi:10.1002/acr.24426. [Epub ahead of print: 19 Aug 2020].

100 López-Medina C, Ramiro S, van der Heijde D, et al. Characteristics and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis: a comparison by systematic literature review and meta-analysis. *RMD Open* 2019;5:e001108.

101 van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017;76:978–91.

102 Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis association of America/Spondyloarthritis research and treatment network recommendations for the treatment of ankylosing spondylitis and Nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2019;71:1599–613.

103 Perrotta FM, Lories R, Lubrano E. To move or not to move: the paradoxical effect of physical exercise in axial spondyloarthritis. *RMD Open* 2021;7:e001480.

104 Kroon FPB, van der Burg LRA, Ramiro S, et al. Nonsteroidal antiinflammatory drugs for axial spondyloarthritis: a cochrane review. *J Rheumatol* 2016;43:607–17.

105 Kristensen LE, Jakobsen AK, Askling J, et al. Safety of etoricoxib, celecoxib, and nonselective nonsteroidal antiinflammatory drugs in ankylosing spondylitis and other spondyloarthritis patients: a Swedish national population-based cohort study. *Arthritis Care Res* 2015;67:1137–49.

106 Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016;75:795–810.

107 Harbord M, Annese V, Vavricka SR, et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016;10:239–54.

108 Regel A, Sepriano A, Baraliakos X, et al. Efficacy and safety of non-pharmacological and non-biological pharmacological treatment: a systematic literature review Informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. *RMD Open* 2017;3:e000397.

109 Gratacós J, Moreno Martínez-Losa M, Font P, et al. Etoricoxib in ankylosing spondylitis: is there a role for active patients refractory to traditional NSAIDs? *Clin Exp Rheumatol* 2016;34:94–9.

110 Sepriano A, Regel A, van der Heijde D, et al. Efficacy and safety of biological and targeted-synthetic DMARDs: a systematic literature review Informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. *RMD Open* 2017;3:e000396.

111 Davis JC, Van Der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003;48:3230–6.

112 Song I-H, Weiß A, Hermann K-GA, et al. Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. *Ann Rheum Dis* 2013;72:823–5.

113 van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006;54:2136–46.

114 Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013;72:815–22.

115 Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study. *Ann Rheum Dis* 2014;73:39–47.

116 Inman RD, Davis JC, Heijde Dvander, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008;58:3402–12.

117 Sieper J, van der Heijde D, Dougados M, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2015;67:2702–12.

118 Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002;359:1187–93.

119 Baeten D, Sieper J, Braun J, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med* 2015;373:2534–48.

120 Deodhar A, Blanco R, Dokoupilová E, et al. Improvement of signs and symptoms of Nonradiographic axial spondyloarthritis in patients treated with Secukinumab: primary results of a randomized, placebo-controlled phase III study. *Arthritis Rheumatol* 2021;73:110–20.

121 van der Heijde D, Cheng-Chung Wei J, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet* 2018;392:2441–51.

122 Dougados M, Wei JC-C, Landewé R, et al. Efficacy and safety of ixekizumab through 52 weeks in two phase 3, randomised, controlled clinical trials in patients with active radiographic axial spondyloarthritis (COAST-V and COAST-W). *Ann Rheum Dis* 2020;79:176–85.

123 Deodhar A, van der Heijde D, Gensler LS, et al. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. *Lancet* 2020;395:53–64.

124 van der Heijde D, Gensler LS, Deodhar A, et al. Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis:

results from a 48-week phase IIb, randomised, double-blind, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2020;79:595–604.

125 Song I-H, Heldmann F, Rudwaleit M, *et al*. Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study. *Ann Rheum Dis* 2011;70:1108–10.

126 Song I-H, Heldmann F, Rudwaleit M, *et al*. One-Year follow-up of ankylosing spondylitis patients responding to rituximab treatment and re-treated in case of a flare. *Ann Rheum Dis* 2013;72:305–6.

127 Sieper J, Porter-Brown B, Thompson L, *et al*. Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results of randomised, placebo-controlled trials. *Ann Rheum Dis* 2014;73:95–100.

128 Sieper J, Braun J, Kay J, *et al*. Sarilumab for the treatment of ankylosing spondylitis: results of a phase II, randomised, double-blind, placebo-controlled study (align). *Ann Rheum Dis* 2015;74:1051–7.

129 Deodhar A, Gensler LS, Sieper J, *et al*. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol* 2019;71:258–70.

130 van der Heijde D, Song I-H, Pangan AL, *et al*. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. *Lancet* 2019;394:2108–17.

131 van der Heijde D, Deodhar A, Wei JC, *et al*. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2017;76:1340–7.

132 van der Heijde D, Baraliakos X, Gensler LS, *et al*. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392:2378–87.

133 Navarro-Compán V, Plasencia-Rodríguez C, de Miguel E, *et al*. Switching biological disease-modifying antirheumatic drugs in patients with axial spondyloarthritis: results from a systematic literature review. *RMD Open* 2017;3:e000524.

134 Landewé RB, van der Heijde D, Dougados M, *et al*. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. *Ann Rheum Dis* 2020;79:920–8.

135 Landewé R, Sieper J, Mease P, *et al*. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. *Lancet* 2018;392:134–44.

136 Navarro-Compán V, Plasencia-Rodríguez C, de Miguel E, *et al*. Anti-Tnf discontinuation and tapering strategies in patients with axial spondyloarthritis: a systematic literature review. *Rheumatology* 2016;55:1188–94.

137 Micheroli R, Tellenbach C, Scherer A, *et al*. Effectiveness of secukinumab versus an alternative TNF inhibitor in patients with axial spondyloarthritis previously exposed to TNF inhibitors in the Swiss clinical quality management cohort. *Ann Rheum Dis* 2020;79:1203–9.

138 Wanders A, Heijde Dvander, Landewé R, *et al*. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum* 2005;52:1756–65.

139 Kroon F, Landewé R, Dougados M, *et al*. Continuous NSAID use reverts the effects of inflammation on radiographic progression in patients with ankylosing spondylitis. *Ann Rheum Dis* 2012;71:1623–9.

140 Sieper J, Listing J, Poddubnyy D, *et al*. Effect of continuous versus on-demand treatment of ankylosing spondylitis with diclofenac over 2 years on radiographic progression of the spine: results from a randomised multicentre trial (ENRADAS). *Ann Rheum Dis* 2016;75:1438–43.

141 Karmacharya P, Duarte-Garcia A, Dubreuil M, *et al*. Effect of therapy on radiographic progression in axial spondyloarthritis: a systematic review and meta-analysis. *Arthritis Rheumatol* 2020;72:733–49.

142 Sepriano A, Ramiro S, Wichuk S, *et al*. Disease activity is associated with spinal radiographic progression in axial spondyloarthritis independently of exposure to tumour necrosis factor inhibitors. *Rheumatology* 2021;60:461–2.

143 Boers N, Michielsens CAJ, van der Heijde D, *et al*. The effect of tumour necrosis factor inhibitors on radiographic progression in axial spondyloarthritis: a systematic literature review. *Rheumatology* 2019;58:1907–22.

144 van der Heijde D, Landewé R. Inhibition of spinal bone formation in AS: 10 years after comparing adalimumab to OASIS. *Arthritis Res Ther* 2019;21:225.

145 Sepriano A, Ramiro S, van der Heijde D, *et al*. Biological DMARDs and disease modification in axial spondyloarthritis: a review through the lens of causal inference. *RMD Open* 2021;7:e001654.

146 Kiltz U, Landewé RBM, van der Heijde D, *et al*. Development of ASAS quality Standards to improve the quality of health and care services for patients with axial spondyloarthritis. *Ann Rheum Dis* 2020;79:193–201.

147 Winthrop KL, Weinblatt ME, Bathon J, *et al*. Unmet need in rheumatology: reports from the targeted therapies meeting 2019. *Ann Rheum Dis* 2020;79:88–93.