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Current Concepts and Medical Management for Patients with Radiographic Axial Spondyloarthritis

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Radiographic axial spondyloarthritis (r-axSpA), a chronic inflammatory disease, can cause significant radiographic damage to the axial skeleton. Regarding the pathogenic mechanism, association of r-axSpA with tumor necrosis factor (TNF) and the interleukin-23/17 (IL23/IL17) pathway has been reported. Development of extraarticular manifestations, including uveitis, inflammatory bowel disease, and psoriasis, has been reported in some patients. The pivotal role of human leukocyte antigen-B27 in the pathogenesis of r-axSpA remains to be clarified. Symptoms usually start in late adolescence or early adulthood, and disease progression can vary in each patient, with clinical manifestations ranging from mild joint stiffness without radiographic changes to advanced manifestations including complete fusion of the spine, and severe arthritis of the hip, and could include peripheral arthritis and extraarticular manifestations. The modified New York criteria was used previously in diagnosis of r-axSpA. However, early diagnosis of the disease prior to development of bone deformity was required due to development of biological agents. As a result of Assessment of SpondyloArthritis international Society (ASAS), the classification was improved in part for diagnosis of spondyloarthritis prior to development of bone deformity. The diagnosis is based on comprehensive laboratory findings, physical examinations, and radiologic findings. Medical treatment for r-axSpA involves the use of a stepwise strategy, starting with administration of nonsteroidal anti-inflammatory drugs and physiotherapy, and progressing to sulfasalazine or methotrexate and biologics including TNF-α inhibitors or IL-17 inhibitors as needed. Use of Janus kinase inhibitors has been recently reported.

Keywords: Ankylosing spondylitis, Axial spondyloarthritis

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OVERVIEW

Spondyloarthritis (SpA) is an umbrella term that includes axial SpA (axSpA), psoriatic arthritis, reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD), and undifferentiated SpA[1].

AxSpA, a chronic systemic inflammatory disease, can cause inflammation of the axial skeleton[2], resulting in structural damage, which can lead to reduced quality of life[3]. Involvement of peripheral joints and extraarticular organs has also been reported[4].

AxSpA patients include those with definite radiographic sacroiliitis meeting the modified New York criteria, classified as radiographic axSpA (r-axSpA), classically termed ankylosing spondylitis (AS), and those without definite radiographic sacroiliitis confirmed by conventional pelvic X-ray but showing sacroiliitis by magnetic resonance imaging (MRI) classified as nonradiographic axSpA (nr-axSpA)[5].

EPIDEMIOLOGY

According to a study using the Korean Health Insurance Review Agency database, the estimated prevalence of r-axSpA increased from 31.6 per 100,000 in 2010 to 52.3 in 2015. The incidence of r-axSpA also increased from 5.7 per 100,000 person-years in 2010 to 7.9 in 2015[6,7]. The reported prevalence of r-axSpA in Korea is almost the same as that reported in Japan, 0.04%[8]. However, the estimated prevalence reported in Korea is lower than that for other parts of Asia, with a reported prevalence ranging from 3.0 to 33.7 per 10,000 persons[9,10].

PATHOGENESIS

r-axSpA is a chronic auto inflammatory disease rather than an antigen-specific autoimmune disease. The primary site of disease development has not been determined[11]. The function of several cytokines including tumor necrosis factor (TNF) and interleukin-23/17 (IL23/IL17), which is critical in the pathogenesis of r-axSpA, has also been associated with the pathogenesis of IBD and psoriasis. In mice, tissue resident thymus-dependent γ/δ T cells expressing IL-23 receptors are located at entheses, in the aortic root, and near the ciliary body located in the eye. This finding suggests that site specific immune cells have a critical function in the anatomic specificity of these lesions (Fig. 1)[12]. The most consistently associated genes are all related to the IL-23 pathway (IL-12B, IL-23R, IL-27, TYK-2, and JAK-2). IL-23 is a heterodimeric cytokine composed of the IL-12B (IL-12p40) subunit shared with IL-12 and the IL-23A (IL-23p19) subunit with specificity to IL-23[11]. IL-23 signaling occurs by way of the Janus kinase (JAK)2 and Tyk2. IL-23 dependent immunity was blocked by inhibition of Tyk2 in a mouse model and is considered protective against r-axSpA.

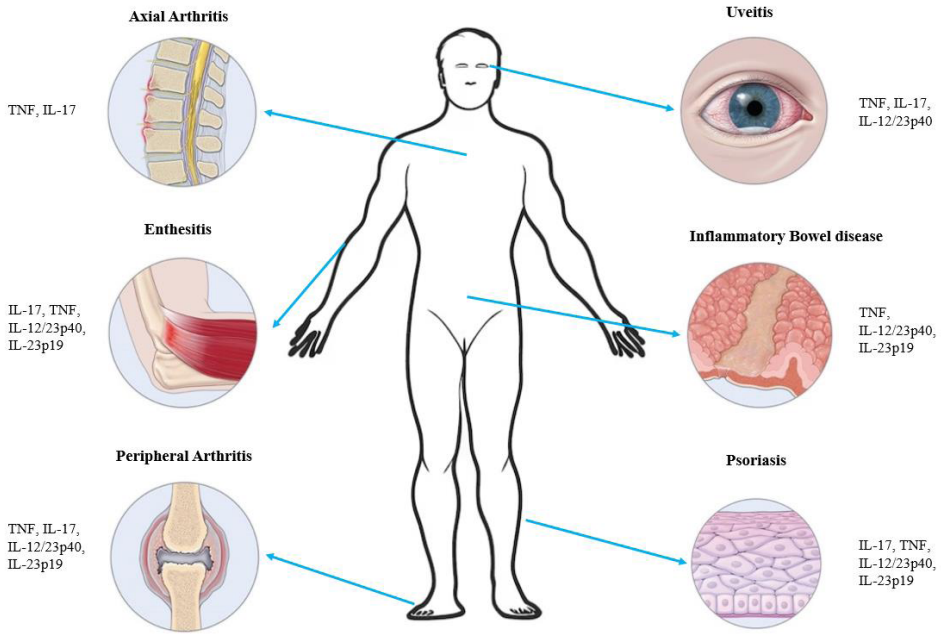

Fig. 1. Proposed hierarchy of cytokine participation in disease pathogenesis in affected tissues in spondyloarthritis, based on the therapeutic response in clinical trials for biologic agents targeting the indicated cytokines[12]. TNF: tumor necrosis factor, IL: interleukin.

Although human leukocyte antigen (HLA)-B27 is known to play a direct role in the pathogenesis of r-axSpA, its precise role remains undetermined[13]. The reported association of r-axSpA with ERAP (endoplasmic reticulum aminopeptidase)1 and ERAP2, which have a strong influence on the major histocompatibility complex class I (MHC class I) peptide group, suggests the importance of peptide binding to B27[14]. Increased levels of CD8+ T cells have been detected in synovial fluid in r-axSpA patients; however, their function in the pathogenesis of r-axSpA remains unclear. Genetic and functional studies have suggested a role for activation of natural killer cells in r-axSpA, possibly through interaction with HLA-B27 heavy chain[15]. Enthesitis observed in patients with r-axSpA can also affect healthy individuals due to repetitive mechanical strain at a particular anatomic site. Thus, it is believed that the threshold for strain-induced entheseal inflammation is lowered by genetic factors and microbial products, resulting in development of widespread, chronic lesions at entheseal sites subjected only to normal use.

Formation of new bone in patients with r-axSpA appears to be a result of enchondral bone formation and occurs only in the periosteal compartment. Development of syndesmophytes is likely in patients with high levels of inflammatory markers and inflammation at vertebral corners on MRI[16]. Therefore, spinal fusion may be reduced with administration of early and prolonged anti-TNF therapy. However, vertebral inflammatory lesions that undergo metaplasia to fat are a preferred site of subsequent syndesmophyte formation despite anti-TNF therapy, whereas early acute inflammatory lesions are resolved, placing emphasis on the importance of early treatment for management of inflammation[17,18].

Because development of r-axSpA can occur after a preceding condition (ReA) or in the context of IBD and exposure to bacteria, systemic inflammation, dysbiosis, and increased intestinal permeability can lead to formation of an amplification loop capable of driving sustained inflammation in SpA.

CLINICAL MANIFESTATIONS

Inflammation, which usually starts in the sacroiliac joints, lasting a few days to many weeks, may fluctuate from one side to the other at first, which some patients may describe as "alternating hip pain", prior to invading the spine. Chronic back pain and progressive stiffness of the spine are typically the first symptoms that cause patients to seek medical support. Symptoms usually develop slowly in late adolescence and early adulthood, and can be aggravated by physical inactivity or prolonged rest, which are usually relieved by exercise or hot showers[19]. Pain can be persistent early in the course of disease and intermittent later with alternating periods of exacerbation and quiescence. Development of symptoms after age 40 has been reported in 5% of patients[20].

Back pain or stiffness is often accompanied by bony tenderness, which can also be the predominant complaint. Direct pressure as well as stress on joints can elicit pain in the sacroiliac joints. Common sites include the costosternal junctions, spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, and heels[21].

Arthritis of the hip has been reported in 25%-35% of AS patients (Fig. 2). Severe isolated arthritis of the hip or bony chest pain may be the presenting complaint, and symptomatic hip disease may be a dominant clinical feature, particularly in patients with juvenile-onset disease. Arthritis of peripheral joints, which is usually asymmetric, may be diagnosed at any point in the disease course. Neck pain and stiffness due to cervical spine involvement may be later manifestations but are occasionally predominant symptoms. Chest pain, a common occurrence at any stage, can be confused with cardiovascular disease[22].

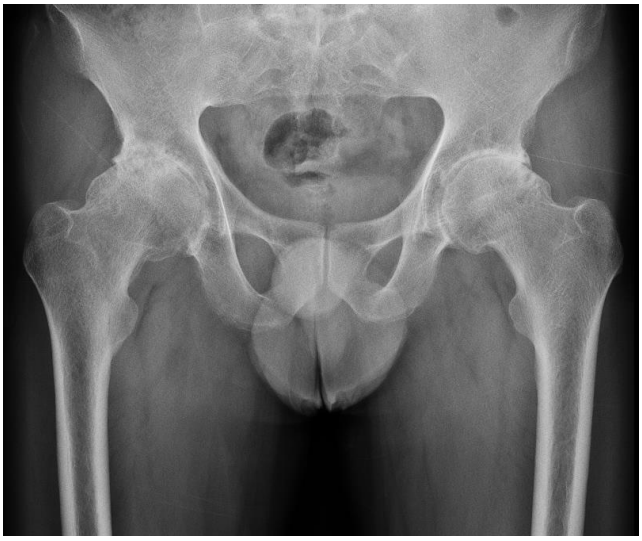

Fig. 2. Radiographs of severe arthritis of the hip with limited hip motion on both sides in a radiographic of axial spondyloarthritis.

The most specific findings include loss of spinal mobility, with limitation of anterior and lateral flexion and extension of the lumbar spine and chest expansion. Limitation of motion is usually not in proportion to the degree of bony ankylosis and may reflect muscle spasm secondary to pain and inflammation.

The disease course is variable, ranging from mild joint stiffness with normal radiographs to complete fusion of the spine and severe arthritis of the hip, and SpA can also affect peripheral joints and extraarticular organs. In a typical case with progression to formation of syndesmophytes, characteristic changes in posture may be observed, with obliterated lumbar lordosis, buttock atrophy, and accentuated thoracic kyphosis. Posing with a forward stoop of the neck or flexion contractures at the hips, compensated by flexion at the knees has been reported (Fig. 3). Disease progression can be estimated clinically based on loss of height, limitation of chest expansion and spinal flexion, and increasing occiput-to-wall distance.

Acute anterior uveitis, which has been reported in up to 50% of r-axSpA patients, is the most common extraarticular manifestation. The features include unilateral, photophobia, and pain with accommodation, which may recur in the opposite eye, and may be followed by cataracts and secondary glaucoma. In addition, inflammation in the colon or ileum, which is usually asymptomatic, has been reported in up to 60% of patients with AS; however, overt IBD has been reported in 5%-10% of patients with r-axSpA. Psoriasis has been reported in approximately 10% of r-axSpA patients. Patients with r-axSpA associated with skin manifestations observed in SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome, such as acne fulminans or hidradenitis suppurativa, have occasionally been reported. There is an apparent increase in the risk of ischemic heart disease. Aortic insufficiency has been reported in a small percentage of patients, usually in cases involving a longstanding disease. Third degree heart block may occur alone or together with aortic insufficiency. Rarely occurring late complications include cauda equina syndrome and fibrosis of the upper pulmonary lobe. Increased prevalence of prostatitis has been reported[23-25].

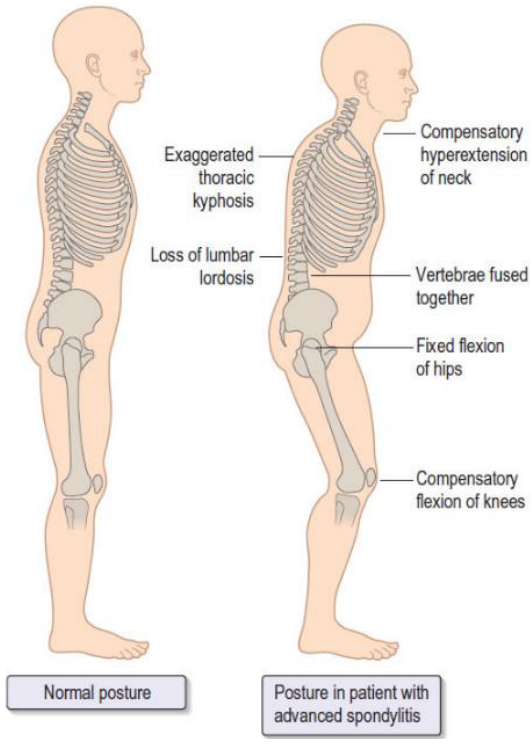

Fig. 3. Posture in patients with radiographic axial spondyloarthritis compared with that in a normal subject.

DIAGNOSIS

Establishment of clinical diagnostic criteria for AS has been attempted many times in recent decades. To date, there are no validated criteria for diagnosis of r-axSpA; we only have the classification (not diagnostic) criteria. Thus, the classification criteria are not sensitive enough for use in establishing the diagnosis of r-axSpA in a clinical setting[5,26-28].

The modified New York criteria published in 1984 were used previously for the diagnosis of AS (Table 1)[28]. The presence of radiographic sacroiliitis (at least either grade 2 bilaterally or grade 3 unilaterally) is required to satisfy these criteria, plus one clinical criterion: either morning stiffness showing improvement with exercise but not with rest or restriction of spinal mobility. However, diagnosis of both radiographic sacroiliitis and restriction of spinal mobility may be a relatively late occurrence during the course of the disease, therefore these criteria are not suitable for classification/diagnosis of early cases. In 2009, Assessment of SpondyloArthritis international Society (ASAS) criteria covering patients with and without radiographic changes in the sacroiliac joint was developed for diagnosis of axSpA (Table 2)[5]. These criteria should be applied in cases involving chronic back pain (>3 months) starting at an age younger than 45 years. Sacroiliitis on imaging re-

Table 1. Modified New York Diagnostic Criteria for Ankylosing Spondylitis

Clinical criteriag
1) Low back pain persisting for ≥3 months, reduced by exercise and not relieved by rest
2) Limited motion in the lumbar spine in coronal and sagittal planes
3) Limited chest expansion compared with normal values for age and sex
Radiologic criterion
Grade 3-4 unilateral or grade 2-4 bilateral sacroiliitis
- Definite ankylosing spondylitis: The radiologic criterion and ≥1 for clinical criteria are fulfilled.
- Probable ankylosing spondylitis: Three clinical criteria are fulfilled or the radiologic criterion alone is fulfilled.

Table 2. ASAS Criteria for Classification of Axial Spondyloarthritis*

Sacroiliitis on imaging plus ≥1 spondyloarthritis feature	or	HLA-B27 plus ≥2 other spondyloarthritis features
Sacroiliitis on imaging • Active (acute) inflammation on MRI highly suggestive of spondyloarthritis associated sacroiliitis and/or • Definite radiographic sacroiliitis according to modified New York criteria		Spondyloarthritis features • Inflammatory back pain • Arthritis • Enthesitis (heel) • Anterior uveitis • Dactylitis • Psoriasis • Crohn's disease or ulcerative colitis • Good response to NSAIDs • Family history of spondyloarthritis • HLA-B27 • Elevated CRP

ASAS: Assessment of SpondyloArthritis international Society, MRI: magnetic resonance imaging, HLA: human leukocyte antigen, NSAIDs: nonsteroidal anti-inflammatory drugs, CRP: C-reactive protein.
*For application in patients with back pain ≥3 months and age of onset <45 years.

mains important, not only when visible on radiographs but also when subchondral bone marrow edema can be observed as evidence of active bony inflammation on MRI.

LABORATORY FINDINGS

Laboratory tests alone are not sufficient for diagnosis of r-axSpA. A positive result for HLA-B27 has been reported in 75%-90% of patients. An increased erythrocyte sedimentation rate as well as the level of C-reactive protein is often, but not always, observed. Rheumatoid factor, anti-cyclic citrullinated protein, and antinuclear antibodies (ANAs) are generally absent unless caused by a coexistent disease, although appearance of ANAs may be observed with anti-TNF therapy. Circulating levels of CD8+ T cells tend to be low, and the levels of serum matrix metalloproteinase 3 show correlation with disease activity. Synovial fluid from peripheral joints is nonspecifically inflammatory. Ventilatory function is usually preserved despite restricted chest wall motion[29,30].

PHYSICAL EXAMINATIONS

1. The Modified Schober Test

This test is considered a useful measurement of lumbar spine flexion. When performing the original Schober test, the patient stands erect, with heels together, and marks are made on the spine at the lumbosacral junction and 10 cm above. The patient then bends forward maximally with knees fully extended, and the distance between the two marks is measured. This distance can increase by ≥5 cm with normal mobility (Fig. 4)[31,32]. In the modified Schober test, which was developed to address the challenge in precise localization of the lumbosacral junction, the patient is standing, while both the posterior and superior iliac spine are marked by the examiner; a horizontal line is then drawn at the center of both marks. A second line is marked 5 cm below the first line, and a third line is marked 10 cm above the first line. The patient is then instructed to flex forward as if attempting to touch his/her toes; the examiner then remeasures the distance between the top and bottom line, which can

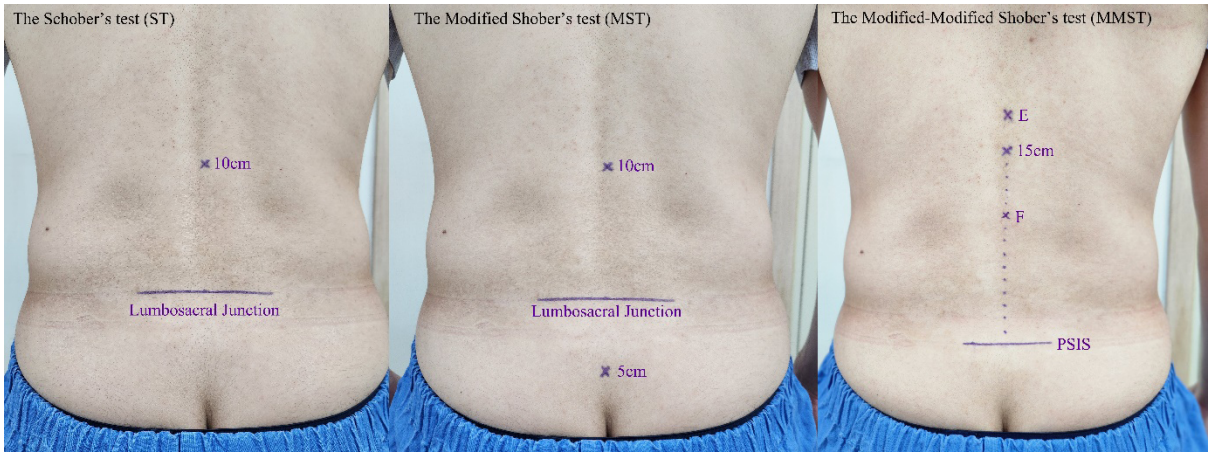

Fig. 4. Land-marking method for the Schober test (ST), the modified Schober's test (MST) and the modified-modified Schober's test (MMST)[32]. When using Shober's test, the range of spinal flexion is defined as the increase in the distance between the lumbosacral junction and a point located 10 cm above it. When using the MST, the reference point is located 10 cm above and 5 cm below the lumbosacral junction. When using the MMST, a line is drawn between two posterior superior iliac spines (PSIS) and a landmark on the spine at 15 cm to obtain the overall lumbar spine flexion. E: extension, F: flexion.

increase by ≥5 cm with normal mobility.

2. Chest Expansion

It can be defined as the difference between maximal inspiration and maximal forced expansion at the level of either the fourth intercostal space or the xiphisternum, with the patient's hands resting on or just behind the head. Normal chest expansion is ≥2.5 cm.

3. Lateral Bending

It can be defined as the distance traveled by the patient's middle finger down the leg with maximal lateral bending; >10 cm is considered normal[33].

4. Limitation or Pain with Motion of the Hips or Shoulders

This can be a typical presentation when these joints are involved.

Several validated measures of disease activity and functional outcome have been used extensively in the study and management of r-axSpA, particularly the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS), both measures of disease activity; the Bath Ankylosing Spondylitis Functional Index (BASFI), a measure of limitation in activities of daily living, as well as several measures of radiographic changes. The new ASAS Health Index is a SpA specific tool for assessing impairment of function and health[34,35].

RADIOLOGIC FINDINGS

In the sacroiliac joint, blurring of the cortical margins of the subchondral bone, followed by erosions and sclerosis are typically the earliest changes observed on standard radiography. Progression of erosions can lead to "pseudowidening" of the joint space; once fibrous, the joints may become obliterated[36].

In the lumbar spine, progression of the disease can lead to loss of lordosis, and osteitis of the anterior corners of the vertebral bodies with subsequent erosion, and formation of new bone causing "squaring" or even "barreling" of one or more vertebral bodies. Progressive ossification can lead to formation of marginal syndesmophytes, visible on plain films as bony bridges connecting successive vertebral bodies on the anterior and lateral side (Fig. 5)[37].

MRI protocols routinely used for evaluation of low back pain have low sensitivity for detecting inflammation, thus false negative results are often obtained when diagnosing axSpA. Visualization of active sacroiliitis is best achieved with use of dynamic MRI on semicoronal slices with fat saturation, either a T2-weighted turbo spin-echo sequence or short tau inversion recovery with high resolution, or T1-weighted images with contrast enhancement (Fig. 6). Use of these techniques can enable detection of early intraarticular inflammation, changes in cartilage, and underlying bone marrow edema in sacroiliitis. Bone marrow edema alone is not specific for axSpA. Specificity can be

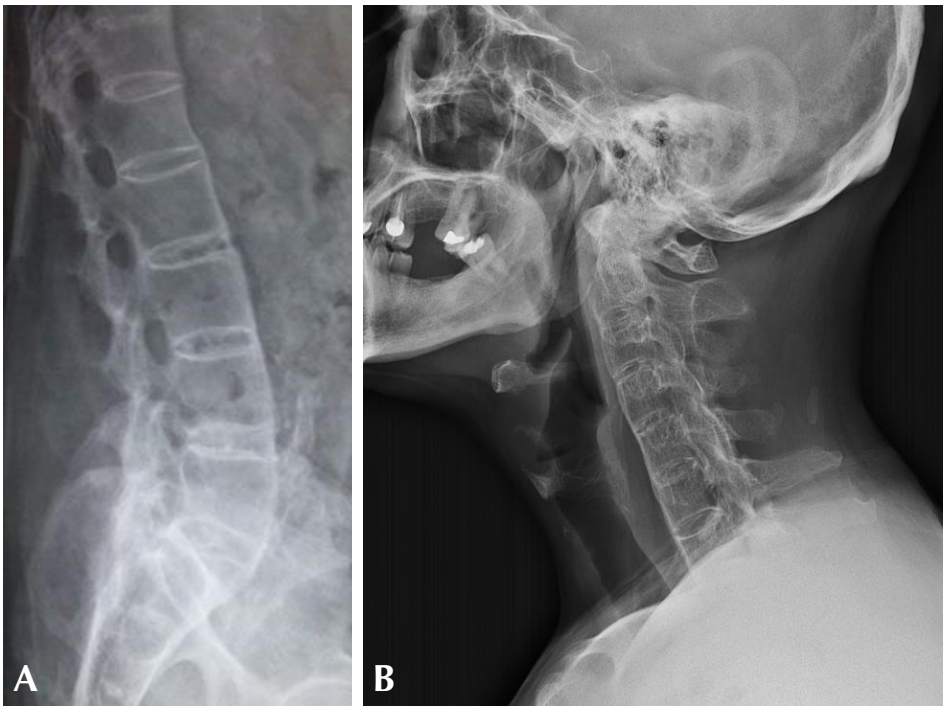

Fig. 5. Progressive ossification with marginal syndesmophytes as bony bridges connecting successive vertebral bodies on a simple X-ray. (A) Lumbar. (B) Cervical spine.

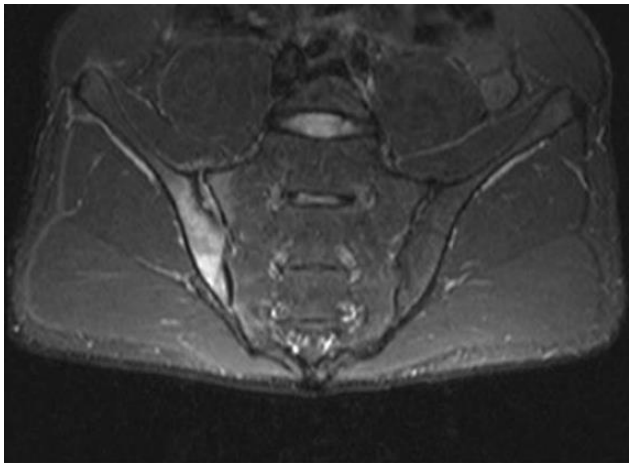

Fig. 6. Active sacroiliitis shown on a short tau inversion recovery magnetic resonance imaging sequence in the ileum and in the upper part of the sacrum of the right sacroiliac joint.

enhanced by the presence of erosions, which are best detected on conventional T1-weighted images[38,39].

DIFFERENTIAL DIAGNOSIS

Ankylosing hyperostosis, also known as Forestier disease or diffuse idiopathic skeletal hyperostosis, can cause excessive formation of new bone along the spine and other sites (Fig. 7). This can result in a stiff spine that may be confused with r-axSpA; however, it is usually observed in older patients. It is characterized by a flowing ligamentous ossification, particularly of the anterior longitudinal ligament, and the absence of typical sacroiliitis, although the clarity of the sacroiliac and facet joints may be diminished on radiographic images due to capsular ossification. Extraspinal involvement with hyperostosis such as olecranon, patella, calcaneus, shoulder, and acetabulum were also observed. Osteitis condensans ilii is another disease that should be distinguished (Fig. 8). This disease is characterized morphologically by sclerosis of the iliac side of the sacroiliac joints without cortical erosions or changes in joint space. This condition is most prevalent in perigestational or postpartum females, thus it was initially presumed that it was related to physiologic changes brought on by pregnancy. However, considerations include joint space widening and ligamentous laxity of the sacroiliac joints as well as no erosion or fusion in sacroiliac joints.

MANAGEMENT

Significant advancements in medical treatment of r-axSpA has resulted in improved outcomes, as well as enhanced quality of life for patients with r-axSpA[40-42]. The current approach involves the use of a stepwise medical strategy, starting with administration of non-

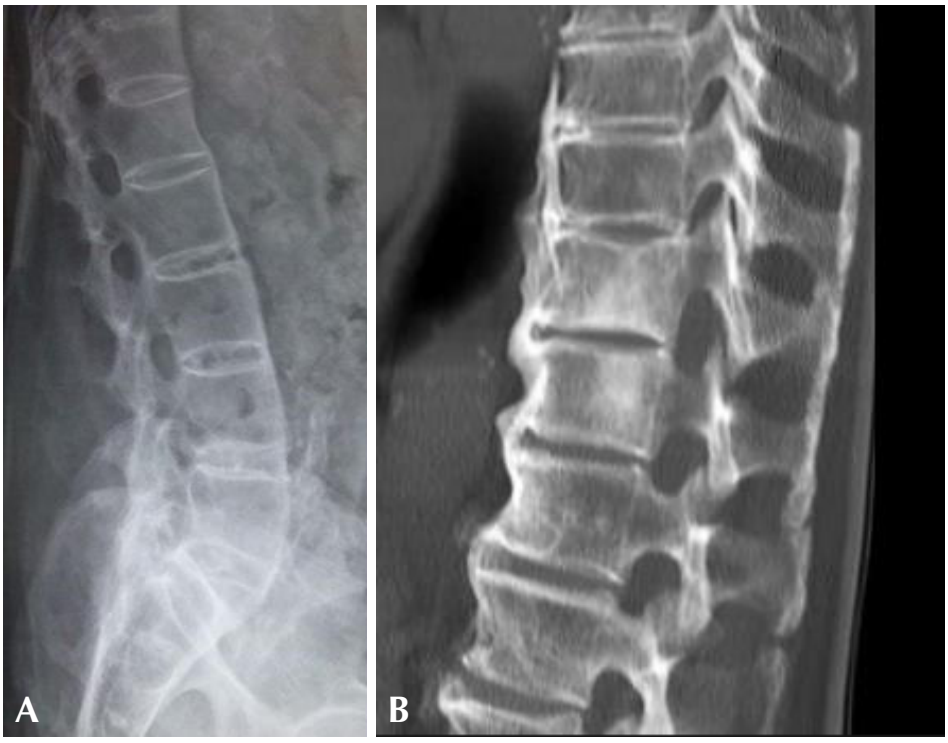

Fig. 7. Features observed on the spine between radiographic axial spondyloarthritis (A) and DISH (diffuse idiopathic skeletal hyperostosis) (B).

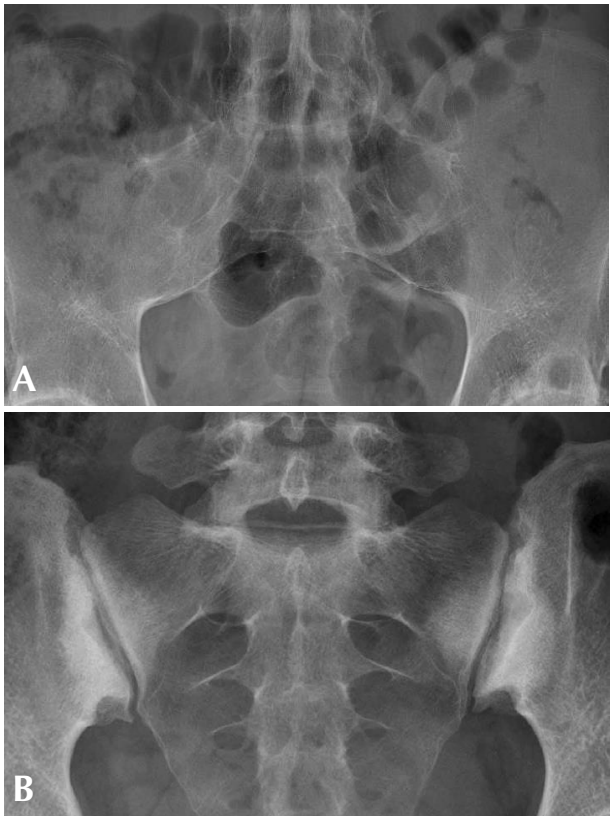

Fig. 8. Features observed in the sacroiliac joint between radiographic axial spondyloarthritis (A) and osteitis condensans ilii (B).

steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, and progressing to sulfasalazine (SSZ) or methotrexate (MTX) and biologics including TNF-α inhibitors (TNFi) or IL-17 inhibitors (IL-17i) as needed[7,43]. Research toward development of novel therapeutic targets and to examine the potential role of personalized medicine in optimizing the management of AS is ongoing[41,42].

1. Pharmacologic Treatment Options

Pharmacologic management of r-axSpA involves the use of a multi-dimensional approach with the goal of reducing pain, inflammation, and disease progression[40]. Relief of symptoms and reduced inflammation can be achieved with use of NSAIDs, which are considered the first-line treatment for r-axSpA[44]. SSZ can be considered as an optional treatment in SpA patients with peripheral disease in cases where NSAIDs are insufficient. Use of biologics including TNFi and IL-17i can be considered in cases where SSZ is contraindicated or ineffective[45]. The efficacy of JAK inhibitors (JAKi), including tofacitinib and upadacitinib, has also been recently demonstrated in clinical trials[46,47]. Each treatment option has its pros and cons, which will be discussed in detail below.

1) NSAIDs

NSAIDs are considered the first-line treatment for AS due to their effectiveness in relieving pain, reducing inflammation, and improving function[43]. Several studies have reported that NSAIDs are effective in approximately 70% of patients with r-axSpA, providing relief of symptoms and assisting in control of disease activity[40,48,49]. Once effective, long-term use is generally recommended in patients with r-axSpA, a chronic condition requiring ongoing management.

The positive impact of NSAIDs on the natural course of r-axSpA, including improved spinal mobility, due to their role in control of inflammation, prevention of joint damage, and slowing progression of the disease has been demonstrated[50,51]. Several studies have suggested that early and continuous use of NSAIDs may result in better long-term outcomes, including reduced radiographic progression and lower risk of spinal fusion[44,49,52]. Continuous use may be preferred for patients who show a good response to NSAIDs and in cases where symptoms recur after stopping NSAIDs, while compared with on-demand treatment, other studies reported that continuous use had no clinical benefits[49,53]. It is important to note that NSAIDs cannot alter the underlying disease process or cure r-axSpA[44]. Although higher dosages may be required for adequate symptom control, long-term use at high doses can increase the risk of adverse effects, such as gastrointestinal complications[48,49].

NSAIDs may not be sufficient for management of all patients with r-axSpA, and additional treatments, such as biologics, may be necessary, particularly for those with more severe disease or inadequate response to NSAIDs[43]. Persistence of active disease even after administering at least two different NSAIDs at the maximal dose with duration of at least two weeks for each is considered an inadequate response to NSAID therapy[7,53]. Addition of analgesics such as opioid-like drugs may be considered based on the patients' symptoms.

2) SSA and MTX

SSZ and MTX belong to a group of therapeutic agents used in the treatment of rheumatoid arthritis. Extensive study of SSZ as a treatment option in management of r-axSpA has been reported[54]. Metabolization of SSZ, a prodrug, to its active form, sulfapyridine, and 5-aminosalicylic acid, occurs in the colon. Although the precise mechanism of action of SSZ in r-axSpA has not been adequately determined, it is believed that its therapeutic effects are exerted by way of several mechanisms, including inhibition of the production of inflammatory mediators such as prostaglandins and leukotrienes. SSZ should be considered for patients with peripheral arthritis as a comorbidity, but not those with isolated axSpA or enthesitis[41,42]. Administration of SSZ may be considered in patients with peripheral joint arthritis. Therefore, symptoms of peripheral joint arthritis may influence the use of SSZ in patients with r-axSpA.

MTX is effective for treatment of rheumatoid arthritis, and thus might be effective in management of AS. It functions as both an antimetabolite and an immunosuppressant[55,56]. It can inhibit the synthesis of DNA, RNA, and T cells and B cells, leading to suppression of the immune response. Thus, MTX can reduce production of pro-inflammatory cytokines and other mediators of inflammation. However, the efficacy of MTX has not been demonstrated in r-axSpA patients without peripheral arthritis[55,57,58]. Therefore, currently, the use of MTX is not recommended for axial manifestations but may be recommended for peripheral arthritis. Isolated use of MTX is also not recommended[55].

3) Biologics

Consideration of biologics is warranted for patients with persistently high disease activity despite conventional treatments, including NSAIDs[59,60]. Use of biologics in the treatment of inflammatory arthritis has increased during the last decade due to their remarkable effectiveness. However, in Korea, insurance coverage for biologics is limited to cases involving the use of two or more NSAIDs or SSZ or MTX for more than three months, where the treatment proved ineffective or had to be discontinued due to side effects[7,61]. Consequently, the use of biologics is limited.

Two classes of biologics that showed efficacy are recommended for the treatment of axSpA: TNFi as the first biologic and IL-17i as an alternative option for treatment of active r-axSpA patients[46,50]. Biologics approved for use in Korea include TNFi (adalimumab, etanercept, golimumab, and infliximab) and IL-17i (secukinumab [SEC] and ixekizumab [IXE])[7,62,63]. The effectiveness of TNFi in reducing disease activity, improving symptoms, and preventing radiographic progression in r-axSpA has been demonstrated. Assess-

ment of efficacy response should be performed after 3-6 months of therapy, with subsequent reassessment every six months for responders. Tapering off, but not discontinuing biologics may be considered for patients who achieve sustained remission[62]. In cases of TNFi failure due to inefficacy or adverse events, other TNFi or IL-17i should be considered if clinically appropriate[46]. SEC and IXE, which have shown comparable levels of efficacy, can be regarded as viable alternatives to TNFi[63].

Because TNF-α is a key mediator against infection, the risk of developing infection such as tuberculosis is higher for patients treated with TNFi[64,65]. Consequently, screening for latent tuberculosis infection is required for r-axSpA patients undergoing treatment with biologics. Therefore, the tuberculosis skin test, known as a Mantoux test or interferon gamma release assay, is recommended for diagnosis of latent tuberculosis infection in immunocompetent patients. Several recent studies have reported that TNFi may be more effective than SSZ or MTX, and updated guidelines recommend the use of TNFi rather than SSZ in patients with peripheral arthritis unless there are contraindications[41,42,64]. Cases involving application of IL-12/23, IL-17, and IL-23i for treatment of psoriasis have also been reported, so that the use of more biologics will be possible in the future[66].

4) JAKi

JAKi target specific enzymes known as Janus kinases, which play a critical role in the signaling process of various cytokines involved in the inflammatory response[67]. These drugs can interfere with the signaling of cytokines such as IL-6 and interferon gamma, which are known to contribute to the inflammatory process in r-axSpA, by inhibiting Janus kinases[46]. Inadequate disease management or undesirable side effects have been reported for approximately 40% of patients with r-axSpA treated with TNFi[45]. JAKi significantly reduced disease activity, symptoms, and signs compared to placebo in patients with active r-axSpA who did not respond to NSAIDs and were well tolerated[47]. The effectiveness of JAKi in management of r-axSpA has been examined in clinical trials, and some of the key findings suggest[47,68,69]: (1) JAKi can reduce pain, stiffness, and inflammation in patients with r-axSpA, leading to improvement in their overall quality of life. (2) Enhanced physical function and mobility, which is essential for patients affected by r-axSpA, as it primarily impacts the spine and may result in reduced flexibility, has been reported for patients treated with JAKi. (3) Some studies have suggested that JAKi might slow the radiographic progression of r-axSpA, potentially preventing or delaying structural damage to the affected joints.

However, JAKi may have side effects, therefore, study of data on long-term safety and efficacy is still underway, and individual responses to JAKi may vary[46]. JAKi can increase susceptibility to infection through suppression of the immune system. Some cases involving serious infections, such as pneumonia or opportunistic infections, have been reported. JAKi can also affect liver function, leading to elevated levels of liver enzyme. Therefore, regular monitoring of liver function is generally recommended during administration of JAKi. Impaired renal function has been reported for drugs including baricitinib and filgotinib[70,71]. According to some reports, JAKi may increase the risk of malignancy[72]. Use of these medications may also lead to development of anemia, leukopenia, or thrombocytopenia, potentially increasing the risk of bleeding or infection. Other side effects including skin rash or allergic reaction should also be considered.

2. Stepwise Medical Treatment

Stepwise medical management of r-axSpA involves the use of a systematic approach to treatment progression based on the individual's disease activity, symptoms, and treatment response[41,42]. The initial emphasis should be on non-pharmacologic interventions, including patient education, exercise, physical therapy, and postural techniques. If sufficient relief cannot be achieved with use of these measures, administration of NSAIDs at the maximum tolerated dose is considered the first-line pharmacologic option. Regular assessment of treatment response is important, including evaluation of pain, stiffness, function, and acute-phase reactants including erythrocyte sedimentation rate and C-reactive protein. Biologics should be considered as the next step in cases where the disease activity remains high despite NSAIDs therapy. The choice of biologics is dependent on factors such as comorbidities, patient preference, and cost considerations. Regular monitoring for treatment response, adverse effects, and infectious complications is required for patients on biologic therapy. In addition, physical therapy and exercise should

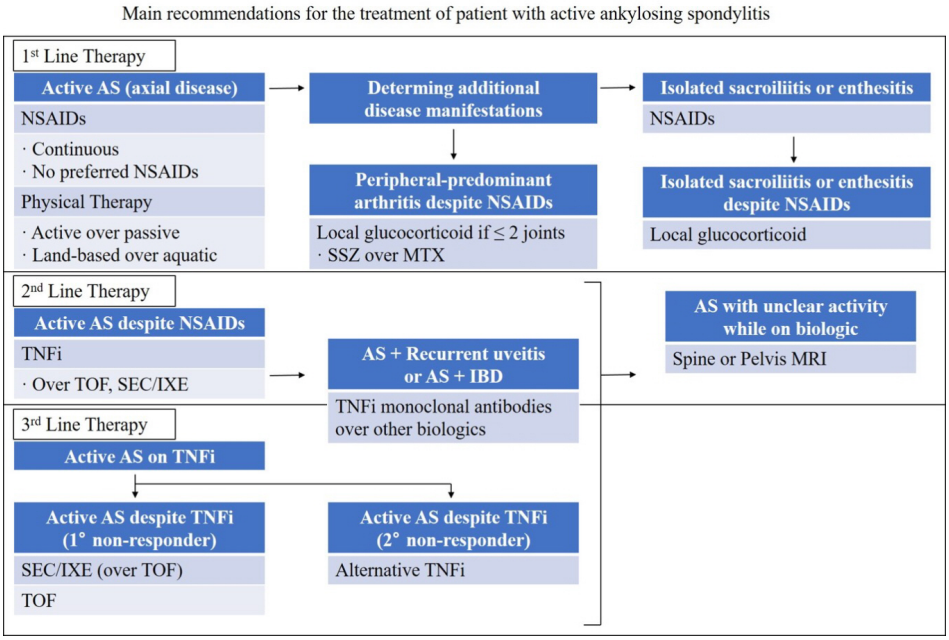

Fig. 9. Main recommendations for treatment of patients with active ankylosing spondylitis. Adapted from the article of Ward et al. (Arthritis Rheumatol. 2019;71:1599-613)[41] with original copyright holder's permission. AS: ankylosing spondylitis, NSAIDs: nonsteroidal anti-inflammatory drugs, SSZ: sulfasalazine, MTX: methotrexate, TNFi: tumor necrosis factor-α inhibitor, TOF: tofacitinib, SEC: secukinumab, IXE: ixekizumab, IBD: inflammatory bowel disease, MRI: magnetic resonance imaging.

be continued as adjunctive measures throughout the treatment process.

1) 2019 American College of Rheumatology (ACR)/ Spondylitis Association of America (SAA)/ Spondyloarthritis Research and Treatment Network (SPARTAN) recommendations[41]

ACR/SAA/SPARTAN presented details on 86 recommendations. Recommendations for management of r-axSpA and nr-axSpA are similar. Continuous treatment with NSAIDs over on-demand treatment is recommended for adult patients with active r-axSpA (Fig. 9). If these are not effective, application of SSZ or MTX can be considered only in cases of prominent peripheral arthritis when TNFi are contraindicated. TNFi are recommended over SEC or IXE as the first biologic. SEC or IXE is recommended over the use of a second TNFi in patients who show a primary nonresponse to the first TNFi. TNFi, SEC, and IXE are favored over JAKi. Co-administration of low-dose MTX with TNFi or discontinuation or tapering of biologics should not be considered for patients with stable r-axSpA. Spine or pelvis MRI may be helpful in assessment of patients with undetermined disease activity. Routine monitoring of radiographic changes using serial spine radiographs (every two years) is not recommended.

On-demand rather than continuous treatment with NSAIDs is recommended for patients with stable r-axSpA (Fig. 10). Continuing treatment with TNFi alone is recommended for patients undergoing treatment with TNFi and NSAIDs or SSZ or MTX. Biologics are not recommended for patients with stable r-axSpA.

2) ASAS-European Alliance of Associations for Rheumatology (EULAR) recommendations[42]

ASAS-EULAR includes five overarching principles and 15 recommendations. NSAIDs up to the maximum dose is regarded as the first-line drug (Fig. 11). For patients who show a good response to NSAIDs, continuous use is preferred for control of symptoms such as pain and stiffness. Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with purely axial disease should generally not be treated with SSZ or MTX. SSZ may be considered in patients with peripheral arthritis. Biologics including TNFi, IL-17i therapy, or JAKi should be considered in patients with persistently high disease activity despite conventional treatments. Current practice starts with administration of TNFi or IL-17i. TNFi is preferred for patients with a history of recurrent uveitis or active IBD. IL-17i may be preferred for patients with significant psoriasis. Switching to another biologic should be considered in cases involving failure of first-line biologics. Tapering of a biologic can be considered for patients who have achieved sustained remission.

3) Difference between 2019 ACR/SAA/SPARTAN recommendation versus 2022 ASAS-EULAR recommendation[42]

Despite many similarities between the two recommendations, there are differences in the format of the recommendations, mainly in areas where strong evidence is lacking. ACR/SAA/SPARTAN consisting of 86 recommendations provides greater detail than ASAS-EULAR recommendations. However, distinct aspects of ASAS-EULAR recommendations are as follows: (1) biologics should be started and continued, (2) including JAKi as a drug class, (3) treatment of axSpA in patients with psoriasis, (4) tapering of biologics, (5) cost consideration, and (6) lack of coercion of follow-up imaging study.

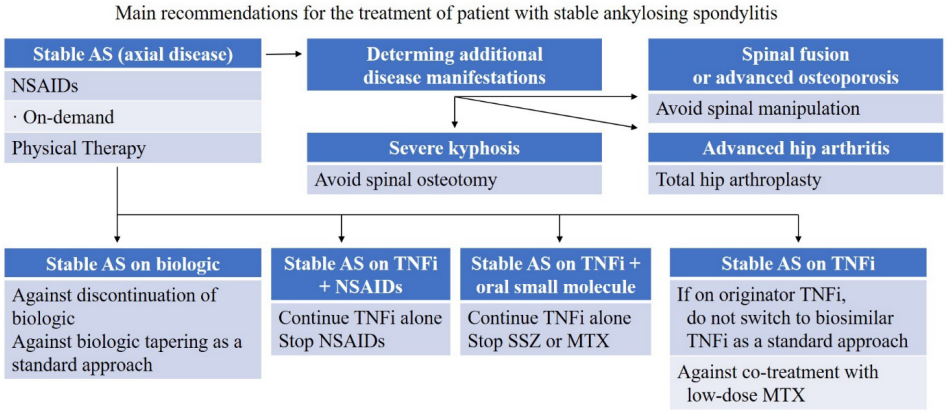

Fig. 10. Main recommendations for treatment of patients with stable ankylosing spondylitis. Adapted from the article of Ward et al. (Arthritis Rheumatol. 2019;71:1599-613)[41] with original copyright holder's permission. AS: ankylosing spondylitis, NSAIDs: nonsteroidal anti-inflammatory drugs, TNFi: tumor necrosis factor-α inhibitor, SSZ: sulfasalazine, MTX: methotrexate.

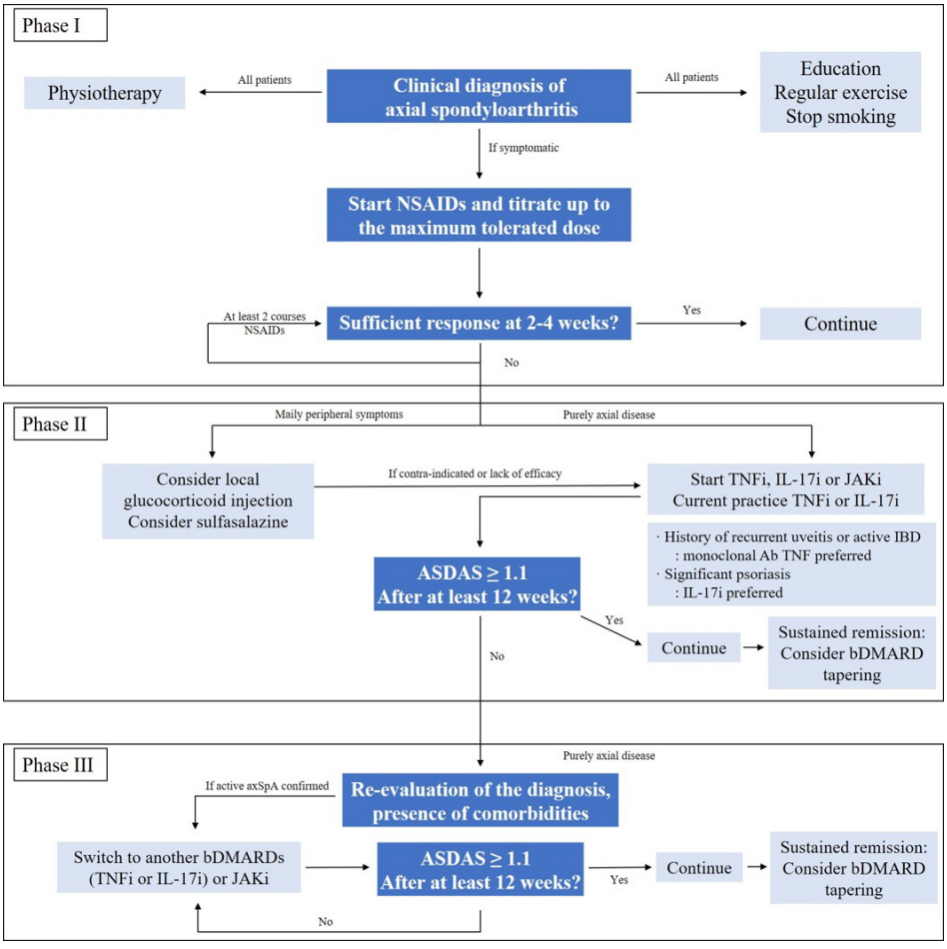

Fig. 11. ASAS (Assessment of SpondyloArthritis international Society)-EULAR (European Alliance of Associations for Rheumatology) recommendations. Adapted from the article of Ramiro et al. (Ann Rheum Dis. 2023;82:19-34)[42] with original copyright holder's permission. NSAIDs: nonsteroidal anti-inflammatory drugs, ASDAS: Ankylosing Spondylitis Disease Activity Score, TNFi: tumor necrosis factor-α inhibitor, IL: interleukin, JAKi: Janus kinase inhibitor, IBD: inflammatory bowel disease, Ab: antibody, bDMARDs: biologic disease-modifying antirheumatic drugs.

3. Surgical Treatment

Surgical treatment may be considered in cases where medical treatment is not effective. Severe arthritis of the hip is the most common indication for surgery in AS patients. Total hip replacement surgery can usually result in dramatic relief of hip pain and stiffness. Surgical correction of a severe flexion deformity of the spine or atlantoaxial subluxation is rare.

SUMMARY

r-axSpA is an axSpA that can cause significant radiographic damage to sacroiliac joints. r-axSpA is a chronic autoinflammatory disease associated with TNF and the IL23/IL17 pathway, and has also been associated with extraarticular manifestation including uveitis, IBD, and psoriasis. Although HLA-B27 is known to play a direct role in the pathogenesis of r-axSpA, its precise function remains undetermined. The initial symptoms are usually first observed in late adolescence or early adulthood and their course can vary. Recent criteria proposed by ASAS, which improved upon the New York criteria, are available for classification and in part for diagnosis of r-axSpA. The diagnosis must include comprehensive consideration of laboratory findings, physical examinations, and radiologic findings. Management of r-axSpA can pose challenges to both patients and their families as well as health-care providers. Medical therapy and physiotherapy should be attempted first, followed by implementation of appropriate stepwise medical treatment according to the disease stage. A typical course may start with administration of NSAIDs for management of pain and inflammation, and biologics for more severe cases or when other treatments are ineffective. Surgical treatment may also be considered in refractory cases. Working closely with medical staff to tailor the treatment plan to their specific symptoms and monitoring for potential side effects is essential for patients.

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Conflict of Interest

Jeong Joon Yoo has been a Section Chief Editor since June 2021, but had no role in the decision to publish this article. No other potential conflict of interest relevant to this article was reported.

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