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The road to a standard medical treatment for patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis — a practical guide

Short title: Treatment of axial spondyloarthritis

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Abstract

Axial spondyloarthritis affects 0.1% to 1% of the general population, depending on the source. Unfortunately, despite new diagnostic criteria, also adapted to non-radiographic axial spondyloarthritis, and advances in imaging modalities (widespread use of magnetic resonance imaging), the late diagnosis of the disease and, therefore, a delay in starting therapy still pose a serious problem. On average, the time between the first symptoms of the disease and its diagnosis is several years. Patients' access to modern treatment methods is also still delayed. This paper presents a practical guide to both the diagnosis and treatment of axial spondyloarthritis in Poland.

Key words: ankylosing spondylitis; axial spondyloarthritis; biological treatment

Introduction

Spondyloarthritis (SpA) is a group of chronic autoimmune inflammatory diseases, including ankylosing spondylitis (AS), psoriatic arthritis (PsA) and arthritis associated with inflammatory bowel diseases (Crohn's disease and ulcerative colitis). All these disease entities share similar pathogenetic factors and common clinical manifestations [1].

SpA is commonly divided into peripheral spondyloarthritis (pSpA), with a predominance of peripheral joint symptoms, and axial spondyloarthritis (axSpA), with a predominance of spinal and sacroiliac joint symptoms [1, 2]. This study discusses axSpA.

Previously, axSpA was mainly associated with AS. However, patients are known to often present with clinical signs typical of AS and meet other criteria for axSpA diagnosis but do not meet radiographic criteria for AS diagnosis. The diagnosis of non-radiographic axSpA (nr-axSpA) has been introduced for such patients. It is unclear whether nr-axSpA represents an early stage of AS or is a separate disease entity. Some patients with nr-axSpA will likely not develop full-blown AS even after many years. Therefore, it appears that treating nr-axSpA as the initial stage of the disease, which then develops into AS, is a simplistic view that is not strictly true. It is now accepted that AS and nr-axSpA are separate disease entities but with the same pathogenesis of lesions, common clinical manifestations and similar course; therefore, they are categorised in the common axSpA group, and the same diagnostic and therapeutic guidelines apply [3–5]. For this reason, both these disease entities are discussed in one paper.

Epidemiology

Axial spondyloarthritis is approximately 2–3 times more common in men than in women. Some 90% of patients develop their first symptoms before the age of 40. Unfortunately, there are no Polish patient registries, so we rely on data from the world. The prevalence of AS in the Caucasian population is approximately 0.1–0.3%. In contrast, the prevalence of nr-axSpA is challenging to estimate due to diagnostic difficulties and often delayed diagnosis. **In patients with nr-axSpA followed up for five years, approximately 5% develop full-blown AS.** For a 10-year follow-up, this rate reaches approximately 20%. This rate for a longer follow-up is unknown, as the very concept of nr-axSpA (related to the development of magnetic resonance imaging) is new and patient follow-up over many years is unavailable [6].

Pathogenesis

Genetic and environmental factors are important in the pathogenesis of axSpA. Genetic factors are primarily histocompatibility antigens: human leucocyte antigen B27 (HLA-B27) (HLA-B*2705, *2702, *2704, *2707 subtypes are significantly associated, while B*2706, *2709 subtypes are unlikely to be related with disease development). Environmental

factors include infections (probable involvement of *Shigella spp.*, *Salmonella spp.*, *Yersinia spp.*, *Klebsiella pneumoniae*, *Escherichia coli*), trauma and biomechanical overload [7, 8].

Early research into the pathogenesis of SpA attributed a key role to T helper 1 (Th1) cells and tumour necrosis factor alpha (TNF-α). Later studies provided evidence of the importance of different pathways, including interleukin 17 (IL-17) [8]. Genetic studies indicate that a specific polymorphism in the receptor gene for IL-23 (rs11209026, Arg381Gln) provides a protective mechanism against the development of AS by impairing the ability of Th17 cells to produce IL-17 under the influence of IL-23 [9]. Additionally, animal models indicate that the HLA-B27 antigen increases Th17 expansion and IL-17 synthesis [10, 11]. Furthermore, animal studies show that overproduction of IL-17 induced a disease similar to SpA in humans, with tendonitis, osteoporosis and increased bone formation [12, 13]. Thus, the predominant role of both TNF-α and IL-17 is now recognised, which also has implications for the biologics used [8].

Clinical picture

AxSpA, a form of arthritis with spinal joint involvement, is a chronic inflammatory disease with a variety of clinical manifestations. The disease can progress with periods of exacerbation and remission but most often has a chronic and progressive course. In approximately 18–30% of patients, the course is severe and accompanied by significant functional impairment; in 20-30%, it is moderate; and in approximately 50%, it is mild. The poor prognosis in axSpA primarily affects males, with disease onset under 16, combined with cervical spine involvement, peripheral arthritis, early syndesmophytes on imaging studies, elevated inflammatory markers [high C-reactive protein (CRP) and increased erythrocyte sedimentation rate (ESR)], and poor response to non-steroidal anti-inflammatory drugs (NSAIDs). This group of patients, in particular, requires intensive treatment from the onset of the disease [8].

Indeed, effective treatment has changed the clinical picture of the disease. Initially, the diagnosis of ankylosing spondylitis was made in a patient with the typical posture due to syndesmophytes on spinal radiographs. Subsequently, a major sign required to make the diagnosis (according to the New York criteria for AS) was the detection of sacroiliitis on radiographs. Nowadays, the diagnosis is made earlier, before morphological changes occur, thus avoiding permanent disability. Successful treatment also allows for the treatment of extra-articular lesions. Extra-articular lesions can affect more than 40% of patients in the

disease course. The most common include anterior uveitis, skin psoriasis, inflammatory bowel disease and cardiovascular symptoms. Typical symptoms, both articular and extra-articular, are included in the classification criteria [14].

Diagnosis

Currently, the *ASsessment of Ankylosing Spondylitis* (ASAS) SpA classification criteria are widely used for the diagnosis of axSpA (Tab. 1).

Table 1. Spondyloarthritis classification criteria according to the 2010 ASsessment of Ankylosing Spondylitis (ASAS).

Axial spondyloarthritis (criteria can be applied to patients whose back pain persists ≥ 3 months and occurred before the age of 45) in the case when:
1) sacroiliitis is evidenced by imaging studies (MRI or X-ray), and there is at least 1 (≥ 1) another sign of SpA *or* 2) HLA-B27 antigen and ≥ 2 other signs of SpA are present
SpA signs: • inflammatory back pain • peripheral arthritis • enthesitis (at the heel) • uveitis • dactylitis • psoriasis • Crohn's disease or ulcerative colitis • good response to NSAIDs • SpA in family history • presence of HLA-B27 • increased serum CRP levels

MRI — magnetic resonance imaging; X-ray — radiological examination; HLA-B27 — human leucocyte antigen B27

However, it should be stressed that the 2009 ASAS classification criteria do not seek to differentiate between nr-axSpA and AS, and it is incorrect to identify the "imaging

pathway" of these criteria with radiographic axSpA and the "clinical pathway" with nr-axSpA. Specific imaging studies are used to differentiate nr-axSpA from AS.

The diagnosis of AS is established using the Modified New York Criteria, according to which the radiographic axSp is diagnosed when at least sacroiliitis grade II signs are present bilaterally or grade III unilaterally on radiographs of the sacroiliac joints. In daily clinical practice, there is little agreement on how to evaluate this imaging study, so an experienced radiologist must interpret the results [15].

Magnetic resonance imaging (MRI) is used to diagnose nr-axSpA. This modality offers great diagnostic possibilities also at an early stage of the disease. However, the potential for false-positive results, e.g. due to overload, sports injuries, etc., should be considered. According to recent studies, MRI of the sacroiliac joints has a high predictive value for SpA when it reveals definite active lesions (signs of none marrow oedema in four different quadrants of the sacroiliac joints in any location or in the same location on three consecutive cross-sections) or definite structural lesions (erosion in three different quadrants of the sacroiliac joints, fat metaplasia in five different quadrants, erosion in the same location on two consecutive cross-sections, fat metaplasia on three consecutive cross-sections or deep > 1 cm fat metaplasia) [4, 5].

Unfortunately, despite new diagnostic criteria, also adapted to nr-axSpA, and advances in imaging modalities (widespread use of MRI), the late diagnosis of the disease and, therefore, a delay in starting therapy still pose a serious problem. On average, the time between the first symptoms of the disease and its diagnosis is several years. Adequate disease activity assessment is also problematic [16].

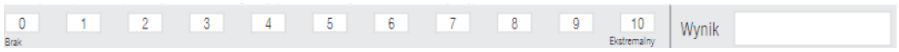
Disease activity assessment

In recent decades, efforts have been made to accurately determine the inflammatory process's activity in spondyloarthritis. Their goal is to assess the performance of biologics and innovative drugs as precisely as possible. Unfortunately, each of the scales used to date to assess ax-SpA activity contains mainly subjective data reported by the patients themselves. Also, the basic laboratory markers of inflammation — ESR and CRP — are considered too insensitive and specific in SpA. MRI offers some possibilities for assessing the severity of inflammatory lesions, but it is not commonly used [17].

In Poland, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) remains the most widely used tool for assessing axSpA activity (Fig. 1) [18].

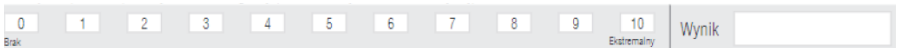
BASDAI—PLEASE TICK THE BOX ON EACH LINE BELOW TO INDICATE YOUR ANSWER TO EACH QUESTION FOR LAST WEEK

1. How would you describe the overall fatigue you experienced?



None Extreme Score

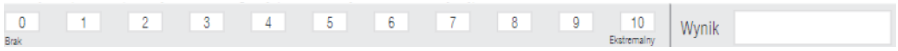
2. How would you describe the overall pain associated with AS in the neck, back or hip joints?



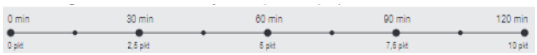
3. How would you describe the overall pain/swelling in joints other than the neck, back or hip joints?

4. How would you describe the overall discomfort in your touch- or pressure-sensitive areas of the body?

5. How would you describe your overall morning stiffness after waking up?



6. How long does your morning stiffness persist after waking up?



The average score for items 5 and 6 should be added to the sum of items 1,2,3,4 and divided by 5.

The average score for items 5 and 6

BASDAI

Figure 1. *The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)*

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is popular in Poland primarily because it is simple and easy to use and because it is compatible with drug programme requirements. The higher the BASDAI score, the higher the disease activity. A score above 4 is considered high disease activity and indicates eligibility for treatment under drug programmes. Unfortunately, the BASDAI is based solely on the patient's subjective assessment of disease activity. For this reason, the Ankylosing Spondylitis Disease Activity Score (ASDAS) is recommended based on literature data from around the world. The ASDAS combines patient-assessed parameters—three items from the BASDAI and an overall disease score—and one of the inflammatory markers (CRP or ESR). CRP is preferred, as its levels correlate with disease activity, MRI lesions, and rapid progression of spondyloarthritis. The ASDAS is currently considered the most objective parameter for assessing disease activity and response to treatment [17].

However, it should be noted that no one index alone will provide complete patient monitoring. Patient monitoring should take into account not only the patient's assessment of disease activity but also other clinical signs (including extra-articular symptoms) and laboratory and imaging findings. The frequency of disease activity monitoring should be tailored to the patient, depending on symptoms, disease severity and treatment type [19].

Treatment

The treatment of patients with SpA should involve the collaboration of doctors with different specialities (due to the clinical diversity of the disease), and a rheumatologist should coordinate the entire treatment. Therapy's primary goal is to improve the patient's quality of life by controlling clinical symptoms (such as chronic pain or morning stiffness), inhibiting inflammation, preventing structural joint damage, and preserving/restoring function and social functioning. Treatment should include non-pharmacological (patient education and rehabilitation) and pharmacological methods.

The treatment regimen for nr-axSpA is the same as for AS. The same non-pharmacological recommendations apply, and the same groups of drugs are used. The focus of this study is primarily on pharmacological treatment.

The efficacy of synthetic disease-modifying antirheumatic drugs (DMARDs) in the treatment of axSpAs is extremely low, and there are virtually no recommendations for their use, excluding patients with possible associated peripheral joint symptoms or other organ lesions. The same applies to glucocorticoids, which should not be used systemically but only possibly topically if peripheral symptoms predominate.

NSAIDs remain the first-line drugs at the maximum recommended and tolerated dose —unless, of course, there are contraindications to their use. Treatment with NSAIDs should include an assessment of risk factors for gastrointestinal, cardiovascular, and renal adverse effects (Tab. 2) [20].

Table 2. Algorithm for the selection of non-steroidal anti-inflammatory drugs (NSAIDs)

	Low cardiovascular toxicity	**Moderate cardiovascular toxicity**	**High cardiovascular toxicity**
Low gastrointestinal toxicity	Aceclofenac Diclofenac Ketoprofen Nimesulide Naproxen Coxibs	Aceclofenac Diclofenac Ketoprofen Nimesulide Naproxen Coxibs	Ketoprofen with ASA Naproxen without ASA
High gastrointestinal toxicity	Coxibs Ketoprofen with lysine and PPI	Coxibs Ketoprofen with lysine and PPI	Topical therapy

ASA — acetylsalicylic acid; PPI — proton pump inhibitor

Failure of NSAID therapy is an indication for the use of biologics (TNF-α inhibitors or IL-17 inhibitors) or targeted synthetic DMARDs [currently Janus kinase (JAK) inhibitors]. Failure of NSAID therapy is confirmed when at least two drugs of this group have been used for at least four weeks, and there is no clinical effect on disease activity expressed by a composite disease activity score, such as an ASDAS of at least 2.1 or a BASDAI of at least 4 [19].

The option of using biologics in axSpA was a breakthrough in treating this group of patients. Global recommendations do not indicate an advantage for any particular originator or biosimilar (which has comparable efficacy and safety to reference drugs) [7]. This, therefore, remains an individual decision, often depending on the presence of other organ lesions. In patients with nr-axSpA, biologics are most often used when objective features of inflammation, such as laboratory inflammatory markers and/or MRI inflammatory lesions of the sacroiliac joints, are present. Biological treatment of nr-axSpA without objective inflammatory changes is therefore controversial. Still, it may be justified in patients with a definite diagnosis of nr-axSpA if there is a high activity of clinical symptoms. ASAS and European League Against Rheumatism (EULAR) recommendations provide detailed data on pharmacotherapy [19].

The current guidelines for ax-SPA therapy were published in 2022 by [who?] The previous ASAS and EULAR recommendations were published in 2016. Due to the introduction of new drugs into treatment and the emerging results of clinical trials and studies from national registries, enough new data have come to light that recommendations need to be updated [19].

The new guidelines include five general recommendations:

1. Ax-SpA is a potentially severe disease with a variety of symptoms, usually requiring multispecialty treatment coordinated by a rheumatologist.
2. The primary goal of treatment for ax-SpA patients is to maintain the highest possible health-related quality of life in the long term by controlling symptoms and inflammation, preventing the progression of structural lesions, and preserving or normalising functional status and participation in social life.
3. Optimal therapy for ax-SpA patients requires a combination of non-pharmacological and pharmacological approaches.
4. Ax-SpA treatment should aim to provide the best possible care and rely on a joint decision between patient and doctor.
5. Ax-SpA is associated with high individual, medical, and social costs, all of which the rheumatologist should consider during treatment.

In contrast, specific recommendations are included in 15 items (Tab. 3), of which eight were unchanged, three had minor modifications (1, 4, 5), two major modifications (9, 12) and two new ones were introduced (10, 11).

Table 2. Treatment recommendations for axial spondyloarthritis (axSPA) according to the 2022 ASsessment of Ankylosing Spondylitis/European League Against Rheumatism (ASAS/EULAR)

	Recommendations for the treatment of axSPA according to the 2022 ASAS/EULAR
1	The treatment of patients with axSPA should be individualised according to presenting disease symptoms (axial, peripheral, and extra-articular symptoms) and patient characteristics, including comorbidities and psychosocial factors.
2	Monitoring should include clinical signs, laboratory tests, and imaging, all performed using appropriate methods and appropriately selected for clinical signs. The frequency of monitoring should be determined individually according to symptoms, disease activity and type of therapy.
3	Treatment should be provided according to a predefined objective.
4	Patients should be educated about axSpA and encouraged to exercise regularly and quit smoking; physical therapy should be considered.
5	Patients complaining of pain and stiffness should use NSAIDs as first-line drugs up to maximum doses, keeping in mind the benefits and risks of their use. In patients who respond well to therapy with NSAIDs, ongoing treatment is preferred as long as it is necessary to control symptoms.
6	Analgesics, such as paracetamol and opioids, can be used for pain control in patients for whom previously recommended treatment is insufficient, contraindicated and/or poorly tolerated.
7	Local injections of GCs into inflamed areas may be considered. Long-term use of systemic GCs is not recommended.
8	AxSpA patients without peripheral lesions should not usually be treated with DMARDs; treatment with sulfasalazine may be considered in patients with peripheral joint involvement.
9	In patients with persistently high disease activity despite conventional therapy, treatment with TNFi, IL-17i, or JAKi should be considered. Currently, treatment usually starts with TNFi or IL-17i.
10	In cases of recurrent uveitis or inflammatory bowel disease, TNFi (monoclonal antibodies) are preferred. IL-17i may be preferred in patients with extensive psoriasis.
11	The lack of response to the treatment should prompt reconsideration of the diagnosis and consideration of the presence of comorbidities.
12	If the first therapy with a given bDMARD or tsDMARD fails, a change to another bDMARD (TNFi or IL-17i) or JAKi should be considered.
13	If a patient is in long-term remission, a reduction in the biologic dose may be considered.

14	Total hip arthroplasty should be considered in patients with pain that is refractory to conservative treatment or those with disability and radiographically evident structural changes, regardless of age; corrective spinal osteotomy may be considered in patients with severe, disabling deformity and should be performed in specialist centres.
15	If the course of the disease significantly changes, causes of the condition other than inflammation, such as a spinal fracture, should be considered, and an appropriate evaluation, including imaging studies, should be performed.

NSAIDs — non-steroidal anti-inflammatory drugs; GCs — glucocorticoids; DMARDs — disease-modifying antirheumatic drugs; bDMARDs — biological disease-modifying antirheumatic drugs; tsDMARDs—targeted synthetic disease-modifying antirheumatic drugs; TNFi—tumour necrosis factor inhibitor; IL-17i — interleukin 17 inhibitor; JAKi — Janus kinase inhibitor

In summary, the main changes and updates included in the current recommendations indicate that:

— significant evidence has accumulated in recent years suggesting that using the ASDAS instead of the BASDAI to assess disease activity is more meaningful. High disease activity as per ASDAS is indicated when the ASDAS is ≥ 2.1;

— drug therapy options have increased. If the patient has active disease and the therapeutic goal has not been achieved with NSAIDs, treatment with tumour necrosis factor alpha inhibitors (TNF-αi), interleukin 17 inhibitors (IL-17i) or Janus kinase inhibitors (JAKi) may be initiated. Due to the longest experience of use and the broadest range of safety data, current practice usually involves the use of TNFi or IL-17i;

— the recommendations outline attempts to personalise treatment. In patients with recurrent uveitis or inflammatory bowel disease, TNF-αi (monoclonal antibodies) are preferred. For extensive psoriasis, IL-17 inhibitors are preferred and have proven to be more effective;

— in case of treatment failure, other possible causes, such as comorbidities, are worth considering. This is particularly important in Poland, as the drug programmes do not provide for an option of restarting a drug that has been discontinued due to ineffectiveness;

— if the patient is in long-term remission, a reduction in the dose of used biologic may be considered [19].

Drug programmes in Poland

In Poland, the choice of therapy depends largely on reimbursement opportunities. The drug programme B36 is dedicated to patients with a diagnosis of AS. Under this programme, drugs with different mechanisms of action can be used:

— adalimumab (anti-TNF);

— certolizumab pegol (anti-TNF);

— etanercept (anti-TNF);

— golimumab (anti-TNF);

— infliximab (anti-TNF);

— ixekizumab (anti-IL-17);

— secukinumab (anti-IL-17);

— upadacitinib (JAKi);

— tofacitinib (JAKi).

Until recently, only two drugs with the same mechanism of action involving TNF-α inhibition (certolizumab pegol and etanercept) were reimbursed in Poland for patients with active spondyloarthritis without radiographic changes typical of AS (programme B82). Now, patients under the B82 programme can also receive IL-17 inhibitors (ixekizumab and secukinumab). This offers Polish patients better treatment opportunities.

The current drug programme provisions are available on the website of the Ministry of Health https://www.gov.pl/web/zdrowie/choroby-nieonkologiczne [21]. It is always advisable to look up the provisions that strictly define the eligibility criteria for treatment, monitoring recommendations and available medicines. The authors of this study hope that drug programmes will be further modified to ensure greater accessibility to modern therapies for patients with nr-axSPA in Poland.

Authors' contribution

D.S. and W.S. wrote the article.

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