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Innovative approaches in axial spondyloarthritis: exploring emerging trends in treatment and management

Jagoda Rogowska*
Medical University of Lodz
https://orcid.org/0009-0004-5995-5802
Corresponding author: jagoda.rogowska@o2.pl

Wiktoria Balińska*
Medical University of Lodz
https://orcid.org/0009-0002-2615-7236

Jakub Wąsik*
Medical University of Lodz
https://orcid.org/0009-0002-7145-8118

Aleksandra Marek*
Medical University of Lodz
https://orcid.org/0009-0002-3391-5082

* Authors contributed equally

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ABSTRACT

Background. Axial Spondyloarthritis (axSpA) is a chronic inflammatory disease affecting the axial skeleton, resulting in chronic pain, reduced mobility, and potential spinal fusion. Traditional therapies emphasise symptomatic control via nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy. Recent advances, however, including biologic agents and JAK inhibitors, have opened new therapeutic possibilities.
Material and methods. A comprehensive literature review was conducted using databases such as PubMed and Scopus. The literature search included English-language publications between January 2018 and February 2024. We included clinical trials, meta-analyses, systematic reviews, cohort studies, and significant basic science studies. Publications outside these criteria or those in other languages were excluded. Methodological rigour and limitations of included studies were critically discussed.
Results. Key recent advances include biologic therapies targeting IL-17 and IL-23 cytokine pathways, demonstrating significant efficacy in controlling inflammation and improving function. Additionally, precision medicine, microbiome-based interventions, and advanced imaging techniques enhance personalised treatment strategies.
Conclusions. Integrating novel pharmacological approaches with lifestyle modifications presents a promising strategy for optimising axSpA management. Long-term studies are required to assess the full impact of these innovations on disease progression.

Introduction

Axial Spondyloarthritis is a chronic, progressive inflammatory disorder primarily affecting the axial skeleton, including the spine and sacroiliac joints. This condition often leads to significant pain, stiffness, and reduced mobility, with severe cases resulting in spinal fusion, known as "bamboo spine" [1]. Typically presenting in young adulthood and demonstrating male predominance, however,

recent studies indicate that 9.9% of axSpA patients present over the age of 45, suggesting a broader age distribution than previously assumed [2]. While the exact aetiology of axSpA remains unclear, it is strongly associated with the HLA-B27 gene, suggesting a genetic predisposition [3].

Traditionally, the management of axSpA has focused on controlling symptoms and maintaining functional ability through NSAIDs and physical therapy. Contrary to prior assumptions, NSAIDs may also have a modest disease-modifying potential, delaying radiographic progression in some patients [4,5]. The introduction of biologic therapies, specifically tumour necrosis factor (TNF)-alpha inhibitors, significantly improved the advancement in axSpA treatment, offering better control over inflammation and slowing disease progression. However, TNF-alpha inhibitors are not considered traditional treatments but rather biological therapies.

Recent developments introduce novel biologic therapies targeting interleukin pathways (IL-17 and IL-23) and Janus kinase (JAK) inhibitors, providing new mechanisms to manage axSpA [6]. These treatments target different inflammatory pathways, giving additional options for patients who do not respond to traditional therapies. Despite pharmacological advances, there is growing recognition of the importance of comprehensive management strategies that include lifestyle modifications, such as exercise, diet, and mental health support, to improve overall patient outcomes [7].

Aim

The purpose of this review is to explore these emerging trends in axSpA treatment, examining the efficacy and potential of new therapeutic approaches, discussing clinical efficacy, potential limitations, and areas necessitating further investigation. The article also highlights the importance of integrating pharmacological and non-pharmacological strategies in the management of this complex disease.

Etiopathogenesis

Axial spondyloarthritis is a chronic autoimmune disorder, where the exact etiopathogenesis remains elusive. Genetic factors play a significant role, with the HLA-B27 gene being strongly linked to axSpA susceptibility [8]. However, the presence of this gene alone does not always lead to the development of the disease, indicating the involvement of other genetic and environmental factors. Recent genome-wide association studies (GWAS) have identified other significant genetic loci, such as ERAP1 (endoplasmic reticulum aminopeptidase 1) and genes within the IL-23/IL-17 signalling axis, which are crucial for the differentiation and function of Th17 cells—immune cells implicated in promoting inflammation in axSpA [8–10].

Additionally, studies indicate that Familial Mediterranean Fever and axSpA may share overlapping etiopathogenic mechanisms, suggesting potential inflammatory pathways common to both diseases [11].

The immune system's dysregulation, particularly involving Th17 cells and cytokines like IL-17 and IL-23, contributes significantly to the inflammatory process. These cells drive the chronic inflammation characteristic of axSpA, which leads to the progressive fusion of the spine. Additionally, environmental triggers such as gut microbiota, particularly *Klebsiella pneumoniae,* may exacerbate the autoimmune response by interacting with HLA-B27, supporting the hypothesis of a gut-joint axis in axSpA pathogenesis [8,9].

Moreover, non-genetic factors like vitamin D deficiency and disturbances in the hypothalamic--pituitary-adrenal axis are also thought to influence disease progression, highlighting the complexity of axSpA etiopathogenesis [12].

Characteristic symptoms and diagnosis

AxSpA presents a variety of characteristic symptoms, primarily involving pain and stiffness in the lower back and hips, particularly in the morning or after periods of inactivity. Other hallmark symptoms include progressive spinal stiffness, loss of spinal flexibility, and in severe cases, fusion of vertebrae (ankylosis), leading to reduced mobility and postural deformities [8,9]. Peripheral joints and entheses (the areas where tendons and ligaments attach to bones) may also be affected, causing pain and inflammation. Additionally, patients

may experience fatigue, weight loss, and, less commonly, extra-articular manifestations such as anterior uveitis, inflammatory bowel disease, and psoriasis [10].

Diagnosing axSpA can be challenging due to its slow progression and overlap with other forms of inflammatory arthritis, which requires a diagnostic combination of clinical evaluation, laboratory tests, and imaging. Magnetic resonance imaging (MRI) is a key tool for early detection, as it can reveal inflammation in the sacroiliac joints before significant radiographic changes are visible. Radiographs can show structural changes in later stages, including syndesmophytes and bamboo spine [8]. Blood tests may reveal elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which are markers of inflammation, although these are not specific to axSpA. The presence of the HLA--B27 antigen can support the diagnosis, though not all patients with axSpA test positive for this gene [9].

Advances in biological therapies in axial spondyloarthritis

The treatment possibilities for axSpA have evolved with the advent of biologic therapies, offering novel options for patients who do not respond adequately to first-line treatments such as NSAIDs [14]. Among the most significant advances are therapies targeting the IL-17 and IL-23 pathways, which play crucial roles in the inflammatory processes driving axSpA [15]

The IL-17/IL-23 pathway is essential in the pathogenesis of axSpA, with IL-17A and IL-17F playing significant roles in inflammation [14,18]. Both cytokines share a receptor complex and can be targeted by the monoclonal antibody bimekizumab, which effectively neutralises their activity. IL-23 is essential for the development and maintenance of Th17 cells, which are prominent in axSpA inflammation. Research has shown a correlation between axSpA risk and polymorphisms in the IL-23 receptor, indicating its involvement in disease mechanisms [14,16].

Table 1. Diagnostic aspects of axial spondyloarthritis [8,9,13].

Aspect of diagnosis	Details
Diagnosis challenges	Early symptoms of axSpA, such as back pain and stiffness, can overlap with other conditions, making early diagnosis difficult.
Supporting diagnostic evidence	Radiographic evidence, especially **sacroiliitis**, is key for confirming the diagnosis.
Primary diagnostic criteria	Diagnosis is based on **clinical presentation**, such as chronic back pain and stiffness, typically in young adults.
Hallmark radiographic feature	**Sacroiliitis** visible on X-rays, with inflammation in the sacroiliac joints being a defining feature of axSpA.
Genetic marker	The **HLA-B27** gene is present in **80–95%** of individuals with axSpA, though it is also found in a significant portion of the general population without the disease. HLA-B27 is not exclusive to axSpA but is a strong genetic predisposition factor
Laboratory tests	A thorough **clinical examination** and detailed medical history, combined with the exclusion of other conditions, are essential for diagnosing axSpA.
MRI findings	**MRI** is valuable in detecting **non-radiographic axial spondyloarthritis**, revealing early inflammatory changes not visible on conventional radiographs. Specific **lesions**, such as erosions and sclerosis, further increase the positive predictive value
MRI findings and lesions of nr-axSpA	– Bone marrow edema in two quadrants in a single section or two consecutive sections in a single quadrant. – Erosion in two quadrants in a single section or two consecutive sections in a single quadrant. – Bone marrow edema and erosion together in any quadrant in a single section.
Degrees of sacroiliitis	– **Mild sacroiliitis**: Subtle imaging changes and minimal inflammation. – **Moderate sacroiliitis**: Pronounced inflammation and pain. – **Severe sacroiliitis**: Intense pain, stiffness, and joint changes. – **Chronic sacroiliitis**: Persistent inflammation and recurring episodes

axSpA – axial spondyloarthritis; nr-axSpA – non-radiographic axial spondyloarthritis; MRI – magnetic resonance imaging

IL-17 inhibitors, such as secukinumab and ixekizumab, have shown remarkable efficacy in controlling inflammation in axSpA. These drugs specifically inhibit IL-17A, a cytokine critical to the immune response in axSpA, reducing disease activity, pain, and improving patients' mobility. JAK inhibitors, such as tofacitinib, upadacitinib, and filgotinib, are also emerging as promising treatment options, especially for patients who do not respond to TNF-alpha or IL-17 inhibitors.

Meta-analyses have demonstrated significant improvements in the proportion of patients with at least 20% improvement in Assessment of Spondyloarthritis International Society (ASAS20) response criteria and ASAS40 (secondary response), with some patients achieving sustained remission even after 16 weeks of treatment with IL-17 inhibitors [16,17].

Meanwhile, therapies targeting the JAK-STAT pathways are emerging as promising options, especially for patients who are intractable to both TNF and IL-17 inhibitors. JAK inhibitors work by blocking Janus kinases, which are critical enzymes that enable the signalling of various cytokines involved in inflammatory processes. By inhibiting these enzymes, JAK inhibitors prevent the activation and proliferation of immune cells, reducing the production of pro-inflammatory cytokines like IL-6, IL-17, and IL-23 [18]. As mentioned before, the IL-23/IL-17 axis is critical in the pathogenesis of axSpA, with cytokines like IL-23 maintaining Th17 cells that produce pro-inflammatory IL-17A and IL-17F; therefore, the mechanism of JAK inhibitors helps alleviate inflammation and tissue damage [18–20].

As mentioned above, several JAK inhibitors, including tofacitinib, upadacitinib, and filgotinib, have shown efficacy in treating axSpA. These inhibitors work by blocking intracellular signalling pathways, allowing for the simultaneous inhibition of multiple cytokines involved in inflammation [21]. For instance, tofacitinib demonstrates preferential inhibition of JAK1 and JAK3, effectively targeting various pro-inflammatory cytokines, while upadacitinib shows strong selectivity for JAK1 [19,22]. Recent studies, including the SELECT-AXIS 2 trial, have supported the efficacy of upadacitinib in treating both radiographic and non-radiographic axial spondyloarthritis, highlighting the expanding role of JAK inhibitors in the management of axSpA [23,24].

The SELECT-AXIS 2 trial assessed the efficacy and safety of upadacitinib in patients with non-radiographic axial spondyloarthritis. The study was conducted on 314 patients who had active disease and inadequate responses to NSAIDs. Results showed a significant improvement in the Assessment of Spondyloarthritis International Society (ASAS) response with upadacitinib compared to placebo (45% vs. 23%; $p < 0.0001$), indicating its effectiveness in managing symptoms of non-radiographic axial spondyloarthritis [24].

Although much progress has been made in the last decade on JAKs and their inhibition, there are still many unanswered questions in this rapidly advancing field. The importance of selectivity for an effective treatment response and reduction of adverse events remains unclear. Moreover, safety concerns regarding JAK inhibitors must be carefully evaluated, as their use has been associated with increased risks of infections, cardiovascular events, and malignancies.

Precision medicine and genetic insights

In the current approach to managing axSpA, personalised medicine is playing an increasingly important role. Advances in genetic research, such as involving the HLA-B27 antigen, are helping clinicians tailor treatments to individual patient profiles. HLA-B27, which has been consistently linked as a key risk factor for axSpA, now provides valuable insights into disease progression and likely treatment response, supporting more targeted and effective therapeutic strategies.

Axial spondyloarthritis has seen significant advancements in understanding genetic susceptibility, particularly through GWAS, which are instrumental in identifying genetic markers associated with treatment efficacy, enabling personalised therapy approaches that consider individual genetic backgrounds [25]. These large-scale studies examine up to a million genetic variants, focusing mainly on common single-nucleotide polymorphisms that appear in over 1% of the population. A groundbreaking study conducted in 2013 by the International Genetics of Ankylosing Spondylitis [26] consortium identified 25 loci related to axSpA, while subsequent

investigations have revealed a total of 115 distinct SNPs (Single Nucleotide Polymorphism) across more than 90 genomic regions [27,28]. These findings highlight the complex genetic background of axSpA and reinforce the potential of genomics in guiding future diagnostic and therapeutic approaches.

A significant number of these genetic variants are located near genes involved in immune function, especially ERAP1 and ERAP2. These genes play a key role in processing peptide antigens for presentation by MHC class I molecules, such as HLA-B27 [28,29]. Interestingly, specific ERAP1 variants that reduce the enzyme's function have been associated with a lower risk of developing ankylosing spondylitis. This observation supports the arthritogenic peptide hypothesis, which proposes that faulty processing of self-peptides may trigger abnormal T-cell responses, contributing to the development of autoimmunity [28].

Research also indicates that HLA-B27 might interact with killer immunoglobulin-like receptors, potentially influencing the risk of axSpA [28,30,31]. Overall, current genetic findings strongly emphasise the role of dysregulated immune signalling – particularly involving cytokines and antigen presentation – in the development of axSpA. However, the underlying mechanisms remain only partially understood, and further studies are needed to fully clarify how these genetic factors contribute to disease onset and progression.

Role of gut microbiota in axSpA

Recent studies have highlighted a strong link between gut microbiome dysbiosis and the development of axSpA. Studies have demonstrated that patients with axSpA often show a significantly different composition of gut bacteria compared to healthy individuals [32]. In particular, there is a noticeable reduction in beneficial species such as *Bacteroides* and an increase in pro-inflammatory bacteria, including various strains of *Prevotella*. Among them, *Prevotella copri* has explicitly been associated with disease activity and immune dysregulation in axSpA [32]. Notably, the presence of specific bacteria like *Prevotella copri* is thought to contribute to immune responses that exacerbate joint inflammation, suggesting a mechanistic role for gut microbiota in axSpA pathology.

The HLA-B27 gene plays a crucial role in the pathogenesis of axSpA and is closely associated with gut dysbiosis [33]. In HLA-B27 transgenic rat models, research has shown that this gene significantly alters the gut microbiome – increasing the presence of *Bacteroides vulgatus* and *Paraprevotella*, while reducing levels of *Rikenellaceae* bacteria [33]. These microbial alterations are linked to immune dysregulation, including elevated Th17 cell populations, which contribute to both intestinal inflammation and joint disease [34,35]. Additionally, transgenic rats showed increased colonisation of *Akkermansia muciniphila* and IgA coating of gut bacteria, further implicating the gut microbiota in axSpA progression [33–35].

Innovative therapeutic strategies targeting the gut microbiota, such as probiotics and faecal microbiota transplantation (FMT), are currently under investigation in the context of axSpA [34]. Probiotic strains, especially those from the *Bifidobacterium* genus, have shown potential in modulating immune responses and helping to restore a healthier microbial balance [36]. Early data from FMT studies also suggest promising results. For instance, increased levels of *Parasutterella* and reduced *Escherichia–Shigella* and *Intestinibacter* align with microbiota changes seen in axSpA patients compared to healthy controls [37].

One fascinating observation is the rise in *Faecalibacterium* levels following FMT, which has been linked to decreased disease activity. This likely stems from its anti-inflammatory properties, including maintaining the Th17/Treg balance and increasing IL-10 production [38,39]. Although previous studies reported higher *Faecalibacterium* levels in axSpA patients, these paradoxical findings may be explained by differences in medication use or disease stage at the time of sampling [37].

However, maintaining long-term remission after FMT remains a challenge. Factors such as lifestyle, diet, and concurrent medications can affect gut microbiota and axSpA disease activity [37]. High dietary fibre and prebiotics may enhance FMT efficacy by promoting beneficial bacteria and increasing short-chain fatty acid production. The interaction between FMT and axSpA treatments

like NSAIDs and tumour necrosis factor inhibitors remains an area for further research [37,39].

Advances in imaging and diagnostics

Early and accurate diagnosis of axSpA is essential to prevent long-term structural damage and improve patient outcomes. To support precise classification, clinicians are encouraged to apply the Assessment of Spondyloarthritis International Society (ASAS)/European Alliance of Associations for Rheumatology (EULAR) classification criteria, mainly when axSpA is suspected based on clinical symptoms and risk factors. According to ASAS, a positive MRI is defined by the presence of:

- Bone marrow oedema in two quadrants in a single section or two consecutive sections in a single quadrant
- Erosion in two quadrants in a single section or two consecutive sections in a single quadrant
- Bone marrow oedema and erosion together in any quadrant in a single section

These criteria help identify early inflammatory changes before radiographic signs become visible [40].

Conventional radiography of the sacroiliac (SI) joints is recommended as the first-line imaging method to assess for sacroiliitis, which is a hallmark feature of axSpA. This method is widely available and can demonstrate structural changes such as joint space narrowing, sclerosis, or bone fusion—all indicative of chronic inflammation [1]. However, in the early stages of the disease, structural damage may not yet be visible on X-rays, underscoring the value of MRI in early detection.

MRI of the sacroiliac joints is particularly recommended in specific clinical scenarios, notably in younger patients or those with a short duration of symptoms, where conventional radiography may not yet reveal structural changes [40]. MRI is also recommended when clinical symptoms strongly suggest axSpA, but X-rays are inconclusive [40,41]. The key advantage of MRI lies in its sensitivity to early inflammatory changes, especially bone marrow oedema, which is considered a marker of active inflammation [42]. Beyond detecting inflammation, MRI can also reveal structural lesions, such as bone erosions, subchondral sclerosis, and fat infiltration, which support the diagnosis and help assess disease progression [42,43].

Recent advancements in imaging techniques, especially functional MRI (fMRI) and positron emission tomography (PET), have significantly improved the early diagnosis and monitoring of diseases such as axSpA [41]. The use of MRI, particularly for visualising early inflammatory changes in the sacroiliac joints and spine, has proven to be more sensitive than traditional X-rays, especially in detecting non-radiographic axial spondyloarthritis (nr-axSpA), an earlier stage of axSpA [40]. This allows for earlier diagnosis, critical for initiating treatment before irreversible structural damage occurs.

Furthermore, artificial intelligence (AI) is revolutionising the field of medical imaging. AI-powered tools, integrated with multimodal imaging, can analyse vast amounts of imaging data to enhance diagnostic precision. Deep learning algorithms, for instance, are being used to enhance PET/MRI images, improving the accuracy of low-dose scans without compromising image quality [44,45]. In axSpA, AI algorithms are being explored to track disease progression and predict treatment response, potentially enabling more tailored and effective therapeutic interventions [45].

These innovations represent a significant step forward in personalised care for patients with axSpA, allowing for earlier and more precise interventions.

Future directions in axSpA treatment

In the future treatment of axSpA, several innovative approaches are poised to transform patient care. One promising direction is personalised medicine, which aims to tailor therapeutic strategies based on individual genetic profiles, environmental exposures, and lifestyle factors. Advances in genomic technologies enable more precise interventions that can address the unique needs of each patient, improving treatment efficacy and reducing side effects [46].

Stem cell therapy also holds significant potential in axSpA management, particularly due to its potential to regenerate tissues damaged by chronic inflammation. Among the most promi-

sing approaches is the use of induced pluripotent stem cells, which can be tailored to individual patients. This personalised strategy may reduce the risk of immune rejection and enhance treatment effectiveness [47].

The study conducted by Li A et al. [48] proved that transfusions of umbilical cord mesenchymal stem cells were not only safe and well-tolerated in axSpA patients but also led to noticeable reductions in disease activity and clinical symptoms. This approach may be especially beneficial in countering the chronic inflammation and joint degeneration characteristic of axSpA.

CRISPR-based gene editing is another promising innovation with potential applications in axSpA. By precisely targeting and correcting genetic mutations linked to the disease, CRISPR technology may one day allow for interventions that prevent disease onset or reduce its severity [49,50]. Recent improvements in CRISPR systems, such as high-fidelity Cas9 variants, have significantly increased the accuracy of gene editing, minimising the risk of unintended genetic changes and bringing this approach closer to clinical application [4].

Taken together, stem cell therapy and CRISPR gene editing represent a new era of regenerative and personalised medicine in axSpA. These technologies could fundamentally change how we manage the disease.

Limitations of the study

This review is limited to English-language publications, which may exclude relevant international research. The included studies vary in design, duration, and patient populations, making comparisons difficult. Some of the discussed therapies, especially those involving the microbiome and gene editing, are still in early stages of research, and their long-term effects remain unclear. Additionally, while recent advances are promising, more robust clinical data are needed to confirm their effectiveness and safety over time.

Conclusions

In recent years, the management of axial spondyloarthritis has progressed significantly, particularly with the introduction of targeted therapies such as IL-17 and JAK inhibitors. These treatments provide effective options for patients who do not respond to conventional approaches and have improved the ability to control disease activity and limit structural damage. The growing understanding of genetic and microbiome-related mechanisms has opened new avenues for personalised care. Imaging innovations and AI-supported diagnostics have enhanced early detection and disease monitoring. While these developments mark substantial progress, their long-term safety and effectiveness still require further investigation. Continued research is essential to validate these approaches and determine how best to combine them in clinical care.

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