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REVIEW ARTICLE

Unraveling Ankylosing Spondylitis: From Immunopathogenesis to Modern Treatment Approaches

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ABSTRACT

Ankylosing spondylitis is a chronic inflammatory rheumatic disease that primarily affects the axial skeleton, resulting in back pain and progressive stiffness. The purpose of this study is to provide an integrated observation in the form of pathophysiology, clinical criteria, and available medical methods. Environmental factors and genetic susceptibility, mainly HLA-B27, are an intricate interaction in AS Etiology. Increased knowledge about immunopathogenesis has added the role of pro-inflammatory cytokines such as IL-17 and TNF-α in the devastating course of the disease. Early diagnosis is indicated but immensely challenging, as the onset is gradual and presenting symptoms are futile. MRI and other radiographic imaging, along with genetic workup and biomarkers, are of most significance in initial identification. With advances in biological therapies with the potential to block various inflammatory cascades, there is hope of improved outcomes and quality of life in patients. Non-pharmacological management in the guise of physiotherapy and lifestyle modification continues to be an integral part of the comprehensive management plan. The review also references the necessity of utilizing a multidisciplinary approach in optimizing patient outcomes in the context of recent advances in the etiology and treatment of AS.

Keywords: Ankylosing spondylitis (AS), Axial spondyloarthritis, HLA-B27, Biological therapy, Targeted therapy, Immunopathogenesis, pro-inflammatory cytokines

1. INTRODUCTION

Ankylosing spondylitis (AS) is a long-term type of inflammatory disease that affects the immune system and mostly affects the axial skeleton[1]. It is part of the most prominent subtypes that are within spondyloarthritis (SpA), which characterizes the features of overlapping genetics, radiography, and various clinical types [2]. Damage to the spine usually occurs insidiously by symptoms, which can eventually appear as structural impairment and complete fusion in advanced cases, otherwise translated into the characteristic 'bamboo spine [3]. Typically, with progressive back stiffness and inflammatory pain. Despite significant advances in the understanding of AS, early diagnosis remains a challenge due to its gradual progression and the nonspecific nature of initial symptoms[4].

The pathogenesis of AS is multifactorial and highly dynamic. On one hand, genetic predisposition triggers the involvement of repeated environmental factors[5]. Associated strongly with AS, the human leukocyte antigen B27 (HLA-B27) varies in prevalence across populations according to the frequency of underlying markers[6]. It has emerged that dysregulated immune pathways, of which oligogenicity and -17 IL-17 features as most important in the pro-inflammatory component of tumor necrosis factor-alpha (TNF-α), are repeatedly associated with disease progression. Such insights have popularized the use of targeted biological treatments: inhibitors of TNF and IL-17, thus altering treatment approaches and greatly improving patient outcomes[7].

The young adult lot faces the highest burden of the disease, with the onset of symptoms occurring in late teenage or early young adulthood. While the disease was regarded as more prevalent in males than females, studies now seem to say that the sex difference may not be as great as previously thought [8]. Without early intervention, AS can lead to enormous structural deformities and disability, thus stressing the necessity for increased awareness and early diagnosis.

To treat any disease successfully, most often, it requires the involvement of different fields: that is, it must include pharmacologic and nonpharmacological aspects like structured physical therapy, and life choices[9]. The way biological agents have changed symptom control and the course of disease, so should complete patient management, including functional rehabilitation and life quality[10]. This review presents a contemporary synthesis of the pathophysiology, diagnostic modalities, and emerging treatment options for AS, mainly focusing on the recent advances in immunopathogenesis and targeted biological therapies.

It is a multidimensional disease management. Medicinal therapy includes non-pharmacological agents such as structured physiotherapy and lifestyle changes. However, the arrival of biological agents changed symptom control and the progression of the disease, but complete patient treatment should consider functional rehabilitation and quality of life. This review is a modern synthesis of pathophysiology, clinical form, and new treatment options for AS, which recently emphasizes the improvement of immunopathogenesis and targeted biological agents. In addition, it also emphasizes early intervention for adapting long-term results for patients and the need for a comprehensive, multidisciplinary approach.

2. ETIOLOGY AND PATHOGENESIS OF ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a chronic, inflammatory, autoimmune disease primarily affecting the axial skeleton, most notably the spine and sacroiliac joints [11]. Its pathogenesis is multifactorial, involving a complex interaction between genetic susceptibility and environmental factors [12]. This section delves into the major components contributing to AS etiology, including the genetic underpinnings, the role of environmental triggers, immune dysregulation, and emerging insights regarding the gut microbiota’s influence on disease development [13].

3. GENETIC SUSCEPTIBILITY AND THE ROLE OF HLA-B27

Genetic factors in AS pathogenesis have been subject to widespread investigations; the most important identified genetic risk factor thus far is the human leukocyte antigen B27 (HLA-B27) [14]. HLA-B27 is a major histocompatibility complex (MHC) class I molecule whose strong association with AS has been thoroughly documented. It is found that AS prevails much more in persons with the HLA-B27 allele. Around 90% of AS patients test positive for HLA-B27[15]. However, the presence of HLA-B27 is a risk factor for AS as opposed to a sufficient condition for the development of the disease. Many individuals carrying HLA-B27 are not afflicted with AS, giving credence to the fact that other genetic and environmental factors might be required in combination for the demonstration of the disease [15].

Currently, there is a lot of activity in terms of understanding how HLA-B27 exposes the individual to AS [16]. One popular theory is the molecular

mimicry hypothesis, in which an aberrant immune reaction is evoked by having HLA-B27, ocean what triggers inflammation. It is postulated that HLA-B27 has some form of misfolding and forms homodimers on the surfaces of the cell, which would be counted by the immune system as foreign and thus generate an inflammatory cascade [17]. In addition, it provides evidence that HLA-27 is upregulated to erroneous activation of T cells, CD8+, which involves the cells in joint and spinal inflammation[18]. Further studies indicate that HLA 27 may be involved with the solid environmental factors regarding the contribution of human genetics to the development of AS because they, together with bacterial antigens, will provide the initial triggers for the disease.

While HLA-B27 remains the most potent genetic risk factor, there are other genes implicated in AS. These include the non-HLA genes IL-23R and ERAP1, and IL-1R, associated with immune regulation and inflammation [19]. For example, IL-23R codes for a receptor whose signaling is critically required for the activation of Th17 cells, a T-cell subset central in AS pathogenesis, especially at the enthesis sites of new bone formation. This provides further evidence of the multi-faceted genetic basis associated with AS [20].

4. ENVIRONMENTAL TRIGGERS AND MICROBIAL HYPOTHESES

Environmental factors are believed to play a critical role in triggering AS in genetically predisposed individuals [21]. While the exact environmental triggers remain elusive, infections, particularly those of the gastrointestinal and urogenital tracts, have been proposed as potential initiating factors[22]. The microbial hypothesis of AS posits that certain bacteria, especially those present in the gut, may trigger an autoimmune response in susceptible individuals, leading to the development of the disease [23].

Enterobacteriaceae, a family of bacterial genera that are characterized by Gram-negativity and commonly found in the gastrointestinal tract, are among the most important microbial candidates for the pathogenesis of AS[24]. Data have reported that patients with AS tend to show changes in the composition of gut microbiota, as reflected mostly by an increased population of specific species of Enterobacteriaceae, for example, Klebsiella pneumoniae [25, 26]. This excessive growth of a bacterium may stimulate AS through an immune reaction that cross-reacts with the tissues of the host, which occurs mostly at the entheses [27]. Gastrointestinal infections or dysbiosis leading to systemic inflammation, and hence effects on the joints, have been proposed by the gut-bone axis hypothesis [28].

Furthermore, AS may also include infection with urogenital pathogens as a possible factor related to gut microbiota [29]. For example, Chlamydia trachomatis has been linked as a cause of AS in certain patients, particularly those who had prior reactive arthritis[30]. It is a key assumption of environmental pathogenesis theory: that microbial antigens cross-react with host tissue, and thus activate autoimmune responses [31]. Despite all this, the direct causative role of certain microbes could never have been fully delineated, as more research needs to be done on the nexus between infections and AS initiation.

5. IMMUNE DYSREGULATION AND KEY INFLAMMATORY PATHWAYS

The immune system represents an important factor in the pathogenesis of AS. The inflammation in AS occurs primarily at the entheses, the areas in which tendons and ligaments attach to bone, and inflammation is accountable for causing new bone formation and possibly fusion of the spine [32]. The major inflammatory pathway involved in AS is the activation of the innate immune system, mainly by pro-inflammatory cytokines that include tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23). These cytokines drive the inflammation that is pathognomonic for AS [33].

TNF-α, a major cytokine for many autoimmune diseases, has been identified as central to AS pathology. It induces the recruitment of immune cells to the site of inflammation, induces other pro-inflammatory cytokines, and induces new bone formation at entheses [34]. Thus, TNF inhibitors have been developed that are extremely effective in alleviating inflammation and disease activity in patients with AS. Considerable evidence also exists pointing to the role of TNF-α in AS, because TNF inhibitors have been found to greatly relieve symptoms and improve functioning in these patients [35].

IL-17 and IL-23 are central when it comes to the pathogenesis of ankylosing spondylitis in the Th17 immune pathway. Th17 cells are a special subset of T-helper cells that secrete IL-17 and other pro-inflammatory cytokines [36]. Aspects of the IL-17 have earlier established what it triggers in other inflammatory mediators like matrix metalloproteinases (MMPs), which, combined, also participate in the damage of tissues and bone remodeling. The IL-23/IL-17 axis plays major roles in the formation of new bone and the chronic inflammation in AS. This explains why agents like REUMAMA are promising therapeutic options for the treatment of AS: they are IL-17 inhibitors and

have proven to be welfare interventions in the alleviation of inflammation as well as improvement of outcomes for patients [37].

New research continues to open the use of innate immune cells such as macrophages, dendritic cells, and, in particular, those operated by natural killer (NK) cells, from the initiation of AS to its propagation [38]. Their interest in very high terms for these innate immune cells implicates recognition of microbial signals or other signals derived from host sources, which contribute to the inflammatory response [39]. In AS pathogenesis, this event is very important as it relates to the release of IL-1β, which is typically known to contribute to the driving force causing inflammation and bone remodeling because activation of the NLRP3 inflammasome, which represents a protein complex responsible for activating the pro-inflammatory cytokines [40].

6. THE ROLE OF GUT MICROBIOTA IN AS PATHOGENESIS

Emerging evidence has demonstrated a critical role of gut microbiota in AS pathogenesis. It is a vast setting with an array of microbes that affect normal immune function [41]. Dysbiosis or imbalance of gut microbiota has been correlated with various autoimmune diseases, including AS. Changes in the gut microbiome in AS patients were noted, where increased abundance was of the family Enterobacteriaceae with decreased diversity of microbial species (**Figure 01**). This microbial shift has the prospect of causing system-wide inflammation affecting the host's innate immune activation or molecular mimicry, i.e., the resemblance of microbial antigens to host tissues [42].

Gut-bone axis hypothesis suggests that dysbiosis in the gut could evoke an attack of systemic inflammation that ultimately gives rise to AS, especially via activation of Th17 cells[43]. This proposal has received credence in animal models because gut microbiome conditioning has been noted to affect the severity of AS-like disease[44]. Modulation of the gut microbiota in AS models by antibiotics and probiotics adds more strength to the argument of the involvement of the gut in the disease pathogenesis[32]. The possibility of utilizing this entryway to target the microbiome as a therapeutic approach for AS is thus an intriguing and promising area of future investigations. Such studies may, therefore, yield an invaluable novel entryway for disease prevention and management strategies[45].

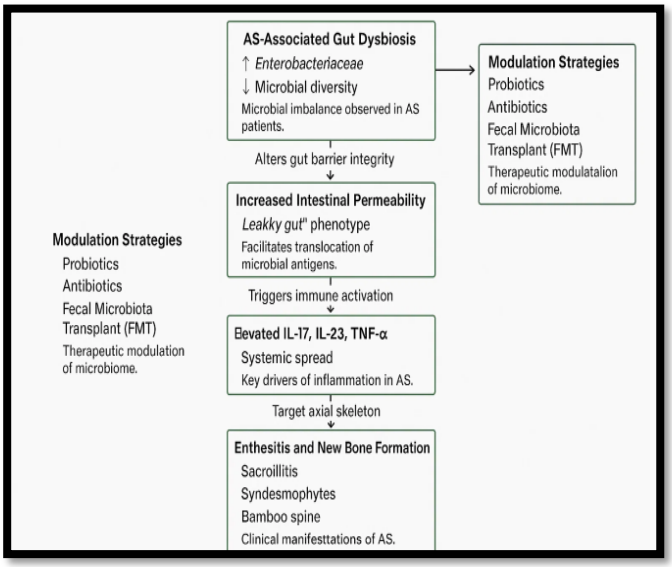

Figure 01. Flowchart of the Gut–Bone Axis in Ankylosing Spondylitis.

Gut dysbiosis in AS is characterized by increased Enterobacteriaceae and reduced microbial diversity, contributing to increased gut permeability. Translocation of microbial antigens activates innate and adaptive immunity, including Th17 cells, via molecular mimicry. Systemic pro-inflammatory cytokines such as IL-17 and TNF-α propagate inflammation at entheses and spinal joints, leading to sacroiliitis and syndesmophyte formation. Modulation strategies targeting the microbiome may represent novel therapeutic approaches.

7. CLINICAL MANIFESTATIONS, DISEASE PROGRESSION, AND DIAGNOSTIC APPROACHES IN ANKYLOSING SPONDYLITIS

CLINICAL MANIFESTATIONS AND DISEASE PROGRESSION

Ankylosing spondylitis (AS), being chronic and progressive, is an inflammatory disorder that mainly affects axial skeletons, the sacroiliac joints, and the spine[46]. From patient to patient, clinical expression of symptoms may vary greatly from mild discomfort to severe disability. These diseases can deceptively subside and rather slow down in their progression, such a case may arise, and major functional involvement is due [47]. This section will explore the clinical manifestations of AS, which include the presentation and early symptoms, extra-articular manifestations, and radiographic progression of the disease [48].

8. EARLY SYMPTOMS AND THE SPECTRUM OF INFLAMMATORY BACK PAIN

The main clinical feature of ankylosing spondylitis (AS) is inflammatory back pain, which typically has an insidious onset in late adolescence or early adulthood, with most patients developing symptoms before the age of 45. Unlike mechanical back pain, which is usually acute and improves with rest, inflammatory back pain develops gradually over weeks to months and is characterized by several distinguishing features. Patients often report morning stiffness lasting more than 30 minutes, improvement with physical activity, and worsening of symptoms during periods of rest. Nocturnal pain is also common, frequently waking patients during the second half of the night. Additionally, nonsteroidal anti-inflammatory drugs (NSAIDs) usually provide temporary symptomatic relief. Patients with AS may experience progressive stiffness and reduced spinal mobility due to ongoing inflammation and fibrosis at the entheses, which are the sites where tendons and ligaments attach to bone [49]. The sacroiliac joints are typically the earliest sites of involvement, resulting in sacroiliitis that manifests as pain in the lower back, buttocks, and hips. Over time, inflammation may extend to the thoracic and cervical spine, leading to structural changes such as severe kyphosis and the characteristic spinal fusion described as "bamboo spine" [50].

9. EXTRA-ARTICULAR MANIFESTATIONS AND COMORBIDITIES

Beyond axial involvement, ankylosing spondylitis (AS) is associated with a range of extra-articular manifestations (EAMs) that contribute substantially to morbidity and diminish patient quality of life. Among these, uveitis is the most frequent EAM, occurring in approximately 25–40% of patients. It is typically characterized by acute anterior uveitis presenting as unilateral eye pain, photophobia, blurred vision, and redness, and is often recurrent, requiring prompt treatment with corticosteroids to prevent complications [51].

Cardiovascular involvement in AS includes aortitis, aortic regurgitation, and conduction abnormalities. Patients with AS are also at increased risk of cardiovascular disease due to chronic systemic inflammation, endothelial dysfunction, and accelerated atherosclerosis [52]. Pulmonary involvement is another important consideration, with restrictive lung disease arising from costovertebral joint involvement and reduced chest wall expansion. Although rare, apical pulmonary fibrosis can develop in advanced stages of the disease [53]. Gastrointestinal involvement is also well documented. A significant proportion of patients exhibit subclinical inflammatory bowel disease (IBD) or chronic gut inflammation, with approximately 5–10% developing clinically apparent Crohn's disease or ulcerative colitis [54]. Additionally, patients with AS are at increased risk of osteoporosis and vertebral fractures, which are driven by chronic inflammation and reduced spinal mobility. Vertebral fractures can be catastrophic, leading to neurological complications and increased mortality [55]. Finally, while AS predominantly affects the axial skeleton, some patients develop peripheral arthritis, typically involving the hips, shoulders, and knees. Enthesitis, or inflammation at the sites where tendons and ligaments attach to bone, such as the Achilles tendon or plantar fascia, is a hallmark of spondyloarthropathies and is commonly observed in AS [56].

10. RADIOGRAPHIC AND STRUCTURAL CHANGES IN THE AXIAL SKELETON

As ankylosing spondylitis (AS) progresses, structural changes in the axial skeleton become increasingly apparent, with radiographic features serving as critical markers of disease severity. One of the earliest and most characteristic radiographic findings is sacroiliitis, which manifests as symmetric sacroiliac joint erosion and sclerosis. While conventional radiography remains the primary diagnostic tool, magnetic resonance imaging (MRI) is often required for early detection of subtle inflammatory changes [57]. Another hallmark of disease progression is the formation of syndesmophytes—bony outgrowths that develop between vertebral bodies as a consequence of chronic inflammation and new bone formation. Syndesmophyte formation contributes to spinal fusion and rigidity, producing the characteristic "bamboo spine" appearance on radiographs [58]. Progressive ankylosis and spinal fusion result from the ossification of spinal ligaments and intervertebral discs, leading to marked reductions in spinal flexibility and an increased risk of fractures. The thoracic and cervical regions are commonly affected, often resulting in a reduced range of motion and kyphotic deformity [59]. In addition, Romanus lesions—representing inflammatory changes at the vertebral corners—are important early features, frequently detected on MRI as bone marrow edema. With disease progression, these lesions can evolve into sclerosis and squaring of vertebral bodies, further contributing to structural rigidity [60]. Early

recognition of these radiographic changes is crucial for timely diagnosis and intervention, highlighting the importance of imaging modalities in AS diagnosis.

11. DIAGNOSTIC APPROACHES

Diagnosing ankylosing spondylitis (AS) presents a considerable clinical challenge due to its insidious onset and the overlap of symptoms with other causes of chronic back pain. A definitive diagnosis often requires a combination of clinical assessment, imaging studies, and laboratory investigations [61]. The Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial spondyloarthritis (axSpA) have become the most widely adopted framework for identifying AS. For patients with radiographic axSpA—also referred to as established AS—the criteria include radiographic sacroiliitis, defined as bilateral sacroiliac joint involvement of grade ≥2 or unilateral involvement of grade 3–4, along with at least one additional spondyloarthritis (SpA) feature such as inflammatory back pain, enthesitis, or HLA-B27 positivity [62]. In cases of non-radiographic axSpA (nr-axSpA), early-stage disease is identified by either HLA-B27 positivity with two or more SpA features, or sacroiliitis detected via magnetic resonance imaging (MRI) along with at least one SpA feature. These classification criteria have facilitated earlier diagnosis, even in the absence of radiographic changes, thereby improving outcomes through timely therapeutic intervention [63]. Imaging plays a central role in the diagnostic workup of AS. Conventional radiography remains the first-line modality for detecting structural changes in the sacroiliac joints and spine; however, it is limited by its inability to detect early inflammatory changes, as radiographic findings often take years to appear [64]. MRI has emerged as the preferred technique for early detection of sacroiliitis and bone marrow edema, enabling diagnosis of nr-axSpA before irreversible structural damage occurs [65]. Computed tomography (CT), while offering superior resolution for sacroiliac joint erosions, is less commonly employed due to its higher radiation exposure [66]. Ultrasound has utility in identifying enthesitis in cases of peripheral involvement but provides limited diagnostic value for axial disease [67].

Laboratory testing, although not definitive, can support clinical and imaging findings. Testing for HLA-B27 is commonly performed due to its strong association with AS, although it is not diagnostic in isolation [[68]. Inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may be elevated in active disease but are normal in a substantial subset of patients [69]. Emerging biomarkers such as calprotectin are under investigation, particularly for their role in identifying subclinical gut inflammation in AS patients [70]. Despite advances in diagnostic modalities, early diagnosis remains problematic. Overlapping symptoms with mechanical back pain and other inflammatory disorders often result in delayed referrals to rheumatologists and prolonged diagnostic latency. Additionally, non-radiographic forms of the disease are frequently under-recognized in primary care settings. Differential diagnoses to consider include degenerative disc disease, mechanical low back pain, rheumatoid arthritis, and diffuse idiopathic skeletal hyperostosis (DISH). Therefore, a comprehensive clinical evaluation supported by appropriate imaging and laboratory findings is essential for accurate diagnosis and timely management of AS [71].

12. CURRENT AND EMERGING TREATMENT STRATEGIES, MULTIDISCIPLINARY MANAGEMENT, AND FUTURE DIRECTIONS IN ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton, leading to progressive pain, stiffness, and, in severe cases, spinal fusion. The therapeutic landscape for AS has evolved substantially in recent decades, particularly with the advent of biological therapies that have revolutionized disease management [72]. Nevertheless, significant challenges persist in optimizing treatment strategies, achieving early detection, and implementing personalized medicine. This section reviews current and emerging therapeutic approaches, the importance of multidisciplinary management, and future directions in the care of patients with AS (**Table 01**).

Table 01. Clinical Outcomes and Drug Development in Ankylosing Spondylitis.

Drug Class / Target	Example Drugs	Mechanism of Action	Clinical Outcomes	Development Status / Notes
NSAIDs	Ibuprofen, Naproxen,	COX inhibition → ↓	Symptom relief,	First-line therapy;

	Diclofenac, Celecoxib	Prostaglandin synthesis	improved spinal mobility, and possible slowing of radiographic progression	risks include GI bleeding and cardiovascular events.
Traditional DMARDs	Methotrexate, Sulfasalazine	General immunomodulation	Limited efficacy in axial disease; benefit in peripheral arthritis	Sulfasalazine is recommended for peripheral joint involvement.
TNF-α Inhibitors	Infliximab, Etanercept, Adalimumab, Golimumab, Certolizumab pegol	TNF-α blockade → ↓ Inflammatory cytokine signaling	Reduced disease activity, improved function, and slowed structural progression	Approved for AS; risk of infections (TB reactivation), malignancies.
IL-17 Inhibitors	Secukinumab, Ixekizumab	IL-17A blockade → ↓ Enthesitis, ↓ New bone formation	Significant reduction in disease activity, improved mobility	Approved for AS; may increase Candida infections.
IL-23 Inhibitors (emerging)	Guselkumab, Risankizumab	IL-23 blockade → Inhibits Th17 differentiation	Promising results in early trials; ↓ IL-17 pathway activity	Under investigation; potential future option for AS.
JAK Inhibitors (emerging)	Tofacitinib, Upadacitinib	Inhibits JAK-STAT signaling pathways	Reduces disease activity in trials; effective in RA, PsA	Clinical trials ongoing for AS; potential oral option.
Microbiome-targeted Therapies	Probiotics, Fecal Microbiota Transplantation (FMT)	Modulates gut dysbiosis	Experimental; potential for reducing systemic inflammation	Research stage; recognizing gut-joint axis in AS pathogenesis.
Adjunctive Non-Pharmacologic Therapies	Physical therapy, Exercise, Lifestyle modification	Maintains spinal mobility, reduces stiffness, and improves posture	Improved long-term function, quality of life	An essential part of multidisciplinary management.

Conventional pharmacological treatment of AS continues to rely on nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy. NSAIDs provide symptomatic relief and improve spinal mobility by inhibiting cyclooxygenase (COX) enzymes and reducing pro-inflammatory prostaglandin production [73]. Both non-selective NSAIDs (such as ibuprofen, naproxen, and diclofenac) and COX-2 selective inhibitors (such as celecoxib and etoricoxib) are used, with the latter offering reduced gastrointestinal toxicity [74]. Continuous NSAID use has been associated with not only symptomatic improvement but also a potential slowing of radiographic progression due to reduced inflammation at the entheses. However, long-term use requires careful monitoring due to risks of gastrointestinal bleeding and cardiovascular events,

highlighting the need for individualized treatment plans.

Traditional synthetic disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate and sulfasalazine, have limited efficacy in treating axial disease but may provide benefits in patients with peripheral arthritis. Sulfasalazine, in particular, has demonstrated utility in reducing inflammation in cases with concomitant peripheral joint involvement, although it does not significantly impact axial manifestations [73].

Biological therapies have transformed AS treatment by targeting specific inflammatory pathways central to disease pathogenesis [74]. Tumor necrosis factor-alpha (TNF-α) inhibitors have shown robust efficacy in reducing disease activity, improving functional outcomes, and slowing radiographic progression [73]. Currently approved TNF inhibitors include infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol. These agents are particularly beneficial for patients who do not respond adequately to NSAIDs. Nonetheless, TNF inhibitors carry risks such as increased susceptibility to infections, reactivation of latent tuberculosis, and potential malignancy, necessitating careful screening and monitoring.

Interleukin-17 (IL-17) inhibitors have emerged as an alternative for patients with inadequate responses or contraindications to TNF inhibitors. IL-17 is a key cytokine in AS pathogenesis, driving enthesitis and new bone formation [77]. Secukinumab and ixekizumab, both targeting IL-17A, have demonstrated significant reductions in disease activity, improved spinal mobility, and sustained symptom relief in clinical trials. However, IL-17 blockade may increase susceptibility to fungal infections, particularly Candida species, due to its role in mucosal immunity.

Future therapeutic targets are under active investigation to improve treatment efficacy and minimize adverse effects. Interleukin-23 (IL-23) inhibitors such as guselkumab and risankizumab, which act upstream in the Th17 pathway, are showing promise in early trials for AS. Janus kinase (JAK) inhibitors, including tofacitinib and upadacitinib, have demonstrated success in other inflammatory diseases and are being studied for their potential to reduce disease activity in AS. In addition, emerging research suggests that gut dysbiosis may play a role in AS pathogenesis, prompting exploration of microbiome-modulating interventions such as probiotics and fecal microbiota transplantation as adjunctive treatments. Advances in genomic analysis and biomarker discovery, including serum calprotectin, C-reactive protein (CRP), and genetic profiling, may eventually enable personalized treatment regimens tailored to individual patient profiles [75]. Optimal management of AS requires a multidisciplinary approach that extends beyond pharmacologic interventions. Physical therapy is a cornerstone of comprehensive care, aiming to maintain spinal mobility, reduce stiffness, and prevent functional impairment. Structured exercise programs should incorporate stretching and range-of-motion exercises to maintain flexibility, strength training to improve core stability, aerobic activities to promote cardiovascular health, and hydrotherapy to alleviate pain and enhance mobility. Supervised physiotherapy has been shown to improve functional outcomes and may slow disease progression.

Lifestyle modification and patient education are also critical components of AS management. Postural training is essential to prevent kyphotic deformities, while smoking cessation is strongly recommended, as smoking is associated with more severe disease progression and increased cardiovascular risk. Dietary interventions emphasizing anti-inflammatory foods rich in omega-3 fatty acids, antioxidants, and fiber may also contribute to reducing systemic inflammation. Weight management is important to minimize mechanical stress on affected joints and limit inflammation. Patient education empowers individuals to engage actively in their care, improving adherence to therapy and overall quality of life.

Psychological and social considerations must also be addressed in the holistic management of AS. Chronic pain and disability can contribute to significant psychological distress, including anxiety and depression. Cognitive behavioral therapy (CBT) can help patients develop effective coping strategies for managing pain-related distress, while mindfulness techniques, yoga, and meditation may further support stress reduction and overall well-being. Participation in patient support groups and networks provides emotional support and practical advice, fostering a sense of community and resilience [76]. Despite these advances, important challenges remain in AS management. Key unanswered questions persist regarding the triggers of disease onset in genetically susceptible individuals, the precise role of gut microbiota, and the interactions between environmental and genetic factors. Diagnostic delays remain common due to the subtle and insidious onset of symptoms, underscoring the need for improved biomarkers and imaging modalities that enable earlier detection. Variability in treatment response highlights the importance of developing individualized therapeutic approaches.

Looking ahead, advances in genomics, biomarker research, and machine learning hold the promise of enabling precision medicine in AS, tailoring treatment to patients' molecular and genetic profiles (**Table 02**). Novel therapeutic targets such as JAK inhibitors and IL-23 blockade, as well as combination approaches that integrate biologics with microbiome-targeted interventions, represent exciting frontiers that may further transform the management of this complex and debilitating disease [77].

Table 2. Precision Medicine in Ankylosing Spondylitis: Therapeutics, Biomarkers & Clinical Trials.

Precision Intervention	Biomarker or Genetic Target	Clinical Trial or Study & Phase	Outcomes & Status
Selective JAK1 inhibitors	JAK–STAT pathway	LNK01001 (JAK1 inhibitor) – Phase II trial; enrolled 177 patients	Achieved ASAS40 at week 12; rapid onset, favorable safety profile; advancing to Phase III
		Upadacitinib – FDA approved for axSpA (Feb 2023)	Oral JAK1 inhibitor, an effective alternative to biologics
Pan-JAK/Selective JAK1 inhibitors	JAK-STAT	Tofacitinib, Filgotinib – under clinical investigation	Filgotinib shows RA efficacy; AS-specific trials ongoing
IL-17A/IL-17F blockade	IL-17 cytokine signaling	Bimekizumab – approved for axSpA (2023 US, 2021 EU)	Dual IL-17A/F neutralization; upper respiratory infections, candidiasis noted
		Izokibep – Phase III planned for axial SpA	IL-17A Affibody; small size may enhance tissue penetration
IL-23p19 inhibition	Th17/IL-23 pathway	Risankizumab – Phase II proof-of-concept; did not reach primary endpoint	No significant ASAS40 improvement; IL-23 may be less central in AS
		Guselkumab, Tildrakizumab – early-phase studies	Target upstream IL-23 axis; awaiting results
NLRP3 inflammasome inhibitors	IL-1β/IL-18 pathway	DFV890 – Phase I safety study in healthy subjects	Well tolerated; next step, AS-focused trials to follow
Apremilast (PDE-4 inhibitor)	cAMP modulation in inflammation	Randomized controlled trial ongoing in AS	Oral agent; moderate efficacy expected from psoriasis/psoriatic arthritis context
Genomics-guided biomarker stratification	HLA-B27, ERAP1, IL23R, ACSL1, SLC40A1, XBP1	Multi-omics: genomics + proteomics + transcriptomics studies	Identified pathways and biomarkers – potential future targets

AI-enabled imaging biomarkers	MRI-based inflammation quantification	VHI (Volume of Hyperintense Inflammation) via deep learning	Enables quantitative monitoring of treatment response

13. CONCLUSION

Ankylosing spondylitis (AS), a chronic inflammatory disease of the axial skeleton, is characterized by progressively worsening pain, stiffness, and finally, spinal fusion. The multifactorial pathogenesis of AS includes extreme genetic susceptibility (especially through HLA-B27), pro-inflammatory cytokine-driven immune imbalance like TNF-α and IL-17, and also perhaps recent findings regarding the role of gut microbiota in the pathogenesis, as suggested by possible relationships between intestinal dysbiosis and systemic inflammation. The clinical manifestations of AS include inflammatory back pain, peripheral arthritis, enthesitis, and extra-articular features like uveitis, cardiovascular disease, and inflammatory bowel disease. Diagnosis has advanced with MRI, which can demonstrate inflammation in the sacroiliac joints before any changes become apparent on conventional X-ray. However, there remain significant delays in the diagnosis itself, indicating a need for better biomarkers and screening techniques.

In terms of treatment, NSAIDs remain the first-line pharmacological therapy, offering symptom relief and potential disease-modifying effects. The advent of biologic therapies, particularly TNF-α inhibitors and IL-17 blockers, has revolutionized AS management by targeting key inflammatory pathways and improving patient outcomes. Novel therapeutic strategies, including IL-23 inhibitors, JAK inhibitors, and microbiome-based interventions, are under investigation and hold promise for patients who do not respond to existing treatments. Beyond pharmacologic interventions, multidisciplinary care encompassing physical therapy, exercise, lifestyle modifications, and psychosocial support is essential for maintaining functional capacity and quality of life in AS patients.

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CONSENT FOR PUBLICATION

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AVAILABILITY OF DATA AND MATERIALS

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