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Evolving Paradigms in Axial Spondyloarthritis Management: A Review of Contemporary Treatment Strategies

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Abstract: Objective: Axial spondyloarthritis (axSpA), encompassing ankylosing spondylitis and non-radiographic axSpA, is a chronic inflammatory disease that imposes a significant burden on patients through pain, stiffness, and potential long-term structural damage to the spine. This review synthesizes the current, state-of-the-art evidence on the management of axSpA, from foundational therapies to advanced biologic treatments and modern strategic approaches.

Methods: A comprehensive literature review was conducted, focusing on influential publications that shape the contemporary standard of care. Sources included the 2019 ACR/SPARTAN/SLR treatment recommendations, pivotal clinical trials, expert reviews on therapeutic mechanisms and outcomes, and meta-analyses of non-pharmacological interventions.

Results: The management of axSpA is built upon a foundation of non-pharmacological interventions, with strong evidence supporting the efficacy of structured exercise programs in improving physical function [8]. NSAIDs remain the first-line pharmacological treatment for symptom control [1]. For patients with an inadequate response to NSAIDs, biologic therapies, particularly TNF-α inhibitors (anti-TNFs), have revolutionized care by providing substantial and rapid improvements in disease activity and quality of life [2, 4]. However, their ability to definitively halt radiographic progression remains a subject of investigation, with structural damage persisting as a key concern [3]. More recent advances include the approval of drugs with different mechanisms of action, such as IL-17 and JAK inhibitors [7]. Furthermore, there is a paradigm shift towards goal-oriented strategies like Treat-to-Target (T2T), an approach validated by the TICOSPA trial, which demonstrated superior outcomes with a tight-control protocol [5, 6].

Conclusion: The therapeutic landscape for axSpA has evolved dramatically, moving beyond simple symptom relief towards a multi-faceted, goal-directed approach. The integration of non-pharmacological methods, established pharmacotherapies, and strategic management frameworks offers the potential to significantly improve patient outcomes. Preventing long-term structural damage, however, remains the critical unmet need guiding future research.

Keywords: Axial Spondyloarthritis, Ankylosing Spondylitis, Non-radiographic Axial Spondyloarthritis, Treat-to-Target, Biologic Therapy, TNF inhibitors, Structural Progression.

Introduction:

Redefining a Spectrum of Disease

Axial spondyloarthritis (axSpA) represents a spectrum of chronic, immune-mediated inflammatory diseases that primarily target the axial skeleton, including the sacroiliac joints and the spine, although peripheral joints and extra-articular sites can also be affected [7]. For decades, the understanding and classification of this condition were anchored to the presence of definitive structural damage visible on plain radiographs. This historical reliance on radiographic

evidence meant that patients could endure years of debilitating symptoms before a definitive diagnosis of ankylosing spondylitis (AS) could be made. This delay in diagnosis was a significant barrier to early intervention. A contemporary understanding, however, recognizes axSpA as a single disease entity with two principal classifications: AS, also known as radiographic axSpA, where clear sacroiliitis is evident on X-rays according to the modified New York criteria; and non-radiographic axial spondyloarthritis (nr-axSpA), a condition characterized by similar clinical symptoms but without the requisite radiographic evidence of structural damage [1, 7]. The establishment of the nr-axSpA classification was a critical evolution, allowing for earlier diagnosis and treatment for a previously underrecognized patient population. This modern classification acknowledges that nr-axSpA is not necessarily a benign or early form of AS but a distinct, often equally burdensome, manifestation of the same underlying disease process, capable of causing significant pain and disability. Patients across the axSpA spectrum share a common pathophysiology driven by complex genetic predispositions, notably the human leukocyte antigen (HLA)-B27 allele, and dysregulated immune pathways, particularly involving cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17).

1.1. The Historical Lens: From Ankylosing Spondylitis to a Broader Spectrum

The term "ankylosing spondylitis," derived from Greek words meaning "crooked" (ankylos) and "vertebra" (spondylos), has been recognized for centuries, describing a condition of progressive spinal stiffness. For most of the 20th century, diagnosis was entirely dependent on the modified New York criteria, which required the presence of definitive radiographic sacroiliitis. This created a paradox: a diagnosis could often only be confirmed after irreversible structural damage had already occurred. This meant that countless individuals, particularly women in whom radiographic progression can be slower, suffered from significant inflammatory back pain and functional decline for 5-10 years on average before meeting the criteria for a diagnosis and, consequently, for effective treatment.

The paradigm shift occurred with the advent of advanced imaging, particularly Magnetic Resonance Imaging (MRI), and a deeper understanding of the disease's early stages. Researchers recognized that a large population of patients had the full clinical syndrome of axSpA—inflammatory back pain, enthesitis, and a strong response to anti-inflammatory medication—but lacked the X-ray changes. This led to the development of the Assessment of SpondyloArthritis international Society (ASAS) classification criteria, which formally introduced the concept of nr-axSpA. These criteria allow for a diagnosis based on either the presence of sacroiliitis on MRI in a patient with typical back pain or the presence of the HLA-B27 gene along with other clinical features of SpA [1, 7]. This conceptual evolution was not merely academic; it was a crucial step toward earlier diagnosis and intervention, aiming to treat the disease before the onset of permanent structural damage.

Table 1. Comparison of Axial Spondyloarthritis (axSpA) Classifications

Feature	Ankylosing Spondylitis (AS) (Radiographic axSpA)	Non-radiographic axSpA (nr-axSpA)	Key Reference(s)
Core Symptoms	Chronic inflammatory back pain, stiffness, fatigue, enthesitis.	Clinically indistinguishable from AS; chronic inflammatory back pain, stiffness, fatigue.	[1], [7]
Radiographic Sacroiliitis (X-ray)	**Required for diagnosis:** Definitive changes according to modified New York criteria.	**Absent by definition:** No definitive radiographic sacroiliitis.	[1]

MRI Findings	May show active inflammation (bone marrow edema) or chronic structural changes.	Often shows active inflammation (bone marrow edema) in sacroiliac joints, supporting diagnosis.	[7]
Patient Burden	Associated with significant functional limitation and reduced quality of life.	Disease burden, including pain and functional impairment, is comparable to AS.	[1]

1.2. The Profound Burden of Axial Spondyloarthritis

The clinical challenge presented by axSpA is profound and multifaceted, extending far beyond localized back pain. The disease imposes a significant and pervasive burden on patients, fundamentally impacting their physical function, social engagement, and overall quality of life through a constellation of debilitating symptoms. The cardinal features are chronic inflammatory back pain and progressive stiffness, which are often worse with rest and improve with activity—a hallmark that distinguishes it from the far more common mechanical back pain. This pain can disrupt sleep and severely limit daily activities. It is frequently accompanied by profound fatigue, an often-underestimated symptom that can be as disabling as the pain itself, alongside enthesitis (inflammation at sites where tendons and ligaments attach to bone) and peripheral arthritis [1].

Beyond the immediate symptomatic burden, the most formidable challenge in the long-term management of axSpA is the prevention of irreversible structural damage. The underlying inflammatory process can trigger pathological new bone formation, leading to the development of syndesmophytes—bony bridges that grow between vertebrae. Over time, this relentless process can result in the complete fusion of the spine, a condition often referred to as "bamboo spine," leading to a severe and permanent loss of spinal mobility and physical function [2, 3]. This structural progression represents the ultimate manifestation of the disease's destructive potential and underscores the critical need for therapeutic strategies that go beyond mere symptom control to actively modify the disease course and preserve long-term function [3].

- Physical Burden: Chronic pain, loss of spinal flexibility, and development of a stooped posture.
- Psychological Impact: High rates of anxiety and depression are associated with chronic pain and disability.
- Socioeconomic Consequences: Significant impact on work productivity, leading to work disability in up to 30-50% of patients over the long term.
- Extra-Articular Manifestations: The disease can affect other organs, including acute anterior uveitis (eye inflammation), psoriasis (skin), and inflammatory bowel disease (gut).
- Increased Cardiovascular Risk: Chronic systemic inflammation is associated with an elevated risk of cardiovascular events.

1.3. Purpose and Structure of this Review

Therefore, the primary objective of this review is to synthesize the current, state-of-the-art evidence on the management of axSpA. We will navigate the evolving therapeutic landscape, charting the journey from foundational, conventional treatments to the era of biologic therapies and the dawn of targeted synthetic molecules. This review will cover the full spectrum of recommended interventions, including essential non-pharmacological approaches, first-line pharmacological treatments with nonsteroidal anti-inflammatory drugs (NSAIDs), and the transformative impact of biologic disease-modifying antirheumatic drugs (bDMARDs). A central focus will be placed on evaluating modern treatment philosophies, most notably the "Treat-to-Target" (T2T) strategy, which advocates for a proactive, goal-directed approach to management. By critically examining the evidence underpinning these strategies, this review aims to provide a comprehensive overview for clinicians and researchers, highlighting both the remarkable progress made in the field and the persistent challenges that continue to drive clinical research.

This article is structured to guide the reader systematically through the key pillars of axSpA management. Following this introduction, the Methods section will detail the literature selection strategy. The

Results section, which forms the core of the review, is organized thematically to present the evidence for foundational, biologic, and strategic interventions. Finally, the Discussion and Conclusion will synthesize these findings, contextualize their clinical implications, and offer a perspective on the future of axSpA care.

Section Summary: The understanding of axSpA has evolved from focusing solely on the late-stage, radiographic form (AS) to a broader spectrum that includes non-radiographic disease (nr-axSpA), allowing for earlier diagnosis. The disease imposes a heavy physical, psychological, and socioeconomic burden, driven by inflammation and the risk of irreversible spinal fusion. This review will explore the full range of modern management strategies, from foundational care to advanced therapies and goal-oriented approaches like Treat-to-Target.

METHODS

This article is a comprehensive, state-of-the-art literature review designed to synthesize the current evidence base and expert consensus guiding the management of axial spondyloarthritis. The methodology did not involve a systematic review protocol with a predefined search algorithm or meta-analytic statistical analysis. Instead, the approach was based on a curated selection of high-impact, peer-reviewed publications that have been influential in shaping the contemporary understanding and clinical practice of axSpA treatment. The selection was intentionally focused on sources that provide a broad yet deep perspective on the evolution of care, from foundational principles to the latest strategic innovations. The rationale for this narrative review approach was to construct a coherent and readable synthesis of a complex and rapidly evolving field, suitable for both specialist and generalist medical audiences.

The scope of this review encompasses evidence-based management strategies for the full spectrum of axSpA, including both non-radiographic axSpA (nr-axSpA) and ankylosing spondylitis (AS). The core sources for this review were chosen for their authority and relevance to modern clinical questions.

- Guideline Documents: The landmark 2019 American College of Rheumatology (ACR)/Spondylitis Association of America (SAA)/Spondyloarthritis Research and Treatment Network (SPARTAN) recommendations were selected as the foundational text for this review, as they represent a rigorous, evidence-based consensus from leading international experts [1].
- Mechanistic and Efficacy Reviews: Targeted reviews and clinical studies examining the role and efficacy of anti-TNF alpha therapy were included to explain the mechanism and impact of the first class of biologic therapies that revolutionized care [2, 4].
- Expert Commentaries on Unmet Needs: Expert reviews that critically assess the persistent challenge of structural disease progression were chosen to highlight the key limitations of current therapies and the primary focus of ongoing research [3].
- Pivotal Clinical Trials and Strategy Papers: Research and reviews that define and evaluate the "Treat-to-Target" (T2T) strategy, most notably the open-label, pragmatic, cluster-randomised TICOSPA trial, were included to provide the evidence base for modern management philosophies [5, 6].
- Summaries of New Advances: Broad-based reviews were used to summarize new advances in diagnosis and the overall management of axSpA, including the introduction of newer classes of therapy [7].
- Meta-Analyses of Non-Pharmacological Care: A comprehensive meta-analysis of randomized controlled trials was selected to quantify the effectiveness of non-pharmacological exercise programs, emphasizing their role as a cornerstone of management [8].

Together, these selected references form a robust and representative basis from which to construct a detailed narrative of the current state of axSpA management, from foundational principles to the cutting edge of therapeutic strategy.

Section Summary: This article is a narrative literature review based on a curated selection of high-impact sources. The methodology involved choosing authoritative guidelines, pivotal clinical trials, meta-analyses, and expert reviews to build a comprehensive and coherent overview of modern axSpA management, covering the entire disease spectrum.

RESULTS

Part I: The Foundational Pillars of axSpA Care

The modern management of axial spondyloarthritis is conceptualized as a multi-tiered pyramid, with a broad and essential base of foundational therapies upon which all subsequent pharmacological interventions are built. The 2019 ACR/SPARTAN/SLR guidelines, along with international consensus, unequivocally recommend that these foundational strategies be offered to every patient with axSpA, irrespective of their disease activity or the specific pharmacological agents they may be receiving [1]. This base layer consists of non-pharmacological interventions, primarily patient education and physical therapy, and first-line pharmacotherapy with nonsteroidal anti-

inflammatory drugs (NSAIDs). Neglecting this foundation significantly compromises the potential success of more advanced treatments.

3.1. Patient Education: Empowering the Individual

Patient education is the absolute starting point of effective management. It is a continuous process that aims to empower individuals with a thorough understanding of their condition, its potential trajectory, and the rationale behind their treatment plan. An informed patient is better equipped to engage in shared decision-making, adhere to complex treatment regimens, and develop self-management skills to navigate the fluctuating course of the disease.

Effective education should cover several key domains:

- Disease Nature: Explaining what axSpA is, the difference between inflammatory and mechanical pain, and the role of the immune system.
- Treatment Goals: Clarifying that the goals are not just pain relief but also maintaining function, preventing structural damage, and improving overall quality of life.
- Pharmacological Therapies: Discussing the risks and benefits of each medication, the time it may take to see an effect, and the importance of adherence.
- Non-Pharmacological Therapies: Emphasizing that exercise is not just helpful but essential, as supported by high-level evidence [8].
- Self-Monitoring: Teaching patients how to recognize the signs of a disease flare versus normal aches and pains, and when to seek medical advice.
- Lifestyle Factors: Discussing the importance of smoking cessation (as smoking is linked to worse disease activity and progression) and maintaining a healthy weight.

3.2. Physical Therapy and Exercise: A Cornerstone Intervention

Central to foundational management is physical therapy, which serves not merely as an adjunctive treatment but as a cornerstone of care [1]. The goals of physical therapy are multifaceted: to alleviate pain, reduce stiffness, improve spinal mobility and posture, strengthen supporting musculature, and enhance overall physical function and quality of life. The recommendation for physical therapy is not based on anecdotal evidence but is strongly supported by rigorous clinical research.

A comprehensive meta-analysis of randomized controlled trials conducted by Pécourneau et al. provides robust evidence for the effectiveness of structured exercise programs [8]. This analysis synthesized data from numerous studies and concluded that regular exercise, whether performed individually or in a group setting, supervised or unsupervised at home, leads to statistically significant and clinically meaningful improvements in key disease outcome measures. The authors found that exercise programs consistently resulted in better scores on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI), which are patient-reported measures of disease activity and functional limitation, respectively. Furthermore, exercise was shown to reduce pain and improve spinal mobility [8]. These findings underscore that physical activity should not be viewed as an optional add-on but as an indispensable component of the treatment regimen for every patient with axSpA.

A comprehensive exercise program for axSpA typically includes:

- Mobility and Stretching Exercises: Focused on maintaining flexibility in the spine, hips, and shoulders.
- Strengthening Exercises: Targeting the core, back extensors, and gluteal muscles to improve posture and support the spine.
- Cardiovascular Fitness: Activities like swimming, walking, or cycling to improve overall health and combat fatigue.
- Breathing Exercises: Deep breathing exercises to maintain chest wall expansion, which can be restricted by costovertebral joint involvement.

3.3. First-Line Pharmacotherapy: The Role of NSAIDs

For patients with active axSpA, nonsteroidal anti-inflammatory drugs (NSAIDs) are the recommended first-line pharmacological treatment [1]. These agents work by inhibiting cyclooxygenase (COX) enzymes (both COX-1 and COX-2), thereby reducing the production of prostaglandins, which are key mediators of inflammation, pain, and fever. By mitigating the inflammatory process, NSAIDs can effectively address the cardinal symptoms of pain and stiffness.

The guidelines recommend a systematic approach to NSAID therapy. A trial of at least two different NSAIDs, each administered at its maximum tolerated dose for a period of 2-4 weeks, should be completed before concluding that a patient has had an inadequate response to this class of medication [1]. This recommendation acknowledges that there can be significant individual variation in response and tolerance to different NSAIDs.

The efficacy of NSAIDs in controlling the symptoms of axSpA is well-established. For many patients, particularly in the earlier stages of the disease, NSAIDs can provide substantial relief from inflammatory back

pain and stiffness, leading to significant improvements in comfort and function. There has been some debate regarding the optimal dosing strategy—continuous daily use versus on-demand (as-needed) use. While on-demand use may be sufficient for some patients with less persistent symptoms, some evidence has suggested that continuous use may not only provide better symptom control but could also have a modest effect on slowing radiographic progression. However, this potential disease-modifying effect remains a topic of ongoing research and is not a primary indication for continuous use. The decision must be individualized, balancing the need for symptom control against the potential long-term side effects of continuous use, which can include gastrointestinal, renal, and cardiovascular risks. For now, the primary role of NSAIDs remains the effective and rapid management of symptoms, serving as the initial pharmacological step before considering more advanced therapies.

Section Summary: The foundation of axSpA care rests on three pillars. First, comprehensive patient education empowers individuals to be active partners in their treatment. Second, structured exercise and physical therapy are essential, evidence-based interventions for improving function and reducing pain. Third, NSAIDs are the first-line pharmacological treatment, used systematically to control the symptoms of active inflammation before escalating to more advanced therapies.

4. Results Part II: The Biologic Revolution and the Challenge of Structural Damage

For a significant proportion of patients with axSpA, foundational therapies with NSAIDs and exercise are insufficient to control disease activity. For these individuals, the advent of biologic disease-modifying antirheumatic drugs (bDMARDs), particularly the tumor necrosis factor-alpha inhibitors (anti-TNFs), represented a paradigm-shifting breakthrough that has fundamentally revolutionized the treatment landscape [4, 7].

4.1. TNF-α Blockade: Mechanism and Unprecedented Efficacy

TNF-α is a pro-inflammatory cytokine that plays a central role in the pathophysiology of axSpA. In a healthy individual, TNF-α is a key part of the immune response to infection. In axSpA, however, it is overproduced and dysregulated, driving a chronic inflammatory state. It is found in high concentrations in the sacroiliac joints and spine of patients with active disease and is a key driver of the inflammatory cascade that leads to pain, stiffness, and ultimately, structural damage. Anti-TNF therapies are monoclonal antibodies or fusion proteins that specifically bind to and neutralize TNF-α, thereby interrupting this inflammatory pathway [4]. The introduction of these agents in the early 2000s provided the first highly effective treatment for patients with axSpA who had an inadequate response to or intolerance of NSAIDs.

The clinical evidence supporting the efficacy of anti-TNFs is overwhelming. Large, randomized, placebo-controlled trials have consistently demonstrated that these agents produce rapid, substantial, and sustained improvements in the signs and symptoms of axSpA [2, 4].

- Rapid Symptom Control: Treatment with anti-TNFs leads to dramatic reductions in disease activity, as measured by composite scores like the ASDAS (Ankylosing Spondylitis Disease Activity Score) and BASDAI. Patients frequently report significant relief from inflammatory back pain, a decrease in morning stiffness, and a reduction in fatigue, often within weeks of starting treatment.
- Objective Inflammation Reduction: The clinical improvement is often corroborated by objective evidence of reduced inflammation on MRI, which can show a marked decrease in bone marrow edema in the sacroiliac joints and spine.
- Broad Efficacy: Anti-TNFs have been shown to effectively resolve inflammation in both the axial skeleton and peripheral joints, as well as in entheseal sites.
- Improved Quality of Life: The profound impact of these therapies on pain, function, and fatigue has established them as the standard of care for patients with active axSpA that is refractory to conventional treatment [1, 2].

4.2. The Central Question: Can Biologics Halt Structural Damage?

While the ability of anti-TNF therapy to control the signs and symptoms of inflammation is undisputed, a more complex and critical question has dominated the research agenda for years: can these powerful agents alter the long-term course of the disease by preventing or slowing down structural damage? The ultimate goal of treatment is not only to make patients feel better but to prevent the irreversible spinal fusion that leads to long-term disability. The evidence on this front has been nuanced and, at times, conflicting.

Several long-term observational studies and post-hoc analyses of clinical trials have suggested that early and sustained treatment with anti-TNFs may indeed have a beneficial effect on radiographic progression. The work by Andreu et al., for instance, reviewed evidence suggesting that while short-term treatment (e.g., 2 years) may not show a clear effect, continuous anti-TNF

therapy for several years (4 years or more) could potentially delay the formation of new syndesmophytes [2]. The hypothesis is that by profoundly suppressing inflammation over a long period, these agents may disrupt the downstream pathways that lead to pathological new bone formation.

However, this optimistic view is tempered by a significant body of evidence and expert opinion suggesting that a complete uncoupling of inflammation and structural progression has not yet been achieved. Neerinckx & Lories argue that despite the remarkable success of anti-TNFs in controlling symptoms and inflammation, structural disease progression remains a major cause for concern [3]. They point to cohort data showing that many patients continue to develop new syndesmophytes and experience radiographic progression even while on effective anti-TNF therapy and in a state of clinical remission. This suggests that the link between inflammation and new bone formation may be more complex than initially thought. It is possible that once the inflammatory process has been initiated, the machinery of bone formation may proceed along a separate or delayed pathway that is not fully inhibited by TNF-α blockade alone. This ongoing debate highlights a critical unmet need in axSpA management and underscores the importance of developing therapies that can more reliably halt the process of structural damage [3].

Section Summary: The introduction of TNF-α inhibitors revolutionized axSpA care, offering rapid and profound control of inflammatory symptoms and dramatically improving quality of life. However, their effect on preventing long-term structural damage to the spine is less clear. While long-term use may slow progression, it does not halt it completely, indicating that the pathways of inflammation and new bone formation may be at least partially separate. This remains the most significant challenge in modern axSpA management.

5. Results Part III: Modern Treatment Paradigms and Strategic Management

The availability of highly effective therapies like anti-TNFs has prompted a fundamental shift in the philosophy of axSpA management. The field has moved away from a reactive approach, where treatments were escalated only in response to severe symptoms, towards a proactive, systematic, and goal-oriented approach. This evolution is best encapsulated by the "Treat-to-Target" (T2T) strategy.

5.1. The Treat-to-Target (T2T) Philosophy Explained

The Treat-to-Target (T2T) strategy, first pioneered in other rheumatic diseases like rheumatoid arthritis and adapted from successful models in conditions like diabetes and hypertension, is a therapeutic concept based on a shared decision-making process between the patient and the clinician to achieve a predefined treatment goal [6]. Rather than adjusting therapy in an unstructured, intuitive manner, T2T provides a clear and dynamic framework for management. The core principles of T2T, as outlined by Danve and Deodhar, involve several key steps [6].

Table 2. Core Principles of the Treat-to-Target (T2T) Framework in axSpA

T2T Principle	Description in axSpA Context	Key Considerations	Key Reference(s)
1. Target Selection	The goal is remission or low disease activity, defined by a validated score. The Ankylosing Spondylitis Disease Activity Score (ASDAS) is preferred.	The target should be mutually agreed upon by the clinician and patient, considering individual factors and preferences.	[6]
2. Monitoring	Disease activity must be measured systematically at regular intervals (e.g.,	Consistent and objective monitoring is crucial to determine if the	[5], [6]

	every 3-6 months) using the chosen instrument (e.g., ASDAS).	target has been met.	
3. Treatment Adjustment	If the target is not achieved, pharmacotherapy should be adjusted according to a predefined algorithm (e.g., switching or escalating therapy).	The decision to adjust therapy should be prompt to minimize time with active disease. The TICOSPA trial provides a model for this tight-control approach.	[1], [5]

The rationale behind T2T is that a systematic and aggressive approach aimed at minimizing disease activity will lead to better long-term outcomes, including improved function and quality of life, and potentially a reduction in structural damage. However, the implementation of T2T in axSpA has faced certain challenges. As Danve and Deodhar discuss, there has been debate over the optimal target, the best instrument to measure it, and the feasibility of applying such a rigorous strategy in routine clinical practice, which can be limited by factors like drug availability, cost, and patient preferences [6].

5.2. Case Study: The TICOSPA Trial and the Evidence for Tight Control

While the concept of T2T is intuitively appealing, its clinical benefit must be demonstrated by high-quality evidence. The TICOSPA trial, a large, open-label, pragmatic, cluster-randomised study, was designed to do just that [5].

- Study Design: Rheumatology clinics (clusters) in France were randomized to either a T2T/tight-control strategy or standard of care. This design tests the strategy in a real-world setting.
- The Intervention Group (T2T): Patients were assessed frequently (every 4 weeks). If their ASDAS score was above the target of 2.1 (indicating active disease), their treatment was escalated according to a predefined algorithm (e.g., optimizing NSAID dose, then starting a bDMARD, then switching bDMARDs).
- The Control Group (Standard Care): Patients were seen at the clinician's usual discretion, and treatment changes were made based on clinical judgment without a strict protocol.
- The Primary Outcome: The key outcome was the proportion of patients with a clinically significant improvement in their ASDAS score at one year.

The results of the TICOSPA trial provided strong support for the T2T approach. Molto et al. reported that patients in the T2T/tight-control group were significantly more likely to achieve a state of low disease activity and experienced greater improvements in function and quality of life compared to those in the standard care group [5]. The study demonstrated that a systematic, goal-oriented strategy leads to superior clinical outcomes without a significant increase in adverse events. This trial provided the first high-level evidence validating the T2T concept in axSpA and has strongly influenced international treatment recommendations, which now advocate for a T2T approach in the management of these patients [1, 5].

Section Summary: The management philosophy for axSpA has shifted to a proactive Treat-to-Target (T2T) model. This strategy involves setting a clear goal (remission or low disease activity), regularly monitoring progress with validated tools like the ASDAS, and systematically adjusting treatment if the target is not met. The TICOSPA trial provided strong, real-world evidence that this tight-control approach leads to significantly better clinical outcomes compared to standard care.

6. Results Part IV: The Expanding Therapeutic Armamentarium

The success of TNF-α blockade paved the way for the exploration of other pathogenic pathways in axSpA. The understanding that TNF-α is not the only critical cytokine involved has led to the development and approval of a new wave of biologic and targeted synthetic DMARDs, providing crucial alternatives for patients who do not respond to, lose response to, or have contraindications to anti-TNF therapy [7]. This expansion of the therapeutic armamentarium allows for a more personalized approach to care.

6.1. Targeting the IL-23/IL-17 Axis

Intensive research has identified the IL-23/IL-17 axis as another pivotal pathway in the pathogenesis of axSpA. In this pathway, the cytokine IL-23 promotes the development of Th17 cells, which in turn produce large amounts of IL-17. IL-17 is a potent pro-inflammatory cytokine that acts on various cells to promote inflammation and is also thought to play a role in the pathological new bone formation seen in axSpA.

This understanding led to the development of IL-17 inhibitors (e.g., secukinumab, ixekizumab). These agents have demonstrated efficacy comparable to that of anti-TNFs in controlling the signs and symptoms of axSpA in large randomized controlled trials. They are now firmly established as a key therapeutic option in treatment guidelines, recommended for patients with an inadequate response to NSAIDs, with a similar standing to anti-TNF therapies [1, 7]. For patients who fail to respond to anti-TNF therapy, switching to an IL-17 inhibitor is a standard and effective strategy.

6.2. The Advent of Oral Therapies: JAK Inhibitors

More recently, the Janus kinase (JAK) inhibitors, which are orally administered small molecules, have also emerged as an effective treatment option. Unlike biologics, which are large molecules that block extracellular cytokines, JAK inhibitors are small molecules that can enter cells and work intracellularly. They disrupt the JAK-STAT signaling pathway, which is a critical communication route used by many different cytokines to transmit their inflammatory signals. By inhibiting this pathway, JAK inhibitors can dampen the inflammatory response driven by multiple cytokines simultaneously.

The approval of JAK inhibitors (e.g., tofacitinib, upadacitinib) has added another important class of medication to the therapeutic armamentarium [7].

- Oral Administration: They offer the convenience of an oral route of administration, which is preferred by many patients over the injections or infusions required for biologics.
- Different Mechanism: They provide a new mechanism of action for patients who may not have responded adequately to biologics that target single cytokine pathways.
- Place in Therapy: They are typically considered as an option for patients with an inadequate response or intolerance to at least one biologic DMARD [7].

The availability of multiple effective therapeutic classes with different mechanisms of action—TNF inhibitors, IL-17 inhibitors, and JAK inhibitors—marks a significant advance, enabling a more personalized approach to treatment and providing viable options for patients who fail to respond to initial therapy.

Table 3. Summary of Key Therapeutic Modalities in Axial Spondyloarthritis

Treatment Modality	Examples	Mechanism of Action	Place in Therapy	Key Reference(s)
Non-Pharmacological	Patient Education, Physical Therapy/Exercise	Improves mobility, function, and reduces pain through physical conditioning.	Cornerstone: Recommended for all patients throughout the disease course.	[1], [8]
First-Line Pharmacological	NSAIDs (e.g., Naproxen, Ibuprofen, Celecoxib)	Inhibition of COX enzymes, reducing prostaglandin synthesis and inflammation.	First-line: For patients with active disease to control symptoms.	[1]
Biologic DMARDs (bDMARDs)	TNF-α inhibitors (e.g., Infliximab, Adalimumab)	Neutralize TNF-α, a key pro-inflammatory cytokine.	Second-line: For active disease with inadequate response to NSAIDs.	[1], [2], [4], [7]
	IL-17 inhibitors (e.g., Secukinumab, Ixekizumab)	Block the action of IL-17, another key cytokine in axSpA pathogenesis.	Second-line: An alternative to TNF-α inhibitors for NSAID-inadequate response.	[1], [7]
Targeted Synthetic DMARDs (tsDMARDs)	JAK inhibitors (e.g., Tofacitinib, Upadacitinib)	Inhibit Janus kinase enzymes, disrupting intracellular inflammatory signaling pathways.	Alternative option: For patients with an inadequate response or intolerance to bDMARDs.	[7]

Section Summary: The therapeutic options for axSpA have expanded beyond TNF inhibitors. Targeting the IL-17 pathway has proven to be an equally effective strategy. More recently, oral JAK inhibitors have provided a new class of therapy with a different mechanism of action and the convenience of a pill. This growing armamentarium allows for more personalized treatment and provides effective options for patients who fail initial therapies.

DISCUSSION: Synthesizing Progress and Persistent Challenges

The management of axial spondyloarthritis has undergone a profound transformation over the past two decades. The therapeutic journey has evolved from a fatalistic approach focused on managing inevitable pain and stiffness to a proactive and ambitious strategy aimed at achieving remission and preventing long-term disability. This review of the evidence synthesizes this evolution, highlighting a clear and decisive shift from a reactive, symptom-based model to a proactive, goal-oriented paradigm. The modern approach is

fundamentally multi-modal, integrating the indispensable contributions of non-pharmacological interventions with a sophisticated, tiered pharmacological strategy that is increasingly guided by the principles of Treat-to-Target (T2T). The current standard of care is no longer about simply alleviating discomfort; it is about fundamentally altering the course of the disease.

7.1. The Central Tension: Symptom Control vs. Structural Progression

A critical analysis of the available evidence reveals a central tension in the current state of axSpA care. On one hand, the development of biologic therapies, starting with TNF-α inhibitors and now expanding to include IL-17 and JAK inhibitors, has been nothing short of revolutionary for symptom control [4, 7]. These agents can rapidly and profoundly suppress the inflammatory processes that cause pain, stiffness, and fatigue, leading to dramatic improvements in patient-reported outcomes and quality of life [2]. However, this remarkable success in controlling inflammation has not translated into a definitive victory over the disease's most insidious threat: structural progression.

As emphasized by Neerinckx & Lories, radiographic progression continues to occur in a substantial proportion of patients, even those who are in a state of clinical remission on biologic therapy [3]. This persistent progression suggests that the molecular pathways driving inflammation and those driving pathological new bone formation may be, at least partially, distinct. While long-term suppression of inflammation with anti-TNFs may confer some benefit in slowing spinal fusion over many years [2], it is not a panacea. This crucial gap between clinical symptom control and structural damage modification represents the single greatest unmet need in the field and underscores the urgent necessity for therapies that can more directly and effectively target the mechanisms of new bone formation.

7.2. The Role of T2T in the Modern Era

Into this context, the emergence of the Treat-to-Target strategy, validated by the TICOSPA trial, provides a powerful strategic framework rather than a new molecule [5]. The success of the T2T approach is not based on the efficacy of any single drug but on the principle that systematic monitoring and timely escalation of therapy lead to better outcomes. It forces a disciplined approach to care, ensuring that effective treatments are used to their maximal potential to drive down disease activity to a minimal level [6]. The implementation of T2T represents a maturation of the field, moving from simply having effective drugs to using them wisely and systematically. However, the ultimate success of a T2T strategy is still dependent on the efficacy of the available therapeutic agents. While T2T can optimize the use of current drugs to control inflammation, it may not be sufficient on its own to solve the conundrum of structural progression until therapies that can reliably halt it become available.

7.3. Unmet Needs and Future Directions

Despite the significant progress, several challenges and unmet needs remain at the forefront of axSpA research and clinical care.

- The Holy Grail of Structural Modification: The development of therapies that can definitively prevent, or even reverse, structural damage remains the primary goal of future research.
- Personalized Medicine and Biomarkers: There is a pressing need for validated biomarkers that can predict a patient's response to a specific therapy, which would allow for a more personalized or precision-medicine approach from the outset, rather than the current trial-and-error method.
- Managing Extra-Articular Manifestations: The optimal management of the extra-articular manifestations of axSpA, such as uveitis, psoriasis, and inflammatory bowel disease, also requires further study to integrate their treatment into a holistic management plan.
- Understanding Disease Heterogeneity: Research is needed to understand why the disease course varies so much between individuals and to identify predictors of severe outcomes.
- Long-Term Safety: As new therapies emerge, long-term data on their safety and comparative effectiveness will be crucial.

Looking to the future, the field is moving towards a more individualized approach to care, leveraging genetic and molecular insights to tailor treatments. The development of novel therapeutic targets beyond TNF and IL-17 continues, and the long-term safety and comparative effectiveness of the expanding array of available therapies will be a major focus of future research.

7.4. Limitations of this Review

This review is not without its limitations. The field of axSpA therapeutics is evolving at a rapid pace, and new data are constantly emerging. This review provides a snapshot based on a curated selection of influential references and is not a systematic review of all available literature. The focus has been on the core principles of management, and a detailed discussion of every available drug or all extra-articular manifestations is beyond its scope. Nonetheless, the synthesis of the selected high-impact evidence

provides a robust and accurate depiction of the state-of-the-art in the management of axial spondyloarthritis.

Section Summary: The Discussion synthesizes the review's findings, highlighting the central tension between excellent symptom control with modern biologics and their incomplete ability to halt structural damage. The Treat-to-Target strategy is presented as a crucial framework for optimizing the use of available therapies. Key unmet needs, including the need for disease-modifying drugs that prevent bone formation and the development of biomarkers for personalized medicine, are identified as the primary focus for future research.

CONCLUSION: A New Era of Hope and a Clear Path Forward

The management of axial spondyloarthritis has entered a transformative era, shifting decisively from a paradigm of reactive symptom management to one of proactive, goal-directed care. The integration of foundational non-pharmacological interventions, such as structured exercise, with a tiered pharmacological strategy provides a robust framework for improving patient outcomes. First-line treatment with NSAIDs remains effective for many, while the advent of biologic and targeted synthetic DMARDs—including TNF-α, IL-17, and JAK inhibitors—has revolutionized the care of patients with refractory disease, offering profound control over inflammatory symptoms and significant gains in quality of life.

Furthermore, the validation of the Treat-to-Target (T2T) strategy marks a maturation of the clinical approach, emphasizing systematic monitoring and timely therapeutic adjustments to achieve and maintain low disease activity or remission. This strategic framework, supported by high-level evidence, empowers clinicians and patients to pursue optimal outcomes aggressively.

Despite these remarkable advances, a critical challenge persists: the disassociation between controlling inflammation and halting long-term structural damage. The prevention of radiographic progression remains the principal unmet need in the field and the ultimate goal of future therapeutic development. The ongoing pursuit of novel biomarkers to guide personalized therapy and new treatments that can directly inhibit pathological bone formation will define the next chapter in the journey to conquer axial spondyloarthritis and prevent long-term disability.

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