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Title:

Evolving Strategies in Targeted Therapy for Ankylosing Spondylitis: A Comprehensive Review

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Abstract

Ankylosing spondylitis (AS) is a chronic, progressive inflammatory disease affecting primarily the axial skeleton. Its pathogenesis remains incompletely understood, but both genetic predisposition and immunologic dysregulation are implicated. Traditional therapies, including nonsteroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying antirheumatic drugs, are often limited by intolerance or insufficient efficacy. The advent of biological agents targeting specific inflammatory pathways has revolutionized AS management, yielding improved symptomatic control, better quality of life, and altered disease progression. This review examines the current landscape of targeted therapies for AS, focusing on agents directed against tumor necrosis factor-α (TNF-α), interleukin (IL)-17, IL-12/23, IL-6, IL-1, and B-cell surface antigens. We summarize pivotal clinical trial evidence, compare the advantages and challenges of different biologics, and discuss their role in shaping an individualized therapeutic approach. By evaluating these agents, we aim to provide a foundation for optimized, evidence-based AS management and highlight future directions in targeted therapy.

1. Introduction

Ankylosing spondylitis (AS), a prototypical axial spondyloarthritis, is characterized by chronic inflammation of the sacroiliac joints and spine, eventually leading to new bone formation, spinal rigidity, and reduced mobility. The disease typically manifests in early adulthood and may also present with peripheral arthritis and extra-articular features, such as acute anterior uveitis and psoriasis-like skin lesions [1,2]. Although NSAIDs remain the first-line therapy, their long-term efficacy in curbing disease progression and controlling inflammation can be limited. Conventional agents, including sulfasalazine and methotrexate, have modest efficacy at best and may be associated with intolerance or organ toxicity [2,3].

The introduction of biologic therapies has transformed the AS treatment paradigm. By targeting specific cytokines and cells involved in pathogenesis, biologics have demonstrated superior outcomes in disease activity reduction, functional improvement, and imaging progression deceleration [4,5]. Tumor necrosis factor inhibitors (TNFi) have paved the way, while more recent therapies have focused on the IL-17/IL-23 axis and other immunological pathways. Despite their remarkable success, challenges such as loss of efficacy, infection risk, and cost persist. This review provides a comprehensive examination of current and emerging targeted therapies in AS, with a focus on TNFi and IL-17 inhibitors, as well as other cytokine blockers, to guide clinical decision-making and future research.

2. Targeting Tumor Necrosis Factor-α

Elevated TNF-α levels in AS contribute to local inflammation, osteoclast activity, and pathological new bone formation [6]. TNFi have demonstrated robust efficacy in improving disease activity, pain, and quality of life for AS patients. Potential

adverse events include infections (notably tuberculosis reactivation), malignancy risks, and autoimmunity induction [4,7].

2.1. Etanercept

Etanercept, a soluble TNF receptor fusion protein, was the first TNFi approved for AS. Randomized controlled trials have shown rapid and sustained improvement in disease activity and spinal mobility [8]. Long-term data support stable control of symptoms and acceptable safety profiles, though infections remain a concern [9].

2.2. Infliximab

Infliximab, a chimeric monoclonal anti-TNF-α antibody, has demonstrated significant efficacy in clinical trials, improving AS symptoms as early as week 2 and maintaining benefits over extended follow-up [10]. In a landmark trial, AS patients treated with infliximab experienced substantial improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and quality-of-life measures [4]. Long-term extension studies confirm its role in altering disease progression [11].

2.3. Adalimumab

Adalimumab, a fully human monoclonal anti-TNF-α antibody, also yields rapid and sustained symptomatic relief in AS [12]. Adalimumab has shown similar efficacy to etanercept, improving BASDAI scores, reducing CRP levels, and slowing radiographic progression. Biosimilars (e.g., ABP 501) have broadened treatment access with comparable efficacy and safety [13].

2.4. Golimumab and Certolizumab Pegol

Golimumab and certolizumab pegol are two additional TNFi that have demonstrated efficacy in AS, providing symptomatic relief and improved physical

function [14,15]. Golimumab's once-monthly subcutaneous regimen can enhance patient adherence [14], while certolizumab's unique Fab' PEGylated structure offers effective TNF blockade with a favorable safety profile [15].

3. Targeting Interleukin-17

IL-17 plays a critical role in the AS inflammatory axis, promoting cartilage destruction, osteoclast activation, and subsequent bone remodeling [16]. Inhibitors of IL-17 have shown considerable promise, particularly for patients who have had inadequate responses or intolerance to TNFi.

3.1. Secukinumab

Secukinumab, a fully human monoclonal antibody against IL-17A, demonstrated robust efficacy in randomized trials. The MEASURE studies confirmed significant improvements in AS activity, pain, and spinal mobility, as well as sustained response over 5 years [8,17]. Secukinumab shows a good safety profile, though candidal infections have been reported.

3.2. Ixekizumab

Ixekizumab, another IL-17A antagonist, has similarly demonstrated significant clinical improvements in patients with active AS. Phase III trials have shown rapid onset of effect and durable efficacy up to 52 weeks, with no unexpected safety findings [18].

3.3. Bimekizumab

Bimekizumab blocks both IL-17A and IL-17F, offering a more comprehensive inhibition of the IL-17 pathway. Early phase IIb data indicate promising efficacy and tolerability in AS, though long-term safety and effectiveness are still under investigation [19].

4. Targeting IL-12/23 Axis

The IL-23/Th17 axis is vital in driving AS inflammation. Ustekinumab, targeting IL-12/23 p40 subunit, showed limited or no efficacy in AS, suggesting that IL-23 inhibition alone may not be sufficient to improve clinical outcomes [20]. Risankizumab, an IL-23p19 inhibitor, failed to demonstrate meaningful clinical improvement in a phase II trial in AS [21]. Thus, IL-23 inhibition currently appears less promising than IL-17 blockade in AS.

5. Targeting IL-1 and IL-6

IL-1 and IL-6 are key cytokines in inflammatory cascades. However, trials targeting these pathways have been less successful in AS.

5.1. IL-1 Inhibition

Anakinra, an IL-1 receptor antagonist, produced only modest improvements in a small proportion of patients with active AS and is not routinely used [22].

5.2. IL-6 Inhibition

Tocilizumab, an IL-6 receptor inhibitor, has shown limited efficacy in controlling AS disease activity in clinical studies [23]. Thus, IL-6 blockade is not currently a mainstay of AS therapy.

6. Targeting B Cells

Rituximab, a CD20+ B cell-depleting antibody, has been explored in small studies of refractory AS. While some patients experienced clinical benefit, larger trials are needed to establish its efficacy and role [24].

7. Safety Considerations and Future Directions

Despite the significant progress, balancing efficacy and safety remains paramount. TNFi and IL-17 inhibitors carry infection risks, and vigilance for latent tuberculosis, hepatitis B reactivation, and fungal infections is essential [25]. The lack of efficacy of IL-23 inhibitors in AS and limited improvements with IL-1, IL-6, and CD20-directed therapies underscore the need for further research to identify novel targets and refine treatment algorithms.

Future studies should focus on predictors of treatment response, sequencing of biologics, and combination strategies. The development of precision medicine approaches, guided by biomarkers and genetic profiles, may enable personalized therapy, improving outcomes and minimizing exposure to ineffective or harmful treatments.

8. Conclusion

Targeted therapies have transformed the management of AS, offering patients substantial relief from inflammation, pain, and disability. TNF-α inhibitors have established a strong foundation, while IL-17 inhibitors have emerged as a critical alternative for patients with inadequate TNFi response. The current landscape reflects a nuanced approach, selecting agents based on disease severity, comorbidities, and patient preferences. Although IL-12/23, IL-1, IL-6, and B-cell-targeted therapies have not gained a strong foothold, ongoing research promises to elucidate their roles and identify new therapeutic avenues. The future of AS treatment lies in refining targeted strategies, improving safety profiles, and delivering truly individualized care.

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Conflicts of Interest

The authors declare no competing interests.