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REVIEW

Exploration of Multidimensional Treatment for Ankylosing Spondylitis: From Traditional Medications to Emerging Immune-Targeted Perspectives

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Abstract: Ankylosing spondylitis (AS) is a chronic immune-mediated disease involving persistent inflammation of the axial skeleton and peripheral joints, often progressing to spinal deformity and irreversible ankylosis. Current therapeutic strategies, primarily non-steroidal anti-inflammatory drugs and biologic agents, focus on symptomatic relief and inflammation suppression. However, these treatments fail to halt long-term structural progression or prevent bone fusion. Recently, advanced immunotherapies, including mesenchymal stem cell (MSC) transplantation and chimeric antigen receptor (CAR)-based therapies, have been proposed as emerging exploratory strategies. While these modalities offer the theoretical potential for deep immune remodeling and might influence pathological ossification, their application in AS remains largely extrapolated from other autoimmune diseases. It is crucial to note that while traditional therapies are supported by robust clinical evidence, advanced targeted cellular immunotherapies in AS are currently in preclinical or early exploratory stages with limited direct clinical data. Globally, AS exerts a substantial socioeconomic burden, affecting young adults and requiring more effective disease-modifying interventions. Unlike existing reviews focused primarily on standard pharmaceutical updates, this article provides a novel synthesis by connecting AS immunopathogenesis with the translational potential of precision cellular engineering, offering a roadmap for future clinical research.

Keywords: ankylosing spondylitis, traditional treatment, immune-targeted therapy, therapeutic targets

Introduction

Ankylosing spondylitis (AS) is a seronegative spondyloarthropathy characterized by chronic progressive inflammation of the sacroiliac joint. It is more prevalent among young and middle-aged men and has a significant familial aggregation tendency.[1] AS has a slow and insidious onset, with most patients initially presenting with mild low back pain or morning stiffness in the lumbosacral region.[2] As the disease progresses, symptoms persistently worsen and can spread from the lumbar spine to the thoracic and cervical vertebrae. In severe cases, it can lead to spinal deformity and ankylosis, and even cause disability.[3] AS imposes a substantial global socioeconomic burden, affecting approximately 0.1% to 1.4% of the population, with a significant predilection for young adults in their most productive years. Despite the availability of non-steroidal anti-inflammatory drugs (NSAIDs) and biological agents (e.g., TNF-α and IL-17 inhibitors), a significant proportion of patients experience an inadequate response or secondary failure. Furthermore, current therapeutic options primarily target systemic inflammation but remain largely ineffective in arresting the progressive pathological ossification and spinal ankylosis that characterize the advanced stages of the disease. Consequently, there remains a significant unmet clinical need for novel, disease-modifying therapies capable of halting structural progression in refractory patients.

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Currently, the clinical treatment methods for AS mainly include NSAIDs, tumor necrosis factor inhibitors (TNFi), and IL-17 inhibitors.[4] In recent years, precision treatment approaches represented by cellular immunotherapy[5] have opened up new possibilities for the treatment of AS.

This article reviews the efficacy and limitations of existing AS treatment methods and analyzes the clinical exploration and future application prospects of immune-targeted therapy in the treatment of AS.

From Etiology to Treatment: Exploring the Pathogenesis of AS and Identifying Therapeutic Targets

The pathogenesis of AS is not yet fully understood, but genetic factors are considered to be the main cause, especially human leukocyte antigen B27 (HLA-B27), which is currently regarded as a high-risk genetic pathogenic factor.[6] Furthermore, the prevalence of HLA-B27 exhibits significant geographic and ethnic variability, which impacts the genetic risk assessment of AS globally. Recent evidence from the Thrace region in Türkiye has highlighted a lower-than-expected frequency of HLA-B27 in AS patients, suggesting that non-HLA-B27 factors may play a more prominent role in disease pathogenesis in certain populations.[7]

The pathophysiology of AS involves abnormal activation of the innate and adaptive immune systems, among which Th17 cells are considered the main effector cells mediating the inflammatory response of AS.[8] During this process, abnormally activated CD4+ T cells can promote the release of prostaglandin E2 (PGE2), which then induces the production of IL-23 by antigen-presenting cells, and through binding to the IL-23 receptor on the surface of T cells, activate the JAK-STAT signaling pathway, promoting the differentiation and expansion of CD4+ T cells into Th17 cells, and generating a large amount of IL-17 and other effector factors.[8] As a core pro-inflammatory factor, IL-17 not only initiates and amplifies the inflammatory cascade, but also directly participates in the pathological cycle of bone erosion and new bone formation.[9] At the same time, tumor necrosis factor-α (TNF-α) through activating the NF-κB signaling pathway, promotes the release of inflammatory mediators such as IL-6 and IL-8, further exacerbating the inflammatory response and new bone formation.[10] Together, they lead to the formation of inflammation and ectopic bone formation in AS. The discovery of these pathological mechanisms provides a theoretical basis for the formation of current AS treatment strategies: NSAIDs as the first-line drugs, by inhibiting cyclooxygenase (COX) effectively reducing the generation of PGE2, thereby alleviating inflammation and pain; TNFi by directly neutralizing TNF-α at the lesion site, blocking its binding to downstream receptors and the generation of inflammatory signals; IL-17 inhibitors directly inhibit the pro-inflammatory effect of IL-17; and JAK inhibitors by more broadly interfering with the signal transduction of various cytokines, including IL-23, achieve regulation of the upstream signaling pathways. The increasingly in-depth study of the molecular mechanism of AS is opening up new paths for its treatment strategies to move towards precision and individualization.

Current Status of AS Treatment: Progress and Challenges

In the treatment of AS, drug therapy holds a central position. The recommended AS treatment drugs by the International Spinal Arthritis Assessment Society (ASAS) and the European League Against Rheumatism (EULAR) include NSAIDs, biologic disease-modifying antirheumatic drugs (bDMARDs), traditional synthetic disease-modifying antirheumatic drugs (csDMARDs), and glucocorticoids,[11] aiming to effectively relieve pain, improve function, and maximize the long-term quality of life and social participation of patients. In recent years, the emergence of mesenchymal stem cell (MSCs) transplantation therapy has provided a new direction for the treatment of AS. But these various treatment methods still have certain limitations (Figure 1).

NSAIDs: Analgesic and Anti-Inflammatory Drugs, the First-Line Treatment for Patients with AS

NSAIDs are the first-line medication for the treatment of AS. They mainly exert anti-inflammatory and analgesic effects by inhibiting the activity of COX and blocking the synthesis of PGE2, effectively alleviating symptoms such as limited mobility and morning stiffness.[12] However, its extensive COX inhibitory effect also brings the risk of multiple adverse reactions across

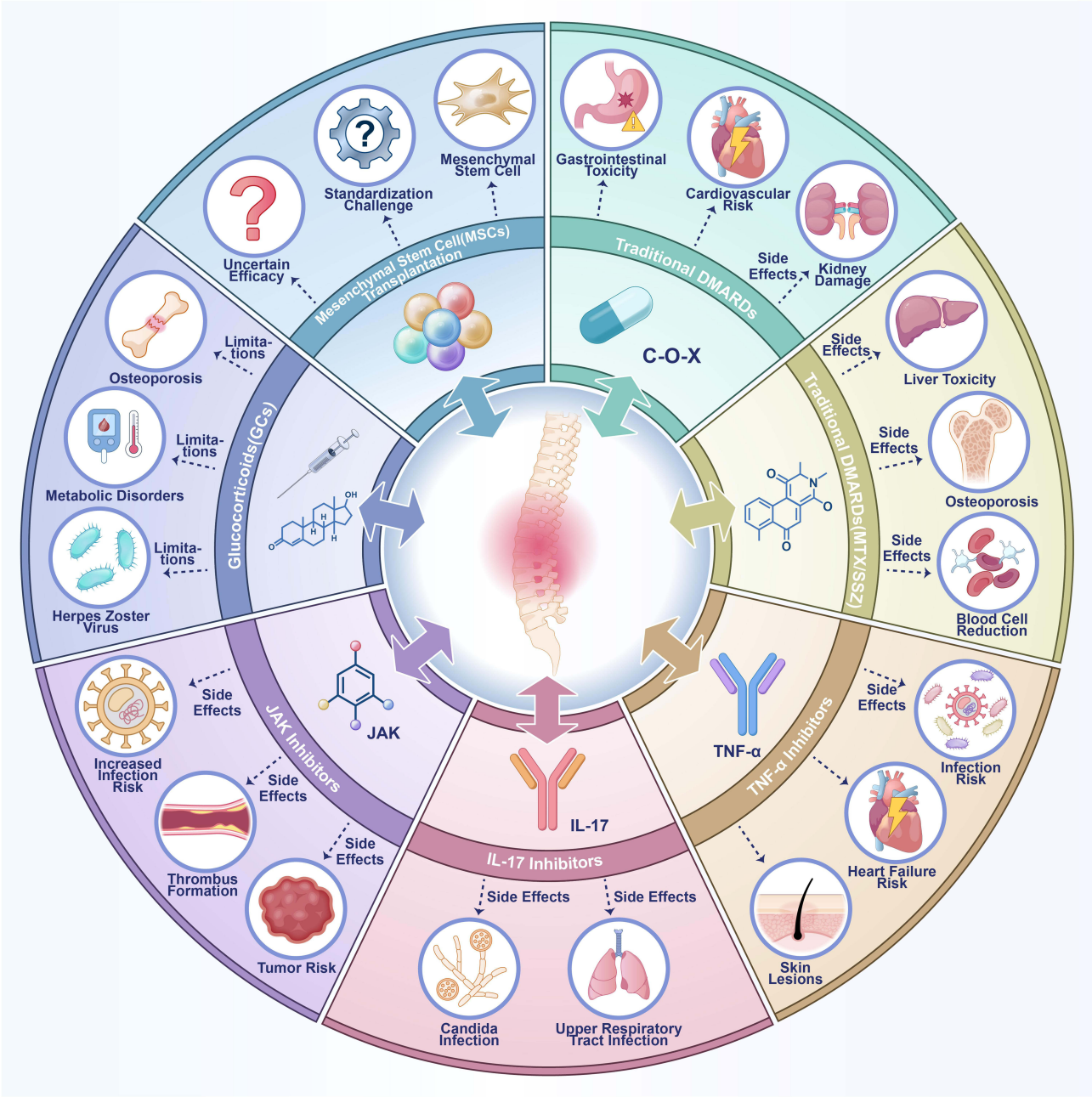

Figure 1 Current treatment methods for ankylosing spondylitis and their respective limitations.

various systems. In the gastrointestinal tract, NSAIDs, especially non-selective ones, can inhibit COX-1, which has a protective effect on the mucosa, leading to the disruption of the gastric acid barrier and causing erosions, ulcers, even bleeding or perforation.[13] In the cardiovascular system, long-term use of NSAIDs, especially selective COX-2 inhibitors, may disrupt the balance between prostacyclin 2 (PGI2) and thromboxane A2 (TXA2), increasing the risk of thrombosis and thereby raising the incidence of myocardial infarction and stroke.[14] In the kidneys, NSAIDs can inhibit the key prostaglandins that maintain the glomerular filtration rate, especially in elderly patients, dehydrated patients, or those using nephrotoxic drugs concurrently, which can easily lead to acute kidney injury.[15] Therefore, if patients respond well to NSAIDs and need such drugs to control symptoms, they can continue to use them.

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CsDMARDs: Effective in Treating Peripheral Joints, but Ineffective in Controlling Axial Symptoms and Weakness

CsDMARDs are mainly used in the treatment of AS to improve symptoms of peripheral arthritis (such as swelling and pain in the knee and ankle joints), by inhibiting lymphocyte activation and proliferation to exert anti-inflammatory effects. The response rate of ASAS20 for peripheral joints (20% improvement standard response rate) is approximately 40–50%, and it can to some extent reduce inflammatory indicators (such as ESR/CRP).[16] However, csDMARDs have no significant effect on axial symptoms (such as spinal inflammation and stiffness). Therefore, they are not recommended as the preferred treatment option for patients with predominantly axial manifestations.[17] Common drugs such as methotrexate (MTX) inhibit folic acid metabolism by inhibiting dihydrofolate reductase, thereby inhibiting the proliferation of immune cells; sulfasalazine (SSZ) exerts anti-inflammatory effects by inhibiting prostaglandin synthesis and reducing the release of inflammatory mediators.[18] Nevertheless the use of high-dose csDMARDs can lead to gastrointestinal reactions (such as stomach pain, nausea, vomiting and peptic ulcers), liver function damage (such as elevated liver enzymes), osteoporosis, increased infection risk, allergic reactions and hematological abnormalities (such as decreased white blood cells and platelets).[19]

The "Double-Edged Sword" of TNFi: Efficacy, Insufficient Response and Risk Considerations

TNF-α is a key inflammatory mediator in the pathogenesis of AS, which can activate white blood cells, promote the release of inflammatory factors,[4] and induce infiltration of inflammatory cells and proliferation of fibroblasts.[20] TNFi, as a biological agent targeting TNF-α, has been widely used in the treatment of autoimmune diseases such as AS. Although TNFi can effectively control inflammation, it cannot inhibit the most characteristic spinal bone process of AS. Patients who had or currently have uveitis or active inflammatory bowel disease should be prioritized for the use of monoclonal antibodies against TNF.[12] However, not all AS patients can benefit from TNFi treatment. Approximately 30% to 40% of AS patients have no response or insufficient response to TNFi treatment.[21] In addition, TNFi also has certain side effects. A study reported that 186 AS patients with heart failure developed deterioration of cardiac function after using TNFi.[22] Another study reported that after introducing TNFi, including adalimumab and infliximab, 1.8% of AS patients developed psoriasis-like skin diseases, which was significantly higher than those receiving conventional drug treatment.[23] The risk of infection is also an important risk factor: TNFi increases the risk of bacterial infection, opportunistic infection, and granulomatous infection (such as tuberculosis). For mild infections, TNFi treatment can continue while using antibiotics; for major infections, medication should be suspended. Before treatment, the risk of infection, physical examination, and tuberculin skin test or interferon-γ release test should be comprehensively evaluated.[24]

IL-17 Inhibitors: They Can Suppress Inflammatory Responses, but They Can Also Lead to a Decline in Immune Function

Although the exact pathogenesis of AS is not yet fully understood, studies have confirmed that the IL-23/IL-17 axis plays a crucial role in the immune inflammatory process of AS.[25] In the peripheral blood and bone joint tissues of AS patients, IL-23 can promote the differentiation of Th17 cells and stimulate the production of IL-17 by various cells. IL-17A and IL-17F themselves have limited pro-inflammatory effects, but they can synergistically amplify the inflammatory response with other inflammatory factors.[26] While the IL-23/IL-17 axis is a central pathogenic pathway in AS, targeting this axis has yielded inconsistent results. Notably, despite the success of IL-17 inhibitors, IL-23 inhibitors have failed to demonstrate significant therapeutic efficacy in AS clinical trials.[27] This failure serves as a crucial reminder of the complexity of AS immunopathogenesis; unlike in psoriasis, where IL-23 inhibition is highly effective, the disease-driving mechanisms in the AS axial skeleton appear less dependent on the IL-23/IL-17 axis, or involve redundant signaling pathways that bypass IL-23. This discrepancy highlights the necessity of a more critical appraisal of translational research and cautions against the direct extrapolation of treatment successes from other spondyloarthritis spectrum diseases to AS. Currently, the commonly used IL-17 inhibitors include secukinumab, ixekizumab, and brodalumab. However, inhibiting IL-17 may interfere with its immune protective function in the skin and mucous membranes, thereby increasing the risk of infection, especially upper respiratory tract

infections and mucocutaneous candidiasis are more common.[28] For example, in the clinical trial of using secukinumab to treat psoriasis, patients experienced adverse reactions such as upper respiratory tract infections and injection site reactions.[29] Additionally, IL-17 inhibitors may also cause immune response imbalance and induce other skin lesions. Some studies have reported that some patients developed paradoxical eczema after using such drugs for treatment, which may be related to the relative enhancement of Th2 response after the inhibition of Th17 function.[30]

JAK Inhibitors: Potentially Therapeutic Targets, Safety Still Requires Close Monitoring

JAK inhibitors inhibit the phosphorylation of JAK proteins in the JAK-STAT pathway, thereby weakening the downstream intracellular signal transduction.[31] They have been widely used in various autoimmune diseases such as rheumatoid arthritis and myelofibrosis. Studies have shown that the JAK pathway is a potential therapeutic target for AS.[32] Lee and Song[33] found that JAK inhibitors have significant efficacy for active AS patients who do not respond adequately or are intolerant to two or more NSAIDs. Although the long-term effects and safety of these drugs still need further evaluation, the existing results have indicated that this type of drug has potential value in the treatment of AS. More long-term studies are still needed to comprehensively evaluate its efficacy and safety. Although JAK inhibitors show good efficacy in the treatment of AS, their safety issues still need to be closely monitored. In current clinical studies, the incidence of adverse events is lower than expected, but there is still a risk of serious adverse reactions, including severe infections such as herpes zoster,[34] tuberculosis, major adverse cardiovascular events,[35] venous thromboembolism, and malignant tumors.[36]

Glucocorticoids (GCs): They Can Control Peripheral Symptoms, but They Also Have Side Effects

GCs mainly exert therapeutic effects in the treatment of AS through its potent anti-inflammatory and immunosuppressive properties. It can inhibit the expression of pro-inflammatory cytokines, suppress the activation and proliferation of T cells and B cells, reduce the infiltration of inflammatory cells, thereby alleviating the inflammatory response and tissue damage.[37] According to the ASAS and EULAR guidelines for the management of spinal arthritis, if the patient mainly presents with peripheral symptoms, local application of GCs can be combined with the use of sulfasalazine.[12] Although GCs have a strong anti-inflammatory effect, their long-term or high-dose use can lead to a series of serious adverse reactions, such as osteoporosis, metabolic disorders, increased infection risk,[38] suppression of adrenal function,[39] and mental and emotional disorders.[40]

MSCs Transplantation Therapy: It Has Certain Therapeutic Effects but the Mechanism is Complex and the Technology is Limited

In 1968, Friedenstein et al[41] first isolated a type of bone marrow cell with self-renewal and multi-lineage differentiation potential, termed mesenchymal stem/stromal cells (MSCs). MSCs are pluripotent progenitors capable of regulating immune responses through cell-to-cell contact and secretion of soluble factors, including indoleamine 2,3-dioxygenase, PGE_2, TGF-β1, and IL-10.[42] In AS, MSCs inhibit the IL-23/IL-22 axis and induce regulatory macrophage polarization, alleviating chronic inflammation and associated pain. They also promote osteogenesis and angiogenesis via multi-lineage differentiation and exosome-mediated mechanisms, offering new strategies for repairing advanced joint damage.[43] MSC transplantation can restore immune balance, reduce autoimmune activity long-term, and repair damaged joint tissues and cartilage. Despite promising prospects, MSC therapy remains in early clinical exploration, with efficacy and safety yet to be fully verified. Key challenges include: 1. lack of standardized cell dosing; 2. unclear effects of administration routes (eg., intravenous vs. intra-articular) on efficacy and safety; 3. variability of MSCs from different sources (bone marrow, adipose tissue, umbilical cord blood); and 4. optimal disease stage for intervention.[44] Future research should focus on source selection, dose optimization, administration strategies, and combination therapies to facilitate standardized clinical application. Overall, AS is a chronic inflammatory disease with complex pathogenesis. Existing treatments, though varied, present safety concerns and high costs, limiting accessibility. Consequently, immunotherapies targeting pathogenic cells represent a promising new direction in clinical research.

Despite the wide array of available therapies, several critical issues in AS management remain unresolved. A major clinical challenge is the persistent structural progression; while conventional and biological therapies effectively suppress systemic inflammation, they often fail to halt pathological new bone formation and spinal ankylosis. Furthermore, there is a lack of consensus on optimal treatment sequencing after biologic failure, leaving a therapeutic gap for refractory patients. The ongoing uncertainty regarding the prevention of osteoproliferation underscores the urgent need for novel disease-modifying therapies that can simultaneously address both inflammation and structural damage.

The Emergence of Targeted Depletion of Pathogenic Cells in the Treatment of AS

Immune-targeted therapy is a new hotspot and hope for the treatment of autoimmune diseases. The arthritis peptide hypothesis suggests that antigen-presenting cells (APC) present antigenic peptides through HLA-B27 expression to CD8+ cells, thereby triggering specific immune responses, leading to the activation and expansion of pathogenic T cells and causing tissue damage and joint inflammation.[45]

Targeted Depletion of Specific Pathogenic T Cells to Achieve Precise Attack

Faham's repertoire sequencing indicated that HLA-B27 might activate CD8+ T cells by presenting common antigens, supporting the "arthritis peptide hypothesis" and confirming the significant association between the TRBV9 gene segment and specific CDR3 amino acid sequences.[46] Subsequently, the Yang[47] team's research identified CD8+ T cells expressing disease-related T-cell receptors (TCRs), and detected 80 antibodies containing specific TRBV9-CDR3-Jβ2.3 chains in the blood and synovial fluid of AS patients. Subsequently, using TCR-driven yeast display libraries based on HLA-B27:05 selection, it was confirmed that CD8+ T cells bind to HLA-B27-presented peptides pathologically through the BV9-CDR3β motif. At the same time, high-throughput T-cell library analysis of synovial fluid and peripheral blood samples from patients with spondyloarthritis showed that TRBV9+ CD8+ T cell clones carrying this characteristic CDR3 amino acid sequence played an important role in driving autoimmune diseases such as AS and other HLA-B27-related autoimmune spondyloarthropathies (including psoriatic arthritis).[48] Therefore, developing targeted therapeutic regimens for TRBV9+ CD8+ T cells is of great significance for preventing the progression of AS.

To evaluate the potential of targeted immunotherapy, Britanova et al[49] conducted preclinical studies: injecting the cytotoxic humanized anti-TRBV9 monoclonal antibody BCD-180 into primate models. The results showed that TRBV9+ T cells in peripheral blood were dose-dependently depleted, and no adverse reactions were triggered, confirming its good safety. The team further treated an AS patient with poor TNF response to anti-TRBV9 antibody therapy (Figure 2). After treatment, the number of TRBV9+ T cells in the peripheral blood of the patient significantly decreased, and symptoms such as pain and stiffness were significantly relieved, with improved activity function and quality of life, without serious adverse events. This indicates that this therapy can achieve targeted T-cell clearance and bring long-term complete remission to refractory AS symptoms. Currently, this treatment strategy has shown significant efficacy in AS patients, especially for those with poor responses to traditional treatments. In the future, such precise methods of eliminating pathogenic T cells without causing widespread immunosuppression may be applicable to other autoimmune diseases, such as type 1 diabetes, multiple sclerosis, and non-HLA-B27-related Crohn's disease. Relevant research is still ongoing.[49]

Targeted Inhibition of Osteoblasts - a Key Strategy for Alleviating Osteosclerosis in AS

Inflammation and pathological new bone formation are the two main pathological features of AS. Osteoblasts are the main cells for bone formation and play an important role in the pathological new bone formation of AS. The ability of MSCs from AS patients to differentiate into osteoblasts is enhanced, leading to excessive bone formation.[50] Based on this, Shen Huiyong's team[51] developed a manganese ferrite nanoparticle (CH6-MF NPs) with an aptamer. By specifically targeting osteoblasts and exerting anti-ROS, anti-inflammatory, and anti-bone formation effects, the drug can be precisely delivered to the lesion site, thereby improving efficacy and reducing systemic side effects.[51] This system is expected to

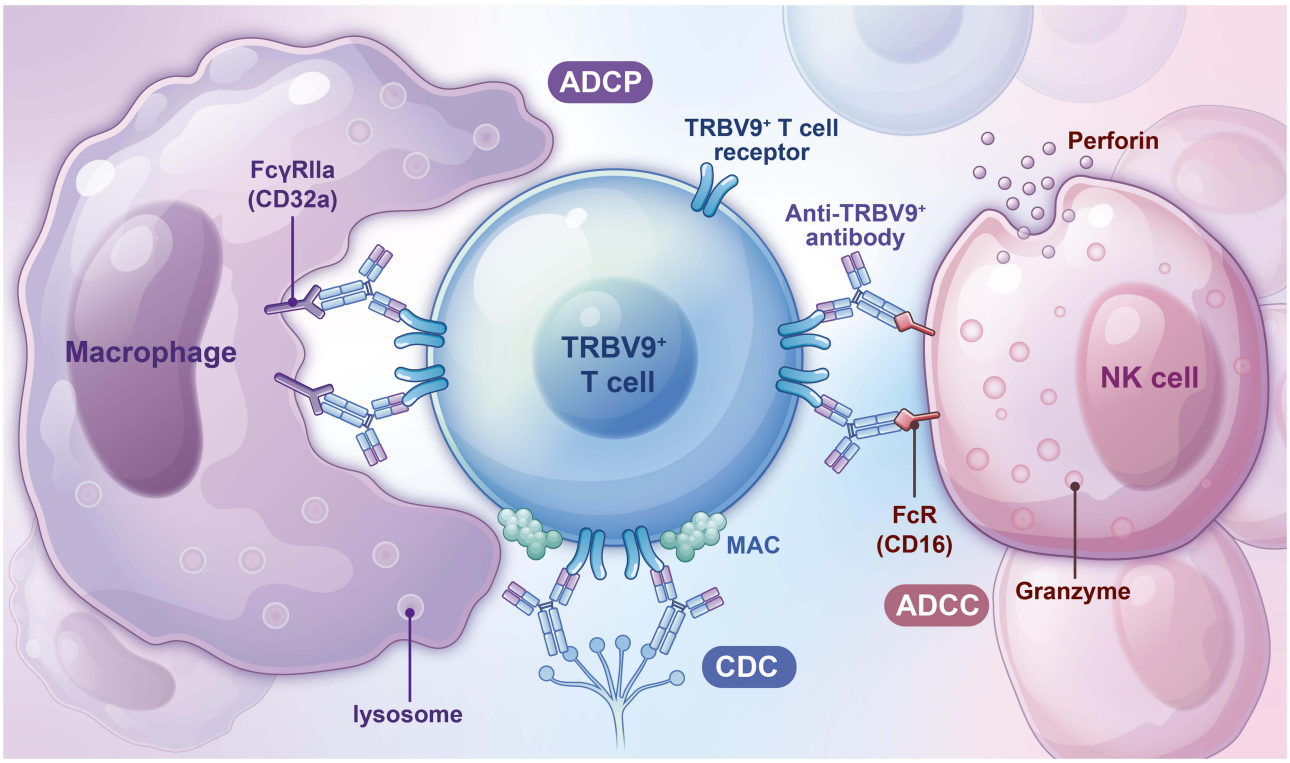

Figure 2 Schematic diagram of the antibody-mediated TRBV9+ T cell depletion immunotherapy process. Anti-TRBV9+ antibodies can mediate the exhaustion of TRBV9+ T cells through the following three pathways: (1) ADCP (antibody-dependent cell-mediated phagocytosis) triggers the phagocytosis of macrophages, eliminating the target cells; (2) ADCC (antibody-dependent cell-mediated cytotoxicity) activates NK cells to release granzymes and perforin to directly kill the target cells; (3) CDC (complement-dependent cytotoxicity) triggers the complement cascade reaction, leading to the formation of membrane attack complexes, causing the target cells to undergo permeabilization and dissolution.

become a new strategy for treating AS. Moreover, the design concept of this delivery system can also be applied to the treatment of other orthopedic diseases, such as osteoporosis and fractures.[52]

Application Prospects and Future Challenges of Targeted Cellular Immunotherapy

Specific targeted therapy has brought new hope for the treatment of AS. It can reset the immune system by eliminating self-reactive immune cells through cytotoxic antibodies, and also precisely regulate or inhibit pathogenic cells to alleviate inflammation and ossification in AS patients, with the potential to cure the disease.[53] However, this therapy still faces many challenges before being widely applied in clinical practice: for instance, developing more precise targeted strategies to reduce off-target effects requires in-depth research to identify AS-specific cell or molecular targets, being vigilant of potential off-target effects and long-term safety issues; and exploring allogeneic cell therapy[54] to improve accessibility and reduce costs. Through multidisciplinary cooperation, targeted cell immunotherapy[55] is expected to become an important breakthrough in the field of AS treatment, providing patients with more effective and long-lasting treatment options.

The Potential of Chimeric Antigen Receptor Therapy in the Treatment of AS

Chimeric antigen receptor (CAR) is a genetically engineered synthetic receptor that enables immune effector cells (such as T cells) to specifically recognize target antigens.[56] CAR comprises three main components: an extracellular antigen-recognition domain, a transmembrane domain, and an intracellular signaling domain.[57] The extracellular domain, typically a single-chain variable fragment (scFv), directly recognizes cell surface antigens independent of MHC presentation, while the transmembrane domain anchors the receptor to the cell membrane. The intracellular domain contains co-stimulatory signaling motifs (eg., CD3ζ, CD28, and 4–1BB) that, upon antigen binding, activate CAR-T cells to proliferate, secrete cytokines, and eliminate pathogenic immune cells.[58] Compared with conventional biologics, CAR

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cell therapy enables deep depletion of autoreactive B cells, plasma cells, and pathogenic T cells, thereby restoring immune homeostasis and offering a promising strategy for refractory autoimmune diseases.[59]

Breakthrough Advances of CAR Therapy in Autoimmune Diseases

CAR-T cell therapy has achieved remarkable success in hematological malignancies, with complete remission rates exceeding 80% in CD19-positive lymphomas. Recently, this technology has been extended to autoimmune diseases, which are often driven by persistent, tissue-damaging autoreactive B cells that traditional therapies like rituximab struggle to eliminate.[59] In 2022, Mackensen's team published a landmark study demonstrating that autologous CD19 CAR-T cells induced sustained, drug-free clinical remission in 5 patients with refractory systemic lupus erythematosus (SLE).[60] Interestingly, despite B-cell recurrence around day 110 post-treatment, the regenerated B cells exhibited a juvenile phenotype, suggesting a profound "resetting" of the immune system.[60]

This long-term efficacy and safety were further validated in a 2024 follow-up study by Müller et al, where 15 patients with severe autoimmune diseases (including SLE, idiopathic inflammatory myopathy, and systemic sclerosis) completely discontinued immunosuppressive agents and achieved long-term drug-free remission.[61] Driven by these breakthroughs, over 119 clinical trials for CAR-T cell therapy in autoimmune diseases were registered globally by 2025.[62] Recent data from the Phase I Breakfree-1 study mirrored these findings, showing that 94% of evaluable patients with systemic sclerosis, SLE, or myopathy successfully stopped chronic immunosuppressive treatment following CD19 NEX-T CAR-T cell therapy, accompanied by robust CAR-T expansion and a re-emerging juvenile B-cell phenotype.[52]

However, because these prominent clinical successes (such as in SLE and systemic sclerosis) are fundamentally centered on B-cell depletion, their findings cannot be directly extrapolated to AS, which is predominantly a T-cell-orchestrated disease. Developing CAR-based strategies for AS requires shifting the focus from pan-B-cell clearance to the precise modulation of pathogenic T-cell subsets within the unique entheseal microenvironment.

Diversified Development of CAR Therapies: From CAR-T to CAR-NK, CAR-Treg and CAR-MSC

To overcome the limitations of the traditional autologous CAR-T cell therapy, such as complex preparation process, long cycle and high cost, researchers are actively exploring diversified CAR cell therapy strategies, including new technical platforms like CAR-NK, CAR-Treg and CAR-MSC (Figure 3).

CAR-NK cell therapy has made significant progress in recent years. NK cells are an important component of the innate immune system and can recognize and kill target cells through non-MHC-restricted mechanisms. Compared with CAR-T cells, CAR-NK cells have the advantages of lower risks of cytokine release syndrome (CRS) and graft-versus-host disease (GVHD), and better safety.[63] In 2025, Professor Xu Huizhi's team systematically reported the therapeutic effect of iPSC-derived CD19/BCMA dual-targeted CAR-NK cells in patients with refractory systemic sclerosis in Cell. This study constructed a treatment platform with large-scale production potential through multi-gene editing and functional enhancement, opening up a new path for "universal" ready-to-use CAR cell therapy.[64]

CAR-Treg cell therapy represents another innovative direction in cell therapy. Regulatory T cells (Tregs) play a core role in maintaining immune homeostasis and suppressing autoimmune responses, and their functional defects are closely related to the onset of various autoimmune diseases.[65] The antigen recognition of polyclonal Tregs lacks specificity, limiting their clinical application. CAR-Treg technology achieves precise immunosuppression of specific target antigens by endowing Tregs with antigen-specific recognition capabilities. In 2024, Doglio et al reported in Nature Communications that CD19-targeted CAR-Treg cells could effectively restore immune homeostasis in SLE animal models, involving the secretion of inhibitory factors such as IL-10 and TGF-β, and direct regulation of effector T cells.[66] Currently, several clinical trials of CAR-Treg cell therapy for autoimmune diseases are underway, including CAR-Treg treatment for rheumatoid arthritis targeting carbamylated vimentin (NCT06201416), etc.[67]

CAR-MSC therapy combines CAR technology with the immunomodulatory properties of mesenchymal stem cells. In 2024, Mayo Clinic reported a new type of CAR-MSC in Nature Biomedical Engineering. This cell not only retains the inherent immunomodulatory and tissue repair functions of MSCs but also acquires the ability to precisely target inflammatory

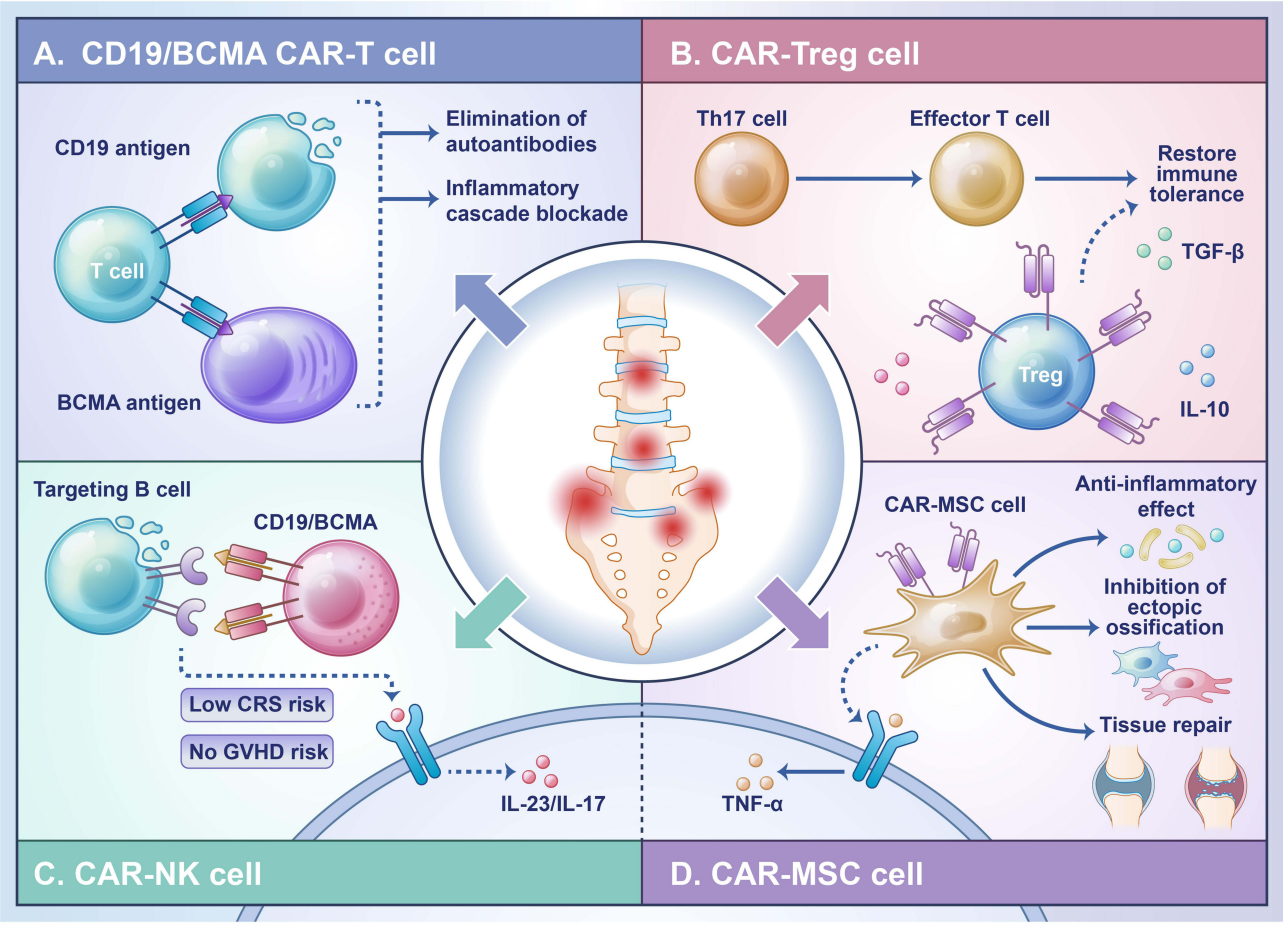

Figure 3 The potential immunomodulatory mechanism of CAR cell therapy for ankylosing spondylitis. This figure illustrates the potential mechanisms of action of various CAR cell therapies in the treatment of AS. (**A**) CD19/BCMA CAR-T cells: By recognizing the CD19 antigen on B cells and the BCMA antigen on plasma cells, they achieve deep elimination of autoreactive B cells and long-lived plasma cells, thereby eliminating the source of autoantibodies and blocking the inflammatory cascade; (**B**) CAR-Treg cells: By expressing CARs targeting specific self-antigens (such as citrullinated proteins, vimentin, etc.), they precisely migrate to the inflammatory sites, secrete inhibitory cytokines like IL-10 and TGF-β, inhibit the activation of Th17 cells and effector T cells, and restore immune tolerance; (**C**) CAR-NK cells: Utilizing the non-MHC-restricted killing characteristics of innate immune cells, they target and eliminate pathogenic B cells, while avoiding GVHD and severe CRS risks; (**D**) CAR-MSC: Retaining the multi-directional differentiation and tissue repair potential of mesenchymal stem cells, they precisely home to the affected joints of AS through CAR mediation, and exert multiple functions locally, including anti-inflammatory, inhibition of ectopic ossification, and promotion of tissue repair.

or lesion areas through CAR technology.[68] This "intelligent" MSC can recognize and home to abnormal immune sites, directly act on inflammatory markers, and achieve precise immunomodulation. Although it is still in the preclinical stage, CAR-MSC therapy has shown potential in various autoimmune diseases such as rheumatoid arthritis, SLE, and multiple sclerosis.

Various CAR cells synergistically regulate the IL-23/IL-17 inflammatory axis, TNF-α pathway, and pathological bone formation process of AS through different mechanisms, and are expected to achieve precise immune intervention for AS. These new CAR cell therapies are gradually breaking through the bottlenecks of traditional CAR-T technology and providing safer, more precise, and scalable treatment options for autoimmune diseases. Relevant clinical studies and target information are summarized in Table 1.[69–74]

Theoretical Basis and Potential Strategies of CAR Therapy in the Treatment of AS

The immunopathological mechanism of AS is significantly different from other B-cell-mediated autoimmune diseases. Studies have shown that the onset of AS is mainly driven by HLA-B27-restricted CD8+ T cells, rather than being dominated by B-cell-mediated humoral immunity.[59] Therefore, directly applying CD19-targeted CAR-T cells to AS may not be the optimal strategy. However, the high flexibility of the CAR technology platform provides multiple potential pathways for precise immunotherapy of AS.

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Table 1 Application of CAR Therapy in Autoimmune Diseases and Potential Therapeutic Targets

Disease Type	Cell Type	Target Spot	Mechanism	Clinic Trial/ References
Systemic Lupus Erythematosus	CAR-T	CD19	Eliminate one's own reactive B cells	NCT03030976[60]
	CAR-T	CD19/BCMA	Simultaneously eliminate B cells and plasma cells	[69]
	CAR-Treg	CD19	Restore immune homeostasis and inhibit effector T cells	[66]
Systemic sclerosis	CAR-T	CD19	Eliminate B cells and reduce fibrosis	NCT06347718[70]
	CAR-NK	CD19/BCMA	Dual-target clearance, low risk of CRS	[64]
Rheumatoid arthritis	CAR-T	CD19	Eliminate pathogenic B cells	NCT06475495[71]
	CAR-Treg	Citrullinated vimentin	Targeted inhibition of local inflammation in the joints	NCT06201416[72]
Myasthenia gravis	CAAR-T	MuSK	Targeted elimination of anti-MuSK B cells	NCT05451212[73]
	CAR-T	BCMA	Eliminate antibody-producing plasma cells	NCT04146051[74]
AS*	CAR-Treg	HLA-B27-related antigen	Inhibit the inflammation mediated by TRBV9+ T cells	In theoretical exploration
	CAR-MSC	Inflammatory chemokine receptor	Targeted homing, local immune regulation and repair	Preclinical study
	Anti-TRBV9 antibody	TRBV9+ T cells	Targeted elimination of pathogenic T cells	NCT05445076[49]

Note: The CAR cell therapy of AS* is mostly at the stage of theoretical exploration or preclinical research.
Abbreviations: BCMA, B-cell maturation antigen; MuSK, Muscle-specific tyrosine kinase; CAAR, Chimeric self-antigen receptor.

Firstly, the immunomodulatory strategy based on CAR-Treg is worthy of in-depth exploration. In AS patients, there is abnormal activation of the IL-23/IL-17 axis and dysfunction of Treg, leading to an imbalance in the Th17/Treg ratio. By constructing CAR-Treg cells targeting AS-related autoantigens (such as HLA-B27-presenting peptide segments), they can precisely migrate to the affected joints and exert local immunosuppressive effects. CAR-Treg cells can inhibit the proliferation of effector T cells and the differentiation of Th17 cells by secreting inhibitory cytokines such as IL-10 and TGF-β, and also block the co-stimulatory signals mediated by CTLA-4 and consume IL-2, restoring immune homeostasis.[65,75] This antigen-specific immunomodulatory approach is expected to achieve precise control of AS inflammation without causing widespread immunosuppression. Secondly, CAR-MSC therapy offers unique advantages for AS treatment. The pathological features of AS include not only chronic inflammation but also pathological bone formation. MSC itself has dual functions of immune regulation and tissue repair, and introducing CAR technology into MSC can further enhance its targeting ability. If the specific chemokine receptors or adhesion molecules expressed in the AS inflammatory sites can be identified, CAR-MSC cells can more effectively gather at the affected joints and simultaneously exert anti-inflammatory and osteogenic regulatory effects.[68] This strategy is expected to break through the bottleneck of existing treatments that can only control inflammation but cannot reverse bone formation. Moreover, although AS is not a typical B-cell-mediated disease, recent studies have found that some AS patients have autoantibodies and abnormal B-cell functions. A study based on a large-scale electronic health record in the United States showed that among 1,363 patients with B-cell non-Hodgkin's lymphoma who received FDA-approved CAR-T treatment, 4 cases were combined with AS. These patients did not have a higher risk of CRS or ICANS than non-autoimmune disease patients after receiving CAR-T treatment, suggesting that CAR-T therapy has acceptable safety in AS patients.[76] This finding provides preliminary safety references for future exploration of CAR-T in AS.

It is particularly noteworthy that Britanova et al reported in Nature Medicine in 2023 that the TRBV9+ T cell-targeted clearance therapy has a similar concept of precise immunotherapy to CAR technology. This study shows that by selectively eliminating CD8+ T cells carrying disease-related TCRs using anti-TRBV9 monoclonal antibodies, a patient with refractory AS achieved complete remission for 4 years.[49] This suggests that in the future, it may be possible to develop CAR-NK or other CAR effector cells targeting TRBV9 to achieve precise clearance of pathogenic T cells in AS. Currently, the anti-TRBV9 antibody (BCD-180/Seniprutug) has entered Phase II clinical trials (NCT05445076), providing important references for the application of CAR technology in AS.

Challenges and Prospects

While the success of CAR-based therapies in hematological malignancies provides a conceptual foundation for immune-targeted intervention, clinical translation into rheumatic diseases like AS presents distinct challenges. Unlike the "clear-the-clone" approach in oncology, the management of AS requires precise immune modulation rather than total ablation, necessitating a critical reappraisal of safety thresholds. Currently, the enthusiasm for CAR-based strategies in AS is largely extrapolated from successes in B-cell-mediated conditions such as SLE; however, there is a notable absence of large-scale, AS-specific clinical trials to definitively support their efficacy.

The translational barriers for AS are threefold. First, genetic and clonal heterogeneity complicates target coverage. For instance, the therapeutic potential of TRBV9+ T-cell depletion may vary significantly across different HLA-B27 subtypes or in HLA-B27-negative patients. Second, systemic safety concerns arise from the risk of "on-target, off-tumor" effects, including the unintended depletion of essential memory T cells or Tregs, which could increase susceptibility to secondary infections or long-term tumorigenicity. Third, the AS-specific microenvironment imposes mechanical and metabolic hurdles. The entheses—the primary site of AS lesions—are characterized by poor vascularity and dense fibrous tissue, which restrict the infiltration of large engineered cells. Furthermore, the local hypoxic and low-pH environment induced by persistent inflammation and mechanical stress can trigger functional exhaustion in CAR cells. Collectively, these challenges, compounded by high costs and manufacturing complexities, highlight the necessity of cautious clinical development.

Looking to the future, the following development directions are expected to promote breakthroughs in CAR therapy for AS treatment: 1. The development of allogeneic universal CAR cell products, such as iPSC-derived CAR-NK or CAR-T cells, can significantly reduce costs and achieve standardized production;[77] 2. Dual-target or multi-target CAR design, targeting B-cell and T-cell related antigens simultaneously, to achieve comprehensive regulation of the complex immune network of AS; 3. Controllable switchable CAR cells, such as the CLBR001 + SWI019 developed by the Calibr-Skaggs Institute, which can switch CAR-T therapy, avoiding lymph clearance pre-treatment chemotherapy and reducing treatment risks; 4. Combined application with nanodelivery systems targeting osteoblasts, to control inflammation while inhibiting pathological bone formation; 5. Artificial intelligence-assisted individualized treatment plan design, selecting the optimal CAR cell type and target combination based on the patient's immune phenotype. In conclusion, CAR cell therapy, as an emerging frontier technology in the field of autoimmune disease treatment, provides a new perspective for precise immune intervention in AS. Although there is currently limited clinical evidence for direct application in AS, with the deepening of understanding of the immune pathological mechanism of AS, continuous optimization of the CAR technology platform, and the discovery of new targets, CAR cell therapy is expected to become an important means to break through the bottleneck of AS treatment. Through multidisciplinary collaboration and translational medical research, this innovative therapy will eventually benefit more AS patients and bring them the hope of long-term remission or even cure.

Conclusion

AS, as a chronic inflammatory disease with a complex pathogenesis, has seen a rising incidence rate year by year, with high risks of teratogenicity and disability, and imposing a heavy burden on patients' quality of life. Current pharmacological strategies encompass several classes: NSAIDs for rapid symptomatic relief, yet they do not alter disease progression; biologic agents that target specific pathogenic pathways, but often fail to halt structural damage; and MSCs transplantation aiming for immunomodulation and repair, although its efficacy in preventing pathological ossification remains unproven. In recent years, targeted cellular immunotherapy, as a new hotspot in the field of autoimmune diseases, has provided novel conceptual frameworks and demonstrated initial potential for the management of AS. Nevertheless, while these advancements signal a promising shift in the therapeutic landscape, it is essential to contextualize these findings within the framework of current evidence-based medicine. It must be emphasized that clinical evidence for CAR-based and targeted cellular immunotherapies in AS is currently largely preliminary, remaining restricted to preclinical investigations or isolated clinical case reports rather than broad clinical application. To move forward, major challenges must be systematically addressed: (1) the current lack of AS-specific large-scale clinical trials; (2) the complexities of the entheseal microenvironment that may hinder cell infiltration and persistence; (3) long-term safety concerns, including CRS, potential off-target effects, and the risk of secondary malignancies; and (4) the high

economic and technical barriers to manufacturing. Overcoming these hurdles through rigorous translational research and multidisciplinary collaboration is essential before these promising modalities can be integrated into clinical practice. Although the treatment of AS still faces many challenges, in the future, more innovative treatment methods will surely emerge, helping patients get rid of the torment of pain and return to a healthy life.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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