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REVIEW

Mesenchymal stromal cell therapy for rheumatoid arthritis: Long-term efficacy, safety, and mechanistic insights

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Abstract

Rheumatoid arthritis (RA) is a multifactorial autoimmune disease primarily characterized by erosive arthritis. It can lead to joint pain, swelling, and deformity, significantly affecting patients' quality of life. RA results from the interaction of multiple factors, including genetic, environmental, and immune components, and its pathogenesis has not yet been fully elucidated. Existing treatment regimens have several limitations. Mesenchymal stromal cell (MSC) therapy has shown promising therapeutic potential in both preclinical and clinical studies due to its unique biological properties, such as multi-lineage differentiation potential, immunomodulatory functions, low immunogenicity, and strong tissue repair capacity. This article provides a comprehensive review of the long-term efficacy, safety, and potential mechanisms underlying MSC therapy on RA, with the aim of proposing MSC-based strategies to optimize therapeutic outcomes.

KEYWORDS

mesenchymal stromal cell therapy, rheumatoid arthritis, safety, therapeutic effects

Key points

- **Rheumatoid Arthritis (RA) Pathogenesis and Limitations of Current Treatments:** RA is a multifactorial autoimmune disease leading to joint pain, swelling, and deformity, with current treatments facing limitations in efficacy and safety.
- **Therapeutic Potential of Mesenchymal Stromal Cells (MSCs):** MSC therapy provides promise for RA treatment due to their multi-lineage differentiation, immunomodulatory properties, low immunogenicity, and tissue repair capacity.
- **Long-Term Efficacy and Safety of MSCs:** This review evaluated the long-term efficacy, safety, and potential mechanisms of MSC therapy, proposing novel strategies to improve therapeutic outcomes for RA patients.
- **Novel MSC-Based Strategies**: The review suggested novel MSC-based therapeutic strategies that can enhance treatment outcomes and overcome the limitations of existing RA therapies.

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by erosive arthritis, which can cause joint pain, swelling, and deformity, significantly impairing patients' quality of life. Globally, RA affects approximately 0.5% to 1% of the population, with a higher prevalence in women than in men. In addition to joint involvement, RA can also affect other organs, including the heart, lungs, and kidneys, leading to complications, such as pericarditis, interstitial lung disease, and renal amyloidosis. These systemic manifestations markedly increase the risk

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of disability and mortality.[1,2] Current treatment strategies for RA rely heavily on medications such as nonsteroidal anti-inflammatory drugs (NSAIDs),[3] glucocorticoids,[4] disease-modifying anti-rheumatic drugs (DMARDs),[5] and biologics.[6] While these drugs can alleviate pain and inflammation to some extent, they require long-term administration, and symptoms often recur after discontinuation, making sustained disease control challenging. Moreover, prolonged use is associated with adverse effects, such as gastrointestinal ulcers, bleeding, and abnormalities in blood glucose and lipid levels, which compromise both the efficacy and safety of treatment.[3,4] These side effects also limit therapeutic options and complicate long-term health management for patients. Given these limitations, there is a pressing need for safer and more effective treatment strategies.

In recent years, mesenchymal stromal cells (MSCs) have garnered significant attention as a potential breakthrough in RA treatment. Their unique biological properties, such as the ability to secrete anti-inflammatory cytokines and growth factors, promote tissue repair, modulate immune responses, and differentiate into multiple cell types,[7] position them as a promising alternative. It is essential to explore the long-term efficacy and safety of MSC-based therapies to promote their clinical application and ultimately improve outcomes for RA patients.

2 | OVERVIEW OF RA

2.1 | Characteristics of RA

RA is a chronic, systemic inflammatory autoimmune disease that primarily targets the synovial membrane of joints, leading to joint pain, swelling, stiffness, and, in severe cases, deformity and loss of function. Pathologically, RA is characterized by chronic synovial inflammation, hyperplasia, and pannus formation, which progressively erode articular cartilage and bone.[8] Clinically, RA typically presents with symmetrical pain, swelling, and stiffness affecting multiple joints—particularly the small joints of the hands, wrists, and feet. A hallmark symptom is morning stiffness, often lasting longer than an hour and improving with movement. As the disease progresses, joint symptoms worsen, resulting in functional impairment and characteristic deformities, such as swan-neck and boutonnière deformities. These changes significantly impact daily activities, including dressing, eating, personal hygiene, and walking, thereby severely diminishing quality of life.

Beyond articular manifestations, RA is associated with a wide range of systemic complications. These include interstitial lung disease, pleuritis, cardiovascular diseases, such as atherosclerosis and pericarditis, hematological abnormalities including anemia, leukopenia, and thrombocytosis, renal impairment, neurological disorders, such as peripheral neuropathy and cervical spine involvement, as well as osteoporosis and secondary Sjögren's syndrome.[9] These extra-articular features substantially increase the risk of disability and mortality, imposing considerable emotional and financial burdens on patients, families, and healthcare systems. Globally, the prevalence of RA between 1980 and 2019 was approximately 0.46%, with variability influenced by geographical location and study methodology.[10]

2.2 | Pathogenesis of RA

The exact pathogenesis of RA remains incompletely understood and is believed to result from a complex interplay among genetic, environmental, and immune factors (Figure 1)[12]. Genetic predisposition plays a pivotal role, with strong associations observed between specific alleles of the *human leukocyte antigen (HLA)-DRB1* gene and increased susceptibility to RA. In addition to HLA genes, non-HLA genes, such as signal transducer and activator of transcription 3 and protein tyrosine phosphatase non-receptor type 22, also contribute to RA pathogenesis. These genetic variants influence immune cell function and immune signaling pathways, thereby increasing the risk of developing RA.[13]

Environmental triggers, including infections and smoking, are also important contributors. For example, proteins from the Epstein-Barr virus (EBV) share structural similarities with synovial membrane proteins. This molecular mimicry may cause the immune system to misidentify joint tissue as foreign during an immune response to EBV infection, thereby initiating and sustaining autoimmunity.[11] Among environmental factors, smoking is one of the most significant risk factors. Both epidemiological studies and animal models have demonstrated its contribution to RA development and progression, likely through immune dysregulation and promotion of systemic inflammation.[14]

Compared with the general population, RA patients face a markedly increased risk of mortality due to cancer and infections. In particular, RA patients with infectious complications have a significantly elevated mortality risk—up to 52% higher than those without such complications.[15] Immune dysregulation is central to RA pathogenesis. In RA, the immune system erroneously targets synovial joint tissue, perceiving it as a foreign antigen and triggering a pathological immune response. This response involves the activation of T lymphocytes, B lymphocytes, and macrophages, which secrete pro-inflammatory cytokines and mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6.[16] These cytokines further recruit and activate immune cells in the synovium, resulting in chronic inflammation, synovial hyperplasia, and pannus formation. Over time, this inflammatory environment promotes the progressive destruction of cartilage and bone, leading to irreversible joint damage and deformity as briefly summarized in Figure 1.

2.3 | Traditional treatment options for RA

Current treatments for RA primarily include pharmacological therapy, physical therapy, and surgical intervention. NSAIDs provide anti-inflammatory and analgesic effects by inhibiting cyclooxygenase (COX) activity, thereby reducing prostaglandin synthesis and presenting rapid relief from joint pain and swelling. However, long-term NSAID use can

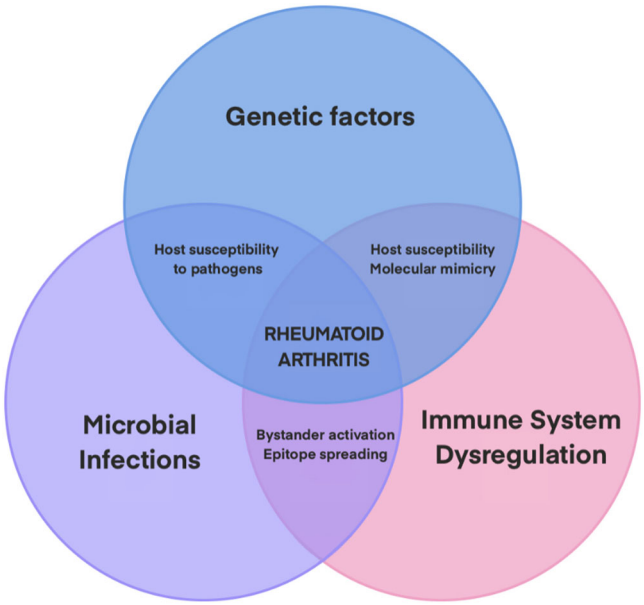

FIGURE 1 Interactions between different factors in rheumatoid arthritis.[11]

cause gastrointestinal complications, such as ulcers and bleeding, as well as cardiovascular and renal adverse effects.[3] Glucocorticoids, known for their potent anti-inflammatory and immunosuppressive properties, deliver quick symptom relief but are associated with serious long-term side effects. These include osteoporosis, increased susceptibility to infections, blood glucose and lipid abnormalities, and hypoadrenocorticism, often resulting in disease flare-ups upon discontinuation.[4]

DMARDs, the cornerstone of RA treatment, slow disease progression and prevent joint damage. However, their slow onset of action—typically 1 to 3 months—and variable efficacy limit their utility. Traditional DMARDs, such as methotrexate, leflunomide, and sulfasalazine, are frequently accompanied by adverse effects including hepatic and renal toxicity, hematological abnormalities, and gastrointestinal disturbances.[5] Biologic agents represent a newer class of therapeutics, including TNF-α inhibitors (e.g., etanercept, infliximab) and IL-6 receptor antagonists (e.g., tocilizumab). Administered via injection or infusion, these drugs target specific immune pathways to exert potent anti-inflammatory and immunomodulatory effects. Although biologic therapies provide rapid symptom relief and slow the progression of joint destruction, their high-cost limits broad accessibility. Additionally, biologics are associated with an increased risk of infections and malignancies, and some patients may experience injection site reactions, allergic responses, or reduced efficacy over time.[6]

Small-molecule targeted therapies, such as Janus kinase inhibitors (e.g., tofacitinib, baricitinib), block intracellular signaling pathways involved in inflammation. These agents provide the advantages of oral administration and rapid onset of action but are also associated with adverse effects, including infections, dyslipidemia, and elevated liver enzymes.[17]

As outlined, current pharmacological treatments for RA have significant limitations. These treatments mainly require frequent administration, and disease relapse or worsening typically occurs after discontinuation, complicating long-term disease management. Furthermore, prolonged use of these medications is associated with several side effects, such as gastrointestinal discomfort and potential liver or kidney damage, which can significantly impact patients' quality of life, highlighting the need for safer alternatives.

Physical therapies—including hot compresses, massage, acupuncture, and physiotherapy—can alleviate symptoms and improve joint function but do not modify the underlying disease course. Surgical interventions, such as joint replacement and synovectomy, are generally reserved for patients with severe joint deformities and functional impairment in advanced disease stages. While these procedures can improve joint function and quality of life, they carry risks of complications, such as infection and prosthetic loosening, along with substantial financial costs.[18]

3 | MSCS

3.1 | Characteristics of MSCs

As illustrated in Figure 2, MSCs possess a variety of unique characteristics that contribute to their functions. MSCs are adult stromal cells with self-renewal capacity and multi-lineage differentiation potential, found in diverse tissues including bone marrow, umbilical cord blood, umbilical cord tissue, placental tissue, and adipose tissue. Their versatile properties have made them a central focus in regenerative medicine and the treatment of numerous diseases. Under specific induction conditions, MSCs can differentiate into multiple cell types, such as osteoblasts, adipocytes, and chondrocytes, demonstrating their remarkable

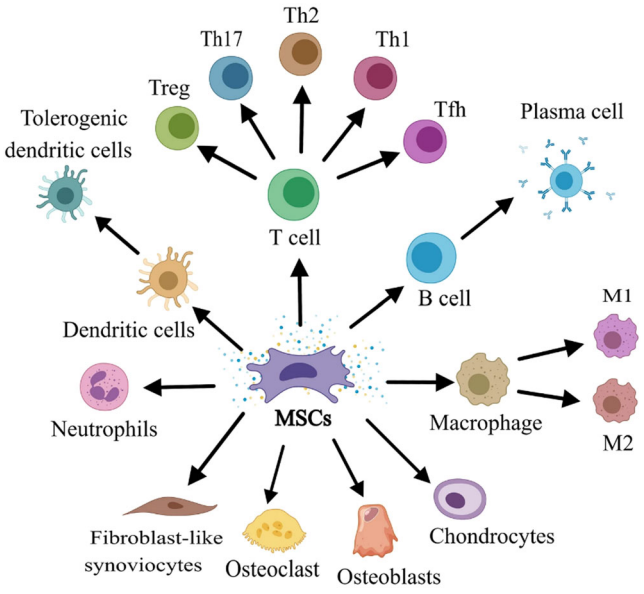

FIGURE 2 Characteristics of MSCs and their and therapeutic mechanisms in rheumatoid arthritis. MSC, mesenchymal stromal cell; Tfh, T-follicular helper; Th, T helper; Treg, regulatory T cells.

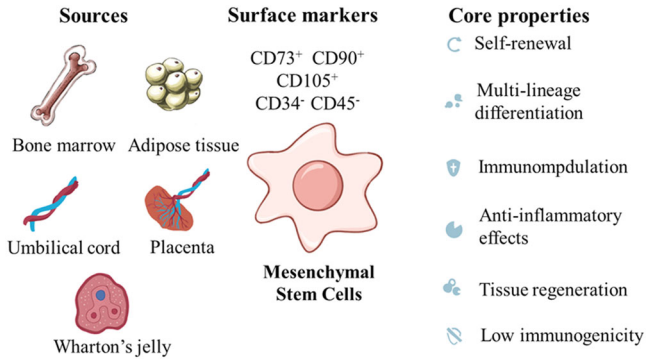

FIGURE 3 Mesenchymal stromal cells: Origin, phenotype, and functional features.

potential for tissue repair and regeneration. Moreover, MSCs exhibit potent immunomodulatory functions: they suppress the proliferation of T and B lymphocytes, inhibit the maturation and activity of dendritic cells (DCs), and regulate natural killer cell functions (Figure 3). These immunomodulatory capacities render MSCs valuable in treating autoimmune diseases and in transplant immunology. Clinical trials have confirmed their safety and efficacy in attenuating immune responses during organ transplantation, positioning MSCs as promising candidates for inducing transplant tolerance.[19]

In alignment with the updated ISCT standards, MSCs are defined as stromal cells rather than stem cells. The traditional stemness criteria, such as trilineage differentiation and adherent growth, are excluded. Instead, the focus is placed on specific cell markers, flow cytometry thresholds, and the tissue source of the cells. The paracrine effects and immunomodulatory functions of MSCs are emphasized, which are more relevant in clinical applications than their differentiation potential.

In addition, MSCs modulate the immune microenvironment by secreting immunoregulatory factors, such as transforming growth factor-beta (TGF-β) and indoleamine 2,3-dioxygenase (IDO), providing novel therapeutic strategies for autoimmune diseases, including RA and systemic lupus erythematosus.[20]

Preclinical studies[21,22] have demonstrated the therapeutic potential of MSCs in animal models of RA, in which MSCs have been shown to reduce joint inflammation, promote cartilage regeneration, and improve overall joint function. For instance, in the collagen-induced arthritis (CIA) mouse model, both intravenous and local administration of MSCs significantly reduced inflammatory markers and joint damage. Clinical studies have confirmed these findings, with MSC therapy showing promise in RA patients by reducing disease activity, alleviating pain, and improving quality of life.

The expression of surface markers, such as CD73, CD90, and CD105, is critical for identifying MSCs according to the new standards. Flow cytometry is used to confirm the absence of hematopoietic markers (e.g., CD34, CD45) as part of the characterization process.

MSCs possess robust self-renewal capabilities, enabling long-term in vitro culture while maintaining their stromal cell properties, thereby providing a reliable source for clinical applications. The use of chemically defined, serum-free media facilitates long-term expansion of human MSCs while preserving their pluripotency and undifferentiated state. This approach addresses challenges, such as batch-to-batch variability and risks associated with animal-derived components in traditional culture systems, providing a scalable and standardized platform for MSC production.[23] Furthermore, platelet lysate or autologous serum can substitute fetal bovine serum without compromising MSC quality.[24] Genetic modifications, such as overexpression of *Oct4* and *Sox2*, significantly enhance MSC proliferative capacity and stemness maintenance, supporting large-scale clinical applications.[25]

MSCs exhibit low immunogenicity, reducing the likelihood of immune rejection in transplantation therapies. This immune evasion is attributed to their low expression of major histocompatibility complex (MHC) class I molecules and the absence of MHC class II and costimulatory molecules. Additionally, MSCs secrete immunosuppressive factors, including TGF-β and IDO.[26] Recent studies have shown that MSC immunogenicity can be modulated; for example, dexamethasone pretreatment enhances the immunomodulatory properties of human MSCs.[27] Cosenza et al.[28] demonstrated that small extracellular vesicles from interferon-gamma (IFN-γ)-pretreated bone marrow–derived MSCs alleviated inflammation in a CIA mouse model, indicating that MSC therapeutic efficacy is highly dependent on IFN-γ levels. This was further confirmed by He et al.,[29] who found that mice treated with IFN-γ receptor knockout MSCs exhibited more severe synovial inflammation compared to those treated with wild-type MSCs. These findings underscore the importance of considering the microenvironment and pretreatment methods in clinical applications to ensure MSCs safety and efficacy.

3.2 | Mechanisms of MSCs in the treatment of RA

The therapeutic mechanisms of MSCs in RA are multifaceted, encompassing immunomodulation, anti-inflammatory effects, promotion of tissue repair, and inhibition of osteoclastogenesis. These mechanisms act synergistically to confer therapeutic benefits in RA. Key aspects include:

Immunomodulation: The pathogenesis of RA is closely linked to dysregulated immune activation. MSCs help restore immune homeostasis by modulating immune cell function via multiple pathways. T lymphocytes play a central role in RA; abnormally activated T cells produce excessive pro-inflammatory cytokines, triggering an inflammatory cascade that damages joint tissues. MSCs inhibit T cell activation and proliferation through various mechanisms. In vitro studies demonstrate significant suppression of T cell activation and

proliferation when cocultured with human embryonic stem cell-derived MSCs (hESC-MSCs). In vivo, intravenous administration of hESC-MSCs enhances infiltration and activation of regulatory T cells (Tregs).[30] MSCs also modulate antigen-presenting cell (APC) function, thereby indirectly influencing T cell differentiation. APCs are critical for T cell differentiation; by altering APC surface molecule expression and cytokine secretion, MSCs modify the differentiation signals received by T cells, inhibiting their development into pro-inflammatory effector subsets.[31] Additionally, MSCs promote the generation of Tregs, a subset of T cells with immunosuppressive functions that maintain immune tolerance and suppress autoimmune responses. Studies have shown that MSCs induce naïve T cells to differentiate into Tregs through the secretion of cytokines, such as IL-10 and TGF-β, enhancing immune regulation and mitigating RA-related immune pathology.[32] B cells are aberrantly activated in RA patients, producing autoantibodies, such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. These autoantibodies form immune complexes that activate the complement system, exacerbating inflammation.[33] MSCs regulate B cell function by inhibiting their differentiation, proliferation, and antibody production, while promoting the generation of IL-10-producing regulatory B cells.[34] Notably, DCs, the most potent APCs, play a pivotal role in initiating and regulating immune responses. In RA, DCs efficiently present self-antigens, activating autoreactive T cells and triggering autoimmune responses. MSCs suppress DC maturation, reduce their production of pro-inflammatory cytokines, and diminish their capacity to stimulate robust T cell responses.

Anti-inflammatory effects: MSCs exert anti-inflammatory effects by inhibiting the production of inflammatory mediators, promoting the secretion of anti-inflammatory cytokines, inducing macrophage polarization, suppressing complement system activation, and enhancing endothelial cell repair.[35] They secrete bioactive molecules, such as IL-10 and TGF-β, which neutralize pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6 in the inflammatory microenvironment, thereby reducing inflammation-induced joint damage. Moreover, MSCs promote macrophage polarization toward the anti-inflammatory M2 phenotype, which decreases the release of inflammatory mediators and further augments anti-inflammatory effects.[36] MSCs also regulate key kinases in the mitogen-activated protein kinase (MAPK) signaling pathway, blocking inflammatory signal transduction. The p38 MAPK pathway governs IL-1 and TNF-α production. Hammaker et al.[37] demonstrated that MAPK kinase (MKK)3 and MKK6 co-immunoprecipitate with p38 in fibroblast-like synoviocytes stimulated by IL-1 and TNF-α. In vitro kinase assays showed that this complex phosphorylates activating transcription factor-2, indicating that MKK3 and MKK6 form functional complexes with p38 in synovial tissue and fibroblast-like synoviocytes. These kinases thus represent potential targets for regulating pro-inflammatory cytokine production in inflamed synovium. A study using MSC-conditioned medium (MSC-CM) in adjuvant-induced arthritis in male Wistar rats revealed that MSC-CM alleviated inflammatory symptoms, reduced serum TNF-α levels, and inhibited intracellular signaling pathway factors.[38]

Anti-inflammatory effects: In RA patients, articular cartilage and bone tissues suffer severe damage. MSCs can differentiate into chondrocytes, osteoblasts, synoviocytes, and other joint tissue cells within the local joint microenvironment, thereby replenishing damaged cartilage and bone and promoting repair and regeneration.[39] MSCs also secrete growth factors and cytokines, such as insulin-like growth factor-1 (IGF-1)[40] and vascular endothelial growth factor (VEGF),[41] which stimulate angiogenesis, enhancing nutrient and oxygen delivery to damaged tissues. These factors also accelerate fibroblast and chondrocyte proliferation and migration, thereby facilitating tissue repair.

Chemotactic effects: MSCs express chemokine receptors, including C-X-C motif chemokine receptor 4 (CXCR4), which detect chemokines, such as CCL2, CCL5, and CXC motif chemokine ligand 12 (CXCL12), released at inflammatory joint sites, enabling targeted migration to areas of inflammation. Stromal cell-derived factor-1 (SDF-1), also known as CXCL12, is a homeostatic cytokine with potent chemotactic ability and represents a potential therapeutic target for RA.[42] Using synthetic biology, researchers engineered biomimetic nanoparticles (MCPNs) by fusing CXCR4-anchored MSC membranes with drug-loaded polymer cores. These nanoparticles serve as decoys targeting SDF-1 in arthritis. Via the CXCR4/SDF-1 chemotactic signaling axis, MCPNs evade immune clearance and accumulate in inflamed joints, significantly suppressing synovial inflammation and ameliorating pathological changes in a CIA mouse model.[43] This chemotactic mechanism allows MSCs to effectively home to inflammatory sites and exert anti-inflammatory and tissue repair effects. The mechanisms underlying MSC therapy for RA are interconnected and synergistic, providing novel strategies and promising potential for RA treatment. As research advances and clinical trials progress, MSCs are poised to become a safe and effective therapeutic option, providing significant relief for RA patients.

Potential risks: Despite the promising therapeutic effects of MSCs, there are potential risks associated with their use. Tumor formation remains a significant concern, as the undifferentiated nature of MSCs can lead to uncontrolled proliferation under certain conditions. Additionally, issues related to MSC differentiation, such as incomplete or abnormal differentiation, may compromise the desired therapeutic effects and even contribute to tumorigenesis. Furthermore, while MSCs generally exert immunomodulatory effects, in some cases, they may provoke immune-related side effects, including graft-versus-host reactions or unanticipated immune responses, especially in patients with compromised immune systems.

Influential factors: Furthermore, the success of MSC-based therapies can be influenced by factors, such as age, disease stage, and comorbidities. Older patients may exhibit a decline in the regenerative potential of MSCs, as cellular senescence can reduce the efficacy of therapy. Similarly, patients with advanced disease or additional

comorbidities, such as cardiovascular disease or diabetes, may have altered MSC function, affecting treatment outcomes. These factors must be considered when designing personalized MSC-based therapeutic strategies.

Preclinical studies on MSC therapy in RA models have highlighted their role in reducing joint inflammation, promoting tissue repair, and regulating immune responses. In CIA models, MSCs significantly suppressed T cell activation and pro-inflammatory cytokine production, providing a foundation for clinical applications. Clinical trials have further confirmed the efficacy of MSCs in modulating the immune response and reducing inflammation in RA patients. For example, one clinical trial[20] demonstrated that a single infusion of Umbilical cord-derived MSCs (UC-MSCs) led to significant reductions in TNF-α and IL-6 levels, along with improvements in disease activity scores (DASs) and quality of life.

MSC-derived exosomes in immune modulation and tissue repair: In addition to direct cell-to-cell interactions, MSCs exert therapeutic effects via the release of extracellular vesicles, particularly exosomes. MSC-derived exosomes are small lipid bilayer vesicles that contain bioactive molecules, including proteins, lipids, and RNAs, which facilitate intercellular communication. These exosomes play a crucial role in the immunomodulatory effects of MSCs in RA. Studies[30,31] have shown that MSC-derived exosomes can suppress T cell activation and proliferation, modulate APC function, and promote Treg expansion, similar to the effects observed with MSCs themselves. Exosomes also reduce the production of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, thereby contributing to the anti-inflammatory effects of MSC therapy. Furthermore, MSC-derived exosomes are involved in tissue repair by promoting the proliferation and migration of chondrocytes and fibroblasts, as well as stimulating angiogenesis through the delivery of growth factors, such as VEGF and IGF-1. Exosomes are being explored as a potential therapeutic alternative to whole MSCs due to their ability to deliver key therapeutic signals without the risks associated with cell-based therapies, such as immune rejection or tumor formation. This makes MSC-derived exosomes an attractive candidate for RA treatment, providing a novel mechanism by which MSCs exert their therapeutic benefits.

3.3 | Influential factors of MSCs in the treatment of RA

The efficacy of MSC therapy in RA is affected by various factors, including intrinsic cellular properties, treatment protocols, and patient-specific differences. MSCs derived from different tissue sources may exhibit distinct therapeutic potentials (Table 1).[44]

Preclinical studies[33,34] have also suggested that the therapeutic potential of MSCs can be influenced by factors such as the source of MSCs, treatment protocols, and microenvironmental conditions. For instance, the differentiation potential and immunomodulatory properties of bone marrow-derived MSCs[45] have been shown to be more potent in animal models of RA than adipose-derived MSCs (AD-MSCs).[46] Clinical studies have echoed these findings, indicating that factors, such as the route of administration (intravenous vs. intra-articular), MSC dose, and patient-specific conditions (e.g., age and comorbidities), also significantly impact treatment outcomes. UC-MSCs offer several advantages, including convenient collection, lack of ethical concerns, low immunogenicity, and high proliferative capacity. These features have contributed to promising therapeutic outcomes in clinical studies.[47]

The key factors influencing the therapeutic regimen of MSCs for RA include the route of administration, dosage, frequency, and pretreatment methods. The MSC dosage is critical in determining treatment efficacy.[48] Insufficient doses may fail to produce the desired therapeutic effects, while excessive doses may increase the risk of adverse reactions.[49] Evidence suggests that within an optimal range, increasing the MSC dose enhances therapeutic outcomes; however, beyond a certain threshold, further dose escalation may yield diminishing returns or even adverse effects.[44] Animal studies administering varying MSC doses to RA models have demonstrated that moderate dosing provides the most favorable therapeutic benefit, effectively reducing joint inflammation and tissue damage without eliciting significant adverse reactions.[44] Common administration routes include intravenous, intra-articular, and local injections, each with distinct impacts on efficacy. Intravenous injection is straightforward and enables MSCs to circulate systemically, reaching inflamed joints via the bloodstream.[50] Intra-articular injection delivers MSCs directly to the affected joint, achieving high local concentrations, but carries risks, such as infection or damage at the injection site.[51] Local injections, including intramuscular or subcutaneous routes, facilitate MSC accumulation in targeted areas, enhancing localized therapeutic effects, though their clinical applicability is comparatively limited.[52] Pretreatment of MSCs before infusion—using cytokines or small-molecule compounds—can potentiate their immunomodulatory and anti-inflammatory properties, thereby improving their

TABLE 1 Comparison of the characteristics of MSCs from different sources.

MSC source	Cell proliferation ability	Immunomodulatory activity	Difficulty of obtaining	Ethical controversy
Bone marrow	Moderate	Relatively strong	Invasive, difficult to obtain	Relatively small
Adipose tissue	Relatively strong	Moderate	Minimally invasive, relatively easy to obtain	Relatively small
Umbilical cord	Strong	Relatively strong	Noninvasive, easy to obtain	Relatively small

Abbreviation: MSC, mesenchymal stromal cell.

efficacy in suppressing inflammation during RA treatment.[27,29]

4 | LONG-TERM EFFICACY AND SAFETY OF MSCS IN THE TREATMENT OF RA

In RA patients who are intolerant or resistant to conventional therapies or those with comorbidities, MSCs offer a promising alternative due to their potent immunomodulatory properties (Table 2,[15,53–64] Figure 4). In a phase I, uncontrolled, open-label trial involving nine RA patients with moderate disease activity, varying doses of MSC transplantation (2.5×10^7, 5×10^7, and 1×10^8) were administered. Four weeks post-infusion, no significant toxicities were observed across all groups, and clinical parameters, such as erythrocyte sedimentation rate (ESR) and 28-joint disease activity score (DAS28) showed improvement. Notably, serum levels of inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α significantly decreased within 24 h after infusion of the highest dose

TABLE 2 Summary of treatments available for rheumatoid arthritis.

Drugs	Mechanism of action	Side effects	References
Conventional synthetic DMARDs			
Methotrexate	Impairs purine and pyrimidine metabolism, inhibits amino acid and polyamine synthesis	Skin cancer and gastrointestinal, infectious, pulmonary and hematologic side effects, bone marrow impairments	[53]
Leflunomide	Inhibits dihydroorotate dehydrogenase enzyme leading to inhibition de novo synthesis of pyrimidine nucleotides	Dyspepsia, nausea, abdominal pain, and oral ulceration	[54]
Sulfasalazine	Suppresses the transcription of nuclear factor-κB responsive pro-inflammatory genes, including TNF-α	Nausea, vomiting, anorexia, dyspepsia, male infertility (reversible), headache, and skin rash	[55]
Hydroxychloroquine	Increases pH within intracellular vacuoles and alters processes such as protein degradation by acidic hydrolases in the lysosome, assembly of macromolecules in the endosomes and post-translation modification of proteins in the Golgi apparatus	Retinal toxicity, neuromyotoxicity	[56]
Biologic DMARDs			
Etanercept, Infliximab, Adalimumab, Golimumab, Certolizumabpegol	Blocks the biological activity of TNF	Infections, neurological diseases, development of multiple sclerosis, and lymphomas	[15]
Anakinra	Binds to IL-1 receptors	Opportunistic and latent infections	[57]
Rituximab	Anti-CD20 monoclonal antibody	Hypogammag-lobulinemia, rarely serious infectious events	[58]
Abatacept	Contains the domain of cytotoxic T lymphocyte–associated antigen 4, blocks interaction between dendritic cells and T cells	Serious infections, increased risk of certain malignancies	[59]
Tocilizumab	Blocks IL-6 receptor	Serious infections, major adverse cardiovascular events, cancers, diverticular perforations, hepatic diseases	[60]
Secukinumab	Primarily targets IL-17A	Nasopharyngitis or infections of the upper respiratory tract, mild-to-moderate candidiasis	[61]
Brodalumab	Prevents the nuclear factor kappa light chain enhancer of activated B cells, IL-6, IL-8, cyclooxygenase-2, MMPs, and GM-CSF	Nasopharyngitis, upper respiratory tract infections, arthralgia, back pain, gastroenteritis, influenza, oropharyngeal pain, sinusitis	[62]
Targeted synthetic DMARDs			
Tofacitinib	Blocks JAK1 and JAK3	Cardiovascular events, neutropenia and lymphopenia, risk of infection (viral reactivation, herpes virus reactivation, opportunistic infections)	[63]
Baricitinib	Inhibits JAK1/JAK2	Hyperlipidemia, viral reactivation, deep venous thrombosis, and pulmonary embolism event	[64]

Abbreviations: DMARDs, disease-modifying anti-rheumatic drugs; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK, Janus kinase; MMPs, matrix metalloproteinases; TNF, tumor necrosis factor.

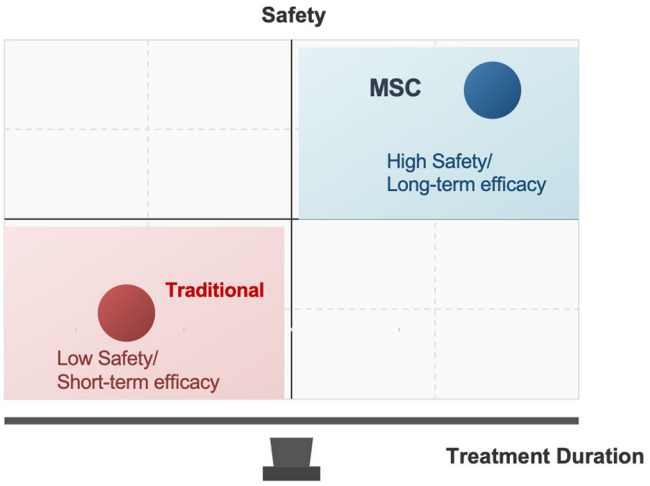

FIGURE 4 Long-term efficacy and safety of MSCs in the treatment of rheumatoid arthritis. MSC, mesenchymal stromal cell.

(1×10^8 cells), indicating rapid control of inflammation.[65] Another study evaluating allogeneic bone marrow-derived clonal MSCs in refractory RA patients reported that monthly infusions over 24 weeks improved visual analog scale scores in three of six patients, with two achieving sustained pain relief and enhanced quality of life. Four patients met the American College of Rheumatology (ACR) 20 criteria by Week 16. Clinical DASs and inflammatory markers, such as C-reactive protein (CRP) and ESR were reduced, while serological analysis showed increased IL-10 and decreased pro-inflammatory cytokines TNF-α and IL-17 in five patients.[66]

These short-term findings provide preliminary evidence supporting MSC efficacy and establish a foundation for long-term studies. In longer-term studies, Liu et al.[67] assessed the safety and efficacy of human UC-MSCs over an 8-month follow-up in 172 active RA patients being refractory to conventional therapy. Participants were assigned to either DMARDs combined with UC-MSC-free medium or DMARDs plus a single intravenous infusion of 4×10^7 UC-MSCs. Following treatment, serum levels of TNF-α and IL-6 were reduced, while the proportion of peripheral $CD4^+CD25^+Foxp3^+$ Tregs increased. Based on the ACR improvement criteria, DAS28, and health assessment questionnaire (HAQ) scores, significant symptom alleviation was found. The therapeutic effects persisted for 3 to 6 months without the need for continuous MSC administration, with repeated infusions further enhancing efficacy. Additionally, MSC therapy was well tolerated.[67]

Long-term follow-up studies are essential to evaluate MSC therapy durability. Liu et al. [68] further examined 64 RA patients (aged 18–64 years) treated with a single intravenous infusion of UC-MSCs (2×10^7 cells/20 mL) alongside individualized low-dose DMARDs. At 1- and 3-year posttreatment, routine blood tests, liver and kidney function, and immunoglobulin levels remained within normal ranges. Inflammatory markers, such as ESR, CRP, RF, and anti-CCP antibodies, were significantly reduced compared to baseline. Functional assessments via HAQ and DAS28 also showed sustained improvement. Table 3[67–70] summarizes some of the long-term clinical studies of MSC

TABLE 3 Long-term clinical studies of MSC therapy for RA.

Studies	Authors	MSC source	Treatment regimen	Sample size	Follow-up duration	Outcome
Study of UC-MSC for Active RA	Wang et al.[67]	UC-MSCs	UC-MSCs (4×10^7 cells/time) intravenously + DMARDs or DMARDs + medium without UC-MSCs	172	Up to 8+ months	No serious adverse events; DAS28 ↓, HAQ ↓, $CD4^+CD25^+Foxp3^+$ T cells ↑, TNF-α ↓, IL-6 ↓;
Clinical trial of BM-MSC for RAI	Ghoryani et al.[69]	Autologous BM-MSCs	Single intravenous (IV) injection of 1×10^6 autologous BM-MSCs per kg body weight	9	1 year	DAS28-ESR ↓, VAS ↓, T-reg cells percentage ↑, Th17 cells percentage↓
Phase I/II	Shadmanfar et al.[70]	Autologous BM-MSCs	Single intra-articular (IA) injection of 4×10^7 autologous BM-MSCs per knee joint	30	1 year	VAS ↓, WOMAC ↓, pain FWD ↑, WD ↑, time to jelling ↑, standing time↑
Prospective Phase I/II Study of UC-MSC for RA	Wang et al.[68]	UC-MSCs	2–5 mg of dexamethasone (or promethazine for patients with hyperglycemia or hypertension) followed by 40 mL of UC-MSC (2×10^7 cells/20 mL) intravenously	64	3 years	DAS28 ↓, HAQ ↓, CRP ↓, ESR ↓, RF ↓,

Note: Outcome: Long-term studies report sustained improvement in disease activity, reduced inflammation, and good safety profiles, although the duration of efficacy may vary between studies. The follow-up duration typically ranges from 1 to 3 years, with varying results depending on MSC source and treatment regimen.

Abbreviations: BM, bone marrow; CRP, C-reactive protein; DAS28, 28-joint disease activity score; DMARD, Disease-Modifying Anti-Rheumatic Drugs; ESR, erythrocyte sedimentation rate; FWD, functional walking distance; HAQ, Health Assessment Questionnaire; IA, intra-articular; IL, interleukin; IV, intravenous; MSC, mesenchymal stromal cell; RA, rheumatoid arthritis; RF, rheumatoid factor; TNF, tumor necrosis factor; UC, umbilical cord; UCB, umbilical cord blood; VAS, visual analog scale; WD, walking distance; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

therapy for RA. A systematic review and meta-analysis of randomized controlled trials further corroborated that MSCs significantly ameliorate joint space narrowing and bone erosion in RA patients.[71]

MSCs inhibit T and B cell proliferation and activation, reduce pro-inflammatory cytokine secretion, modulate immune responses, and mitigate inflammation without causing excessive immunosuppression, thereby avoiding complications, such as opportunistic infections.[72]

5 | DISCUSSION

Overall, MSC therapy has emerged as a highly promising and innovative approach for the treatment of RA, demonstrating remarkable long-term efficacy alongside a favorable safety profile in both preclinical and clinical settings. Clinical evidence accumulated over the past decade indicates that MSC administration not only effectively alleviates hallmark symptoms of RA—including joint pain, swelling, and stiffness—in the short term but also induces sustained and meaningful improvements in joint function and overall disease activity over extended follow-up periods. These improvements are characterized by reductions in key inflammatory biomarkers, such as ESR, CRP, RF, and anti-CCP antibody levels, which are strongly correlated with decreased synovial inflammation and joint destruction.

Moreover, MSC therapy contributes to the deceleration of cartilage degradation and bone erosion, processes that are pivotal in the progression of RA and often lead to irreversible joint damage and disability. Notably, some patients treated with MSCs have shown histological and radiological evidence of joint tissue repair, reflecting the unique regenerative capabilities of MSCs through their differentiation potential and secretion of growth factors, such as IGF-1 and VEGF. This dual ability to modulate immune responses and promote tissue regeneration underscores MSCs' potential to fundamentally alter the natural course of RA, offering hope for not just symptom control but also structural restoration.

Importantly, the safety profile of MSC therapy is well established through multiple clinical trials involving diverse patient populations, including those that are refractory to conventional treatments. To date, no serious adverse events directly attributable to MSC infusion have been reported, and the incidence of complications, such as infection, immune rejection, or aberrant cell differentiation, remains minimal. Potential risks, including immune reactions, uncontrolled differentiation, and microbial contamination, are systematically mitigated through rigorous cell quality control measures encompassing standardized protocols for cell isolation, culture expansion, characterization, storage, and administration. Furthermore, pretreatment strategies, such as cytokine priming or genetic modification, have been employed to enhance the immunomodulatory efficacy of MSCs while maintaining safety. These efforts collectively ensure that MSC-based therapies meet the stringent regulatory requirements necessary for broad clinical translation.

Genetic engineering of MSCs presents a promising direction for enhancing their efficacy in RA treatment. By modifying MSCs to express specific therapeutic genes, such as cytokines or growth factors, their immunomodulatory and tissue-regenerative properties can be further optimized. For instance, genetic modification of MSCs to overexpress IL-10 or TGF-β can enhance their anti-inflammatory effects and promote tissue repair in RA patients. Additionally, MSCs can be engineered to carry therapeutic genes that target the underlying mechanisms of RA, such as those regulating osteoclastogenesis and cartilage degradation. These genetic modifications enable MSCs to better address the multifaceted nature of RA pathology, improving clinical outcomes. Biological delivery platforms are also being developed to improve the targeted delivery and sustained release of MSC-based therapies. Nanoparticles, hydrogels, and biomimetic scaffolds have been explored as vehicles for MSC delivery, ensuring more efficient migration to the inflamed joint and enhancing their therapeutic effects. For example, nanoparticles can be engineered to encapsulate MSCs or MSC-derived exosomes, protecting them from immune clearance and improving their homing to specific tissues. These delivery systems can provide controlled release of therapeutic factors, reducing the frequency of MSC administration and improving long-term efficacy. Moreover, incorporating targeting ligands into these delivery platforms can further enhance the specificity of MSC therapy, ensuring that MSCs or their exosomes are directed to sites of inflammation, thereby minimizing off-target effects and optimizing therapeutic outcomes.

Given their multifaceted mechanisms—immunomodulation, anti-inflammatory effects, promotion of Tregs, suppression of autoreactive B cells, and chemotactic migration to inflamed tissues—MSCs represent an attractive therapeutic alternative for patients with refractory RA, especially those who have limited response or intolerance to current pharmacological agents, such as DMARDs, biologics, and small-molecule inhibitors. The ability of MSCs to restore immune tolerance without inducing generalized immunosuppression reduces the risk of opportunistic infections, a common complication of traditional immunosuppressive therapies. Wang et al.[68] assessed the long-term efficacy and safety of UC-MSCs along with DMARDs for the treatment of RA, and they found that UC-MSCs plus DMARD therapy can be a safe, effective, and feasible therapeutic option for RA patients. Other scholars[73] demonstrated that UC-MSCs exhibited promising efficacy and tolerability in RA patients and have emerged as a notable alternative in the management of RA. The pathogenesis of RA is related to disorders of immune mechanisms and cytokines. UC-MSCs are widely available and have low immunogenic responses, and the limitations, such as the lack of traditional stem cell sources, allogeneic rejection, and ethics, have been overcome.[73]

Despite the promising outcomes observed in recent studies, MSC therapy is not without its limitations. Clinical trials to date have frequently been characterized

by small sample sizes, heterogeneous patient populations, and variability in the sources, dosages, and administration protocols of MSCs. These factors complicate direct comparisons across studies and limit the broader applicability of the results. Furthermore, the long-term persistence, homing efficiency, and fate of infused MSCs in inflamed joints remain incompletely understood. In addition, the immunomodulatory effects of MSCs may be influenced by factors, such as the stage of the patient's disease, the microenvironmental conditions in the joint, and prior treatments, all of which contribute to variability in clinical responses. Although the potential for unwanted differentiation or fibrosis is rare under controlled conditions, it remains a concern that necessitates ongoing vigilance. Biomanufacturing obstacles also present a significant barrier to the widespread clinical application of MSC therapies, particularly in ensuring consistent cell quality, potency, and scalability. Moreover, the development of cost-effectiveness analyses and the establishment of standardized regulatory frameworks are critical to promote equitable access to, and reimbursement for, MSC-based treatments.

Looking ahead, ongoing and future research efforts aim to refine MSC therapy by optimizing critical parameters, such as dosage, frequency, and routes of administration to maximize therapeutic efficacy and minimize risks. Combination strategies integrating MSCs with existing pharmacotherapies or novel agents are under exploration to harness potential synergistic effects. Advances in cell manufacturing technologies—including the use of serum-free culture systems, genetic enhancement, and biomimetic delivery platforms—are poised to improve MSC yield, potency, and consistency, facilitating scalable production that meets clinical demand.

Furthermore, a deeper understanding of MSCs' interactions with the RA microenvironment and their molecular mechanisms of action will enable the development of predictive biomarkers for patient stratification and treatment monitoring. These scientific and technological advances are expected to lower treatment costs, enhance accessibility, and accelerate regulatory approval processes, thereby expanding the clinical applicability of MSC therapy.

In conclusion, MSC therapy holds tremendous promise as a transformative treatment modality for RA, providing not only symptomatic relief but also the potential for durable disease modification and tissue regeneration. While challenges remain, ongoing innovations and rigorous clinical research are steadily addressing these limitations, paving the way for MSC-based interventions to become an integral component of the therapeutic armamentarium against RA, providing renewed hope and improved quality of life for millions of patients worldwide.

AUTHOR CONTRIBUTIONS

Dr. Yingjia Chen conceptualized the overall framework of this review, summarized the core arguments based on systematic field research, and was responsible for drafting and revising the entire manuscript as the primary contributor. Lingyun Sun provided insightful guidance and many key revision suggestions. Ruiyu Gao, Xing Guo, Genhong Yao, Xiaojun Tang, and Yile E. Liu contributed to literature collation and partial content refinement.

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CONFLICT OF INTEREST STATEMENT

Lingyun Sun is a member of the Rheumatology & Autoimmunity editorial board and is not involved in the peer-review process of this article. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors have nothing to report.

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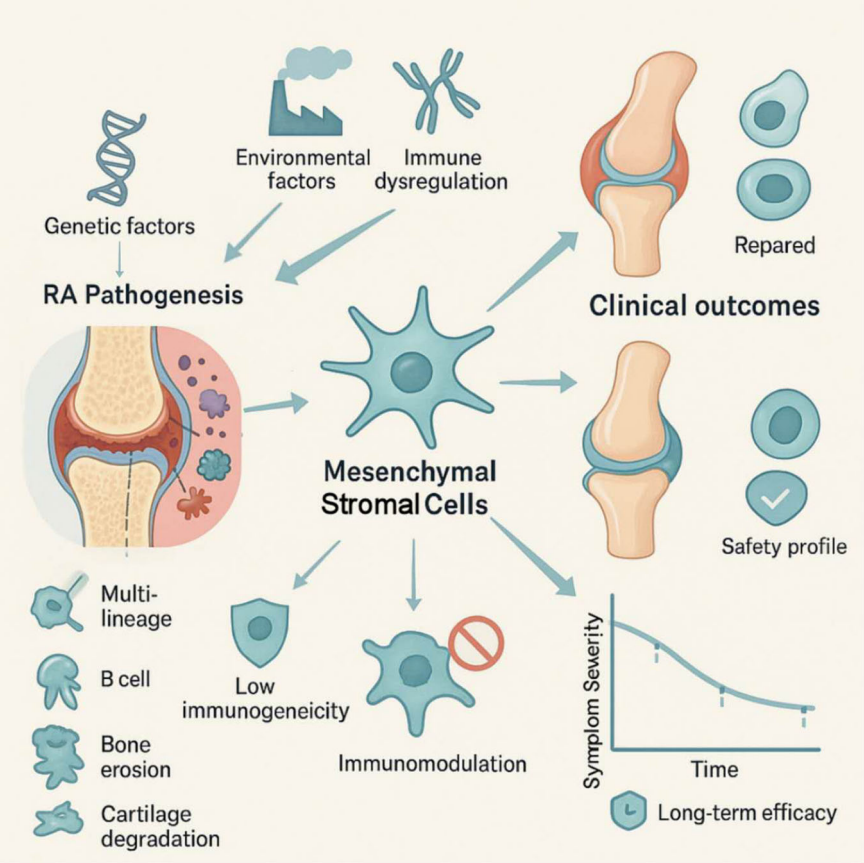
GRAPHICAL ABSTRACT

This graphical abstract will be a part of HTML, Online and Print versions.



Graphical abstract summarizing the multifactorial pathogenesis of rheumatoid arthritis (RA) and the therapeutic potential of mesenchymal stromal cell (MSC) therapy. MSCs provide promising benefits through their immunomodulatory properties, low immunogenicity, ability to promote tissue repair, and multi-lineage differentiation, presenting a potential alternative to conventional RA treatments. This review explores the long-term efficacy, safety, and mechanisms underlying MSC-based strategies for improving RA management.