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REVIEW

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Efficacy and safety of mesenchymal stromal cell transplantation in the treatment of autoimmune and rheumatic immune diseases: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective This study aims to assess the effectiveness and safety of mesenchymal stem cell (MSC) transplantation in the treatment of autoimmune and rheumatic immune diseases through randomized controlled trials (RCTs).

Methods Two researchers conducted a comprehensive search of Chinese and English databases from their inception until Dec. 2023. The literature screening and data extraction were then performed. Statistical analysis was carried out using RevMan 5.4 software.

Results A total of 42 relevant RCTs, involving 2,183 participants, were ultimately included in this study. These RCTs encompassed four types of rheumatic immune and bone diseases, namely rheumatoid arthritis (RA), osteoarthritis (OA), spondyloarthritis, systemic sclerosis arthritis, systemic lupus erythematosus (SLE), inflammatory bowel disease, multiple sclerosis, primary Sjögren's syndrome (PSS). The systematic review indicates that MSC transplantation may improve spondyloarthritis, RA, PSS. The meta-analysis reveals that MSC transplantation significantly improved symptoms in patients with OA [VAS (visual analogue scale): bone marrow: SMD = −0.95, 95% CI −1.55 to −0.36, $P=0.002$; umbilical cord: SMD = −1.25, 95% CI −2.04 to −0.46, $P=0.002$; adipose tissue: SMD = -1.26, 95% CI -1.99 to −0.52, $P=0.0009$)], SLE [Systemic lupus erythematosus disease activity index (SLEDAI): SMD = −2.32, 95% CI −3.59 to −1.06, P = 0.0003], inflammatory bowel disease [clinical efficacy: RR = 2.02, 95% CI 1.53 to 2.67, $P<0.00001$]. However, MSC transplantation may not improve the symptoms of multiple sclerosis and systemic sclerosis (Ssc). Importantly, MSC transplantation did not increase the incidence of adverse events (OA: RR = 1.23, 95% CI 0.93 to 1.65, $P=0.15$; SLE: RR = 0.83, 95% CI 0.28 to 2.51, $P=0.76$; Inflammatory bowel disease: RR = 0.99, 95% CI 0.81 to 1.22, $P=0.96$; Multiple sclerosis: RR = 1.12, 95% CI 0.81 to 1.53, $P=0.50$), supporting its safety profile across the included studies.

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These findings suggest that MSC transplantation holds promise for several rheumatic and autoimmune diseases while highlighting areas where further research is warranted.

Conclusion MSC transplantation may have the potential to treat autoimmune and rheumatic immune diseases. Moreover. MSC transplantation appears to be relatively safe and could be considered as a viable alternative treatment option for autoimmune and rheumatic immune diseases.

Keywords Autoimmune diseases, Rheumatic immune diseases, Mesenchymal stem cells, Systematic review, Meta-analysis

Introduction

Autoimmune and rheumatic immune diseases are characterized by immune dysregulation, leading B cells and T cells to abnormally target the body's own tissues. These conditions can affect any organ system and impact individuals across all age groups, with a notably higher prevalence among women [1]. Currently, autoimmune diseases rank as the third most significant threat to human health after cardiovascular diseases and cancer. Additionally, disability and mortality rates resulting from these diseases have been rising steadily each year [1, 2]. Pathogenesis of autoimmune and rheumatic immune diseases involves environmental and genetic factors, especially in genetically susceptible individuals, driving specific clinical outcomes through molecular processes [3, 4]. Autoimmune and rheumatic immune diseases, varied in nature, are often degenerative initially, followed by inflammation, contributing to disease characteristics [5]. Inflammation-associated rheumatic immune diseases result from abnormal immune responses and metabolic issues, involving specific cells like mast cells, macrophages, fibroblasts, and others migrating via the bloodstream to target organs [6–8]. The close association of target tissues with blood vessels and immune cells fosters rheumatic diseases influenced by impaired immune regulation and vascular disruption [9]. Epidemiological data highlights around 200 types of autoimmune and rheumatic immune diseases, affecting approximately 10% of individuals and posing significant economic challenges [10]. These diseases categorize into connective tissue degeneration, systemic autoimmune diseases marked by autoantibodies, and other inflammatory conditions [11–13]. Treatment typically involves immunosuppression, with biologics and small molecule drugs emerging as key agents, although prolonged use poses risks of side effects [14–16]. The large population of patients with autoimmune and rheumatic immune diseases currently relies on treatments that focus primarily on symptom relief, functional maintenance, and slowing tissue damage, yet curative options remain unavailable. This significant patient burden, combined with unmet clinical needs, highlights the urgency for innovative therapies in autoimmune and rheumatic immune diseases treatment. As cell therapies advance in treating autoimmune and rheumatic immune diseases, interest in cellular approaches, including chimeric antigen receptor (CAR)-T cells, is at a turning point. However, CAR-T cell products are experimental, patient-specific, and associated with potential adverse events, underscoring the demand for safe, ready-to-use cell products with the capacity to induce immune tolerance [17, 18]. Unlike traditional immunosuppressants, mesenchymal stem cells (MSCs) demonstrate regenerative potential and immunomodulatory properties, modulating anti-inflammatory factors and promoting immune tolerance for maintaining homeostasis [19, 20].

MSCs are spindle-shaped, plastic-adherent multipotent stem cells with self-renewal, multilineage differentiation, and immunoregulatory capabilities. MSCs can be isolated from diverse tissues such as adipose tissue, bone marrow, placenta, umbilical cord, Wharton's jelly, endometrium, dental pulp, and gingiva [21, 22]. The International Society for Cellular Therapy (ISCT) defines MSCs as cells showing adherence to plastic culture flasks, high expression of CD105, CD73, and CD90, and low expression of CD45, CD34, CD14, CD11b, CD19, and HLA-DR [23]. MSCs exhibit potential to differentiate into osteoblasts, adipocytes, and chondrocyte progenitor cells in vitro and in vivo [23]. Their immunomodulatory properties make them valuable for age-related and inflammatory disease treatments, with allogeneic MSC products showing high safety profiles in clinical trials due to low HLA molecule expression [24, 25]. Notably, MSCs' characteristics enable them to evade allogeneic T cell and NK cell recognition, survive in xenogeneic hosts, and exhibit bidirectional immunomodulation, distinguishing them from other adult stem cells [26, 27]. In clinical settings, MSCs show promise for tissue injuries and immune disorders, with ongoing research exploring their efficacy in treating autoimmune diseases as alternatives to traditional therapies [28–32]. However, limitations in cell culture control, intricate trial designs, and effective evaluation methods underscore the necessity for comprehensive systematic reviews and meta-analyses of MSC therapy for autoimmune and rheumatic immune

diseases. To address this need, we have registered a protocol on PROSPERO for a thorough evaluation, aiming to provide new evidence for clinical practice.

Materials and methods

Protocol

This systematic review and meta-analysis were conducted in strict adherence to the protocol registered in PROSPERO (CRD42023450114) and followed PRISMA guidelines (see supplementary materials).

Search criteria

Participants

Participants were individuals who met recognized diagnostic criteria for the respective autoimmune and rheumatic immune diseases. For instance, individuals diagnosed with rheumatoid arthritis (RA) were included if their diagnosis aligned with either the criteria set by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010 or the criteria set by ACR in 1987.

Intervention methods

The experimental group received interventions involving the utilization of mesenchymal stem cells (MSCs), either in isolation or in combination with other therapeutic approaches. On the other hand, the control group underwent non-MSC therapies, which may conventional therapy, placebos, etc.

Outcomes

The outcomes comprised efficacy measures specific to various inflammatory arthritic conditions, such as the Western Ontario and McMaster universities osteoarthritis (WOMAC) index for osteoarthritis (OA) and the disease activity index for rheumatoid arthritis (RA), along with safety indicators.

Study design

The randomized controlled trial (RCT) without any restrictions.

Exclusion criteria

(1) Patients presenting with a combination of multiple inflammatory arthritic conditions; (2) Case reports; (3) Reviews; (4) Animal experiments; (5) Control group that includes MSC treatment.

Research databases

Chinese databases (such as CNKI, VIP database, Wanfang Database, Sinomed) and English databases (such as Embase, Medline, PubMed, and Web of Science) were searched from the inception of the databases until Dec. 1st, 2023. Additionally, we searched the Cochrane Library and ClinicalTrials.gov. The retrieval strategies for Embase and PubMed can be found in Supplementary Table S1.

Research screening, extraction and quality assessment

Initially, two researchers conducted a rigorous elimination process to eliminate duplicate literature, considering factors such as title, author, and publication year. Subsequently, abstracts were meticulously scrutinized for relevance, followed by a comprehensive analysis of full texts utilizing predefined criteria for literature selection and data extraction [33]. The risk of bias was independently assessed by the researchers using the Cochrane Risk Bias Assessment Form from the Cochrane Collaboration [34]. Screening of the literature, data extraction, and evaluation of RCT quality were carried out independently by the two researchers. Any discrepancies were resolved through discussions involving a third researcher.

Statistical analysis

For conducting the meta-analysis, the Revnan5.4 software was employed [35]. Relative risks (RR) with 95% confidence intervals (CIs) were used to present dichotomous variables, such as adverse events, while mean differences (MD) with 95% CIs were utilized for continuous variables, such as VAS scores. The chi-square test was utilized to examine heterogeneity among the RCTs, with a significance level set at $P < 0.1$. The degree of heterogeneity was determined using the I^2 statistic. If I^2 exceeded 50%, it indicated high heterogeneity, while values below 50% implied low heterogeneity. To account for potential clinical variations in the preparation of MSCs, a random-effects model was employed to assess all outcomes, irrespective of the level of heterogeneity.

Results

Search results

A total of 7938 relevant articles were initially identified for this study. After excluding 7891 articles based on the review of titles and abstracts, 52 articles underwent full-text review. Following further screening based on inclusion and exclusion criteria, a total of 42 articles were included [36–77] and 10 articles were not included [78–87] (Fig. 1).

Description of included trials

The included randomized controlled trials encompassed eight types of rheumatic immune and bone diseases, including RA, OA, spondyloarthritis, systemic sclerosis arthritis, SLE, inflammatory bowel

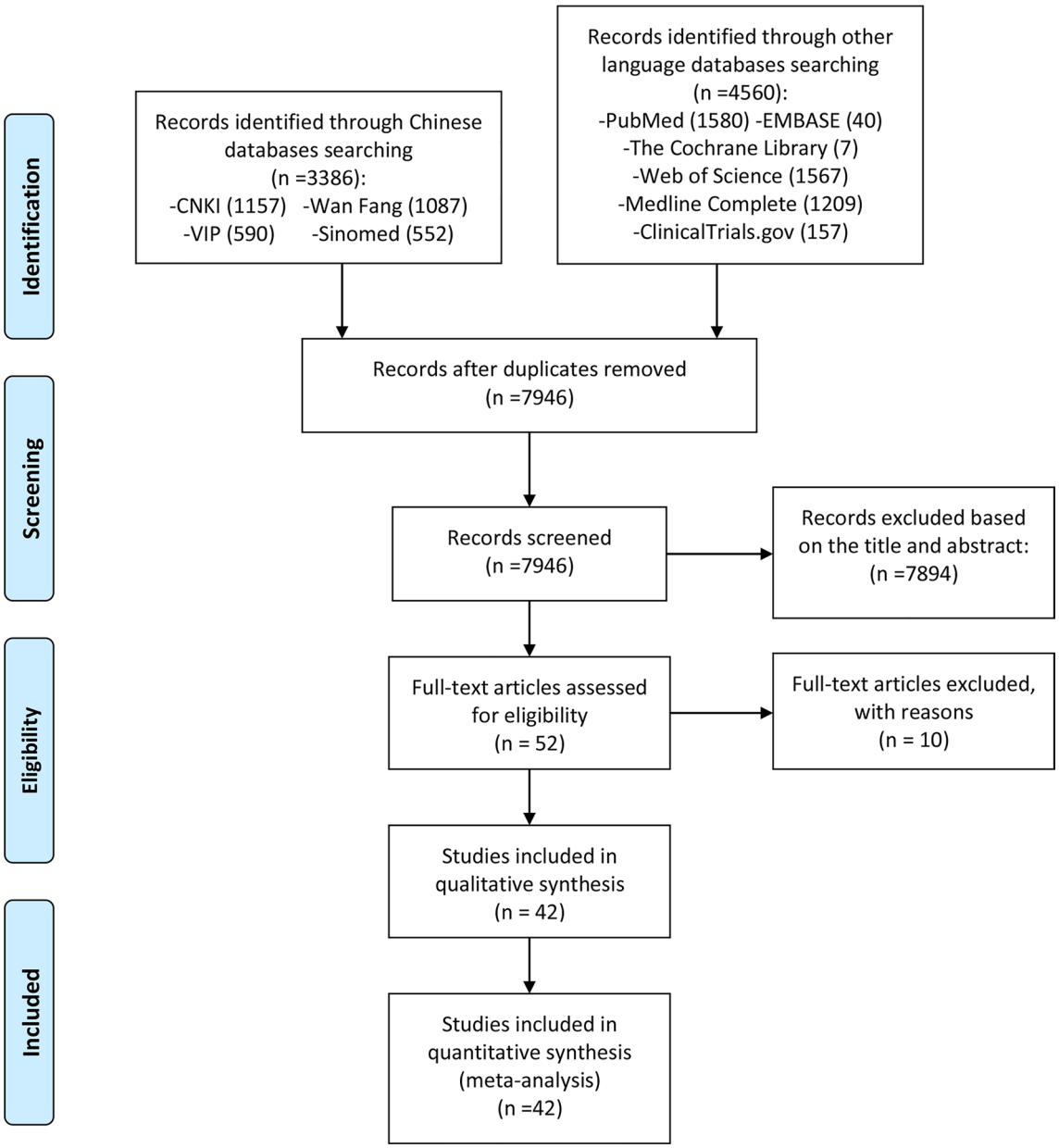

Fig. 1 Flow diagram of research screening

disease, multiple sclerosis, primary sjögren's syndrome (PSS). Several RCTs consisted of multiple groups, and for the purpose of meta-analysis, they were categorized as subgroups a, b, and c. The characteristics of the included studies are presented in Table S2.

Risk of bias assessment

The summary and graph of risk of bias ware shown in Figs. 2 and 3.

The outcomes of MSC for spondyloarthritis

Only 1 RCT examined the use of MSC in the treatment of ankylosing spondylitis. The study conducted by Su et al. in 2020 revealed that after a six-month course of MSC therapy, there was a potential improvement in the overall effectiveness compared to treatment involving Fliximab. Furthermore, MSC treatment demonstrated reductions in erythrocyte sedimentation rate, intercellular adhesion molecules, and serum TNF-α

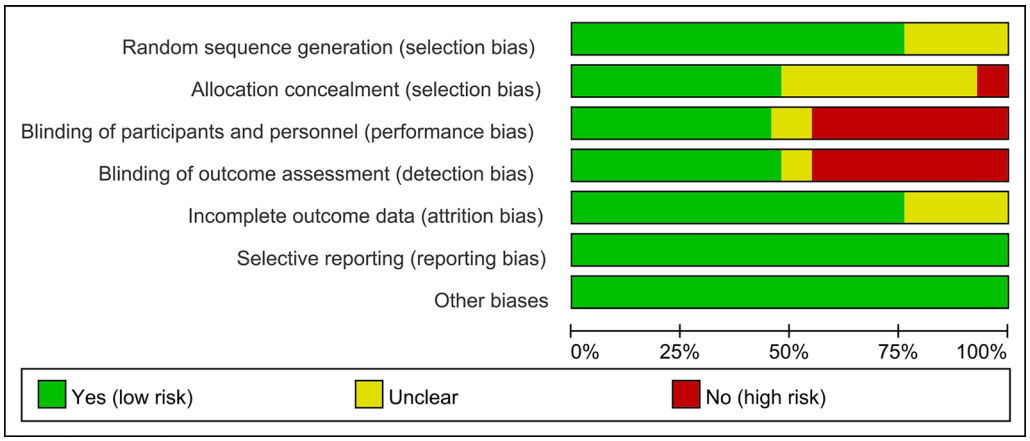

Fig. 2 Risk of bias graph

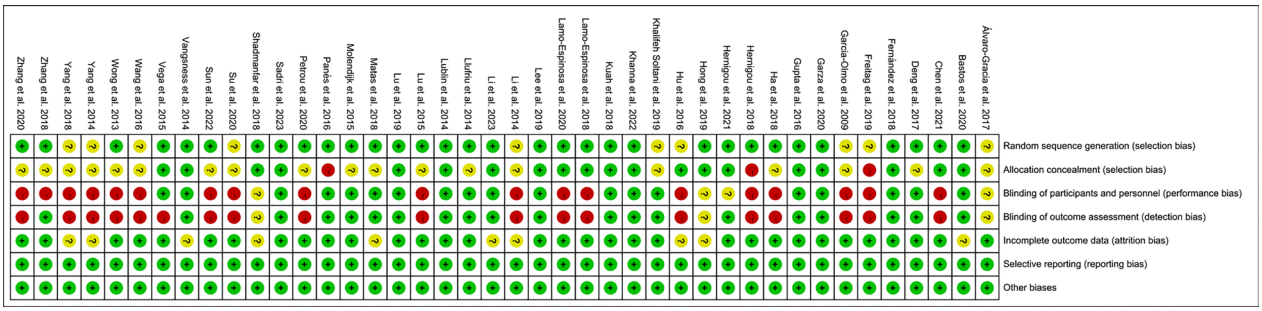

Fig. 3 Risk of bias summary

levels. Remarkably, it exhibited promising outcomes in relieving pain and improving mobility.

The outcomes of MSC for RA

In order to evaluate the safety and effectiveness of MSC treatment in RA, a comprehensive review was conducted with a focus on three different RCTs that presented data using diverse methods. The overall findings indicate that the administration of bone marrow mesenchymal stem cells is generally well-tolerated and safe for patients with RA. Álvaro-Gracia et al. in 2017 reported moderate success in achieving comprehensive ACR 20, ACR50, and ACR70 responses among patients, although fewer individuals experienced a 50% or 70% improvement in their condition [38]. Conversely, Yang et al. in 2018 demonstrated that MSC treatment resulted in a reduction in disease activity and significant improvement in clinical symptoms, lasting up to 12 months, with an overall clinical effectiveness rate of 54%. The patients in the response group experienced pain and swelling at 24 weeks, leading to increased levels of ESR and CRP. Moreover, the intervention led to a gradual decrease in the dosage of prednisone acetate for 23 patients in the experimental group. Immunologically, the response group exhibited an increased percentage of CD4 + CD25 + Foxp3 + Tregs, a decreased percentage of CD4 + IL-17A + Th17 cells, and significantly lower levels of IL-6 and TNF-α [37]. Similarly, Shadmanfar et al. in 2018 suggested that MSC treatment has the potential to improve standing time, WOMAC total score, and reduce reliance on methotrexate and prednisolone. Among patients with knee involvement, more than 50% experienced a significant reduction in knee pain [39].

The outcomes of MSC for SSc

Only 1 RCTs assessed the efficacy of autologous adipose-derived regenerative cell therapy for improving hand function in systemic sclerosis (SSc) patients. The study results revealed marginal enhancements in hand function following ADRC treatment in comparison to the placebo group; however, these improvements did not achieve statistical significance. In the case of patients diagnosed with diffuse cutaneous SSc (dcSSc), there was a notable difference of 6.3 points in Cochin Hand Function Scale (CHFS) scores and 0.17 points in the Health Assessment Questionnaire Disability Index (HAQ DI), which serves

as a secondary measure, at the 48-week mark. The study indicated that more than half of the dcSSc patients who underwent ADRC treatment reported significant improvements in CHFS and HAQ DI compared to those in the placebo group. The procedure involving the extraction of adipose tissue in small volumes and subsequent ADRC therapy was well-tolerated. Although the study did not yield statistically significant outcomes, there was an observable trend suggesting the efficacy of ADRC treatment in dcSSc patients, thereby underscoring the necessity for additional clinical trials to investigate the potential of ADRC therapy within the context of dcSSc.

The outcomes of MSC for OA

Bastos et al. (2020) and Wong et al. (2013) focused on different clinical indicators without reporting the specific outcomes reported in our study. In Bastos et al. (2020), it was observed that the groups treated with MSCs alone or MSCs in combination with corticosteroids exhibited a significantly higher percentage of improvement in the majority of KOOS domains and overall scores compared to the corticosteroid group ($P < 0.05$).

VAS

In the study conducted by Hernigou et al. in 2021, patients underwent total knee arthroplasty (TKA) on one knee and received MSCs via intraosseous injection in the subchondral bone lesion of the contralateral knee. The findings indicated that MSCs treatment in subchondral bone marrow lesions led to a reduction in the volume of bone marrow lesions in the medial femoral compartment within 24 months, accompanied by a decrease in patient-reported VAS scores. Lee et al. in 2019 demonstrated a significant reduction in VAS scores after MSC treatment when compared to the normal saline group ($P < 0.05$).

Twelve RCTs reported VAS data that could be extracted for meta-analysis. The heterogeneity test indicated a significant level of heterogeneity across all three subgroups, necessitating the use of a random effect model. The findings demonstrated a significant reduction in VAS scores among patients with osteoarthritis following MSCs treatment (bone marrow: SMD = −0.95, 95% CI −1.55 to −0.36, $P = 0.002$; umbilical cord: SMD = −1.25, 95% CI −2.04 to −0.46, $P = 0.002$; adipose tissue: SMD = −1.26, 95% CI −1.99 to −0.52, $P = 0.0009$), as shown in Fig. 4.

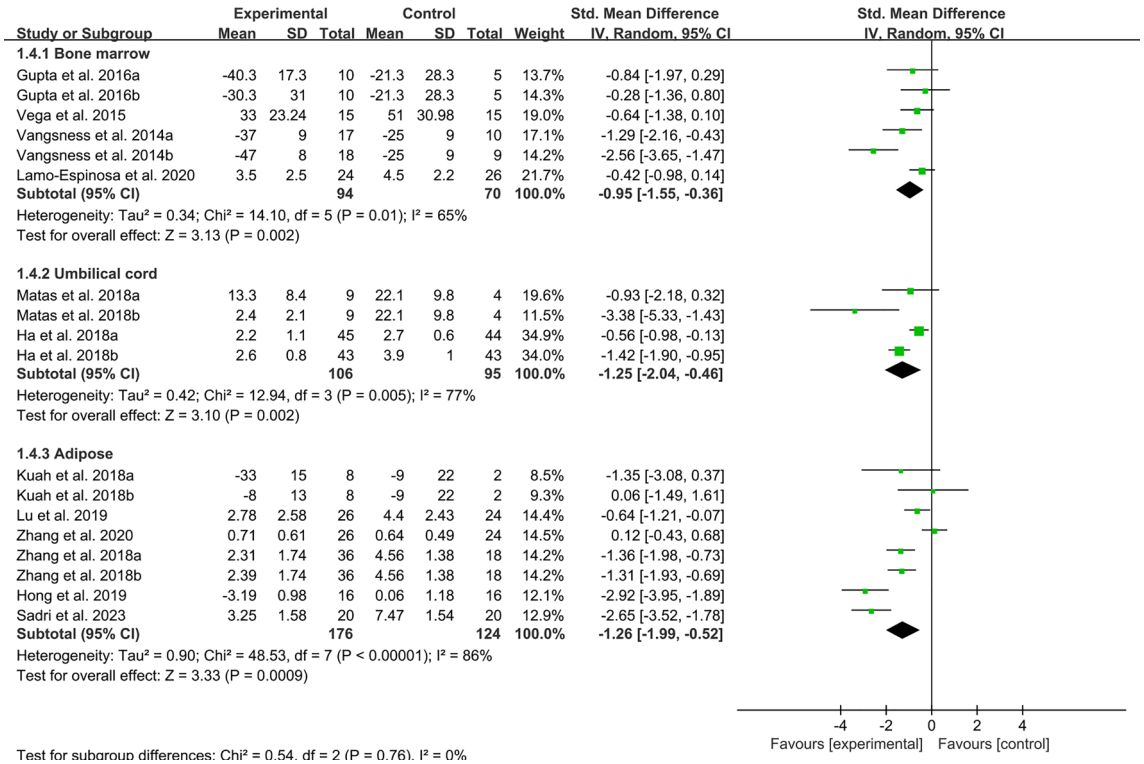

Fig. 4 VAS of OA after MSC therapy

WOMAC

Eighteen studies reported changes in WOMAC after treatment. In the study conducted by Lu et al. in 2015, the specific components of the WOMAC assessment were not explicitly mentioned, resulting in the execution of a descriptive analysis only. Lu et al. found a statistically significant distinction between the post-treatment WOMAC scores of the MSC group (40.9 ± 20.2) and the control group (51.4 ± 21.1) ($P < 0.05$).

(1) WOMAC pain: The studies conducted by Lee et al. in 2019 and Freitag et al. in 2019 both illustrated a noteworthy decrease in WOMAC pain scores following MSC treatment, in comparison to the group treated with normal saline ($P < 0.05$). Nine RCTs reported WOMAC pain data that could be extracted for meta-analysis. The heterogeneity test indicated a significant level of heterogeneity across subgroups, necessitating the use of a random effect model. The findings indicated that MSCs treatment resulted in a noteworthy reduction of WOMAC pain scores specifically within the adipose subgroup (SMD = −1.25, 95% CI −1.89 to −0.61, $P = 0.0001$). However, no statistically significant decrease in WOMAC pain scores was observed in the bone marrow and umbilical cord subgroups (bone marrow: SMD = −0.72, 95% CI: −1.47 to 0.03, $P = 0.06$; umbilical cord: SMD = −0.75, 95% CI −1.92 to 0.42, $P = 0.21$), as shown in Fig. 5.

(2) WOMAC stiffness: Six RCTs reported WOMAC pain data that could be extracted for meta-analysis. The heterogeneity test indicated a significant level of heterogeneity across several subgroups, necessitating the use of a random effect model. The findings indicated that there was no significant enhancement in WOMAC stiffness with the use of MSCs treatment when compared to the control group (bone marrow: SMD = −0.11, 95% CI −0.62 to 0.40, $P = 0.67$; umbilical cord: SMD = −0.48, 95% CI −1.48 to 0.52, $P = 0.34$; adipose tissue: SMD = −0.52, 95% CI −1.12 to 0.08, $P = 0.09$), as shown in Fig. 6.

(3) WOMAC physical function: Six RCTs reported WOMAC pain data that could be extracted for meta-analysis. The heterogeneity test indicated a significant level of heterogeneity across several subgroups, necessitating the use of a random effect model. The findings indicated that MSCs treatment resulted in a noteworthy reduction of WOMAC pain scores specifically within the adipose subgroup (SMD = −0.52, 95% CI −0.84 to −0.20, $P = 0.001$). However, no statistically significant decrease in WOMAC pain scores was observed in the bone marrow and umbilical cord subgroups (bone marrow: SMD = −0.13, 95% CI −0.61 to 0.36, $P = 0.60$; umbilical cord: SMD = −0.53, 95% CI −1.70 to 0.64, $P = 0.37$), as shown in Fig. 7.

(4) Total WOMAC scores: Six RCTs reported WOMAC pain data that could be extracted for meta-analysis. The heterogeneity test indicated a significant level of heterogeneity across several subgroups, necessitating the use of a random effect model. The

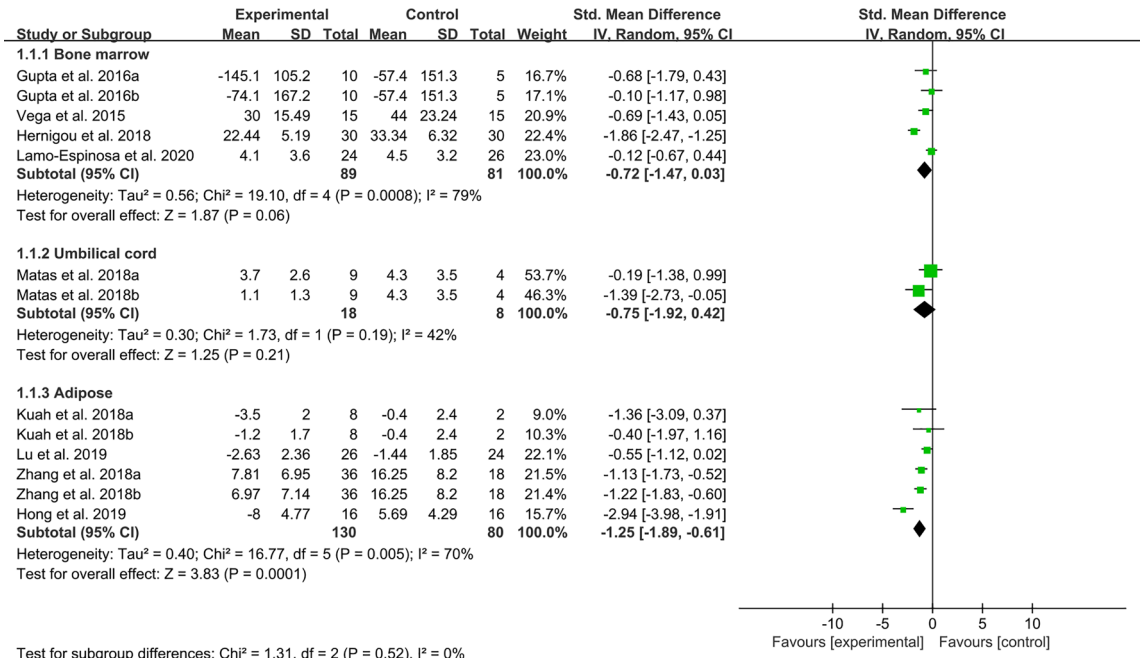

Fig. 5 WOMAC pain of OA after MSC therapy

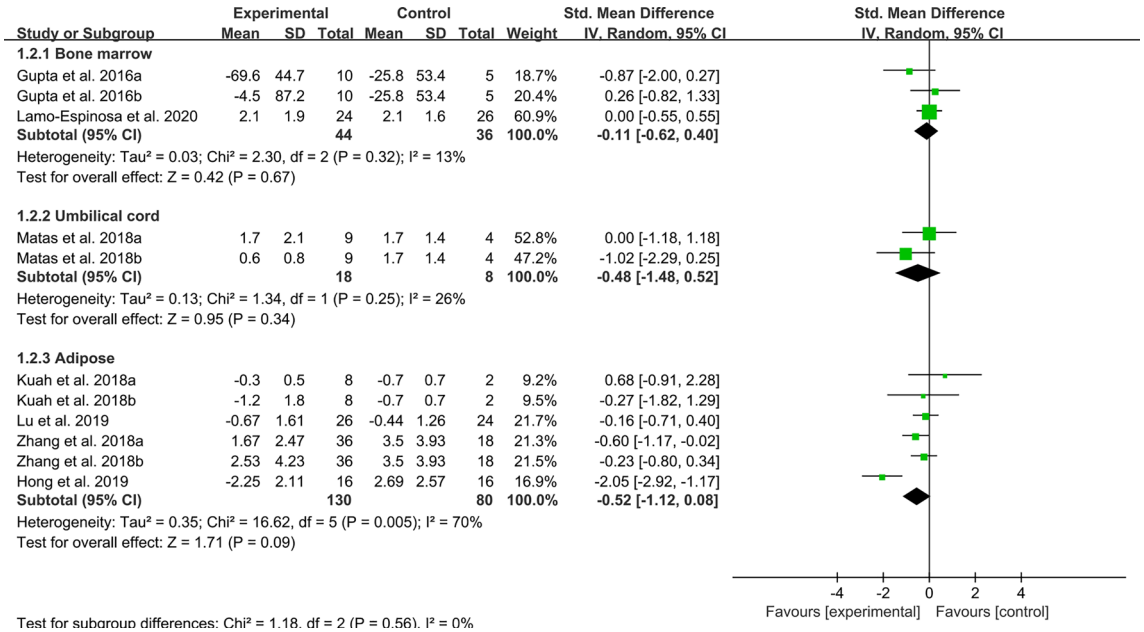

Fig. 6 WOMAC stiffness of OA after MSC therapy

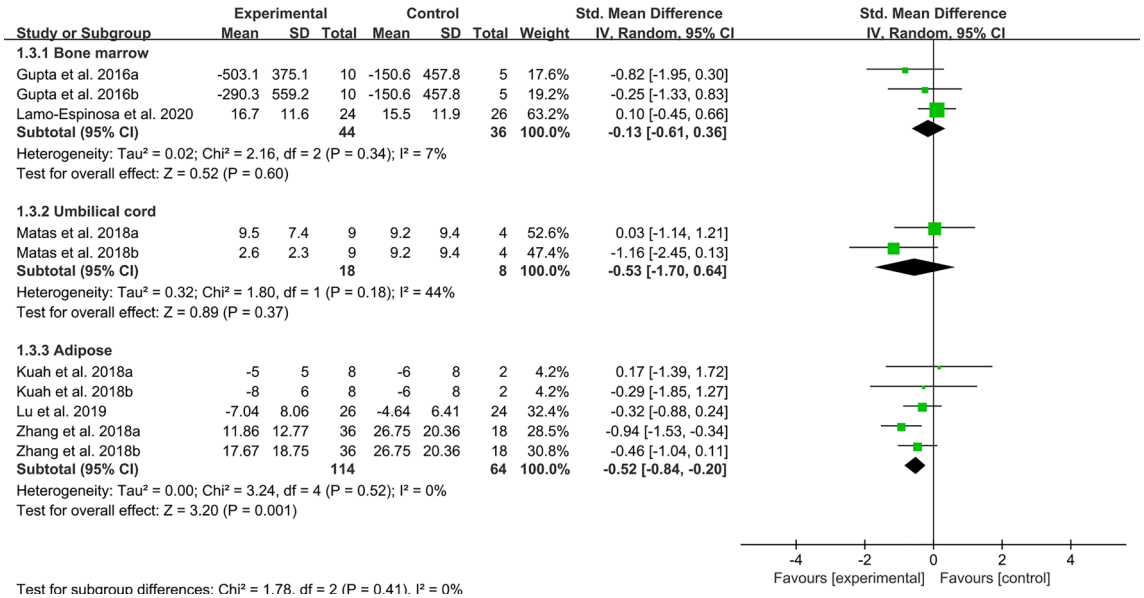

Fig. 7 WOMAC physical function of OA after MSC therapy

findings indicated that MSCs treatment was able to reduce the total WOMAC scores in the adipose subgroup (SMD = − 1.07, 95% CI − 1.66 to − 0.49, $P = 0.0003$) and umbilical cord subgroups (SMD = − 1.43, 95% CI − 2.25 to − 0.62, P = 0.0006). However, no statistically significant decrease in WOMAC pain scores was observed in the bone marrow (SMD = − 0.23, 95% CI − 0.62 to 0.16, $P = 0.26$), as shown in Fig. 8.

Adverse events

Fifteen studies reported adverse events after MSCs treatment. No reports of significant adverse events were found in these RCTs conducted by Hernigou et al. 2018, Lamo-Espinosa et al. 2018, Matas et al. 2018, Garza et al. 2020, and Lamo-Espinosa et al. 2020. The heterogeneity test indicated low heterogeneity, necessitating the use of a fixed effect model. The findings indicated that MSC

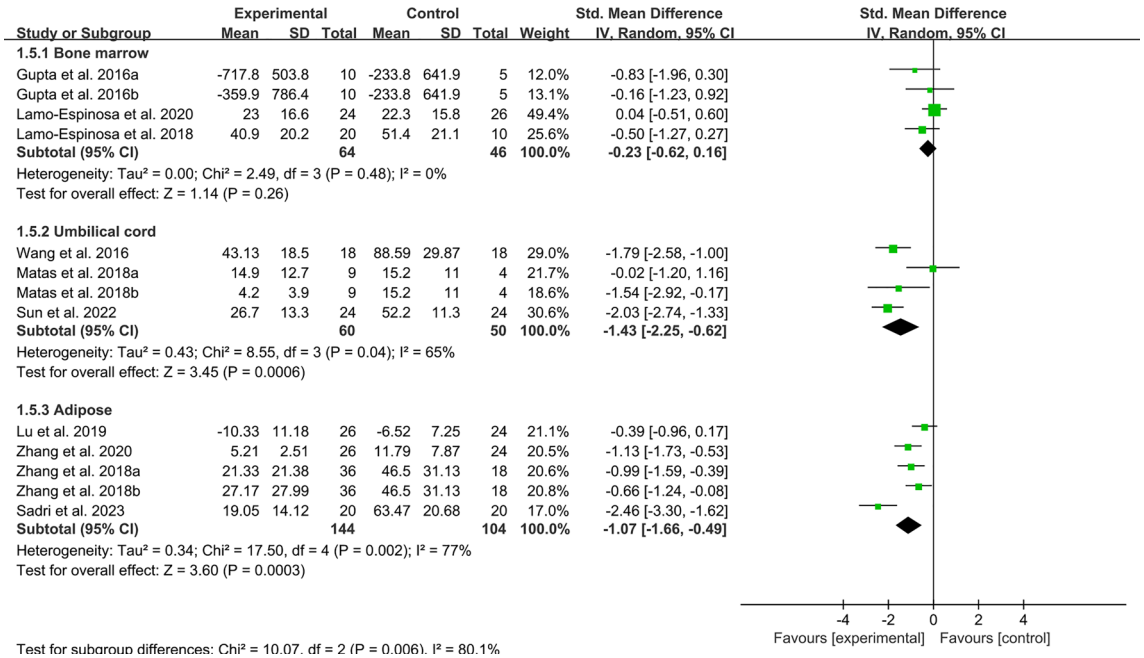

Fig. 8 Total WOMAC scores of OA after MSC therapy

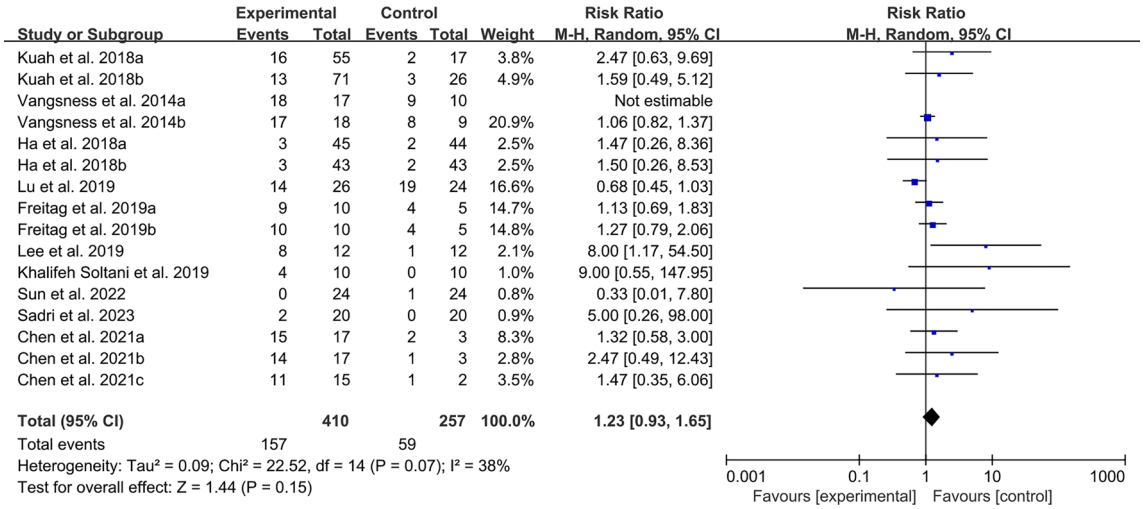

Fig. 9 Adverse events of MSC therapy for OA

treatment does not increase the incidence of adverse events compared to the control group (RR = 1.23, 95% CI 0.93 to 1.65, $P = 0.15$), as shown in Fig. 9.

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus disease activity index (SLEDAI)

Two RCTs reported SLEDAI. The heterogeneity test indicated low heterogeneity, necessitating the use of a fixed effect model. The findings indicated that MSC treatment may decrease SLEDAI compared to the control group (SMD = − 2.32, 95% CI− 3.59 to − 1.06, $P = 0.0003$) (Fig. 10).

Urine Protein

Two RCTs reported urine protein. The heterogeneity test indicated low heterogeneity, necessitating the use of a fixed effect model. The findings indicated that MSC treatment may decrease urine protein compared to the control group (SMD = − 0.94, 95% CI-− 1.20 to − 0.68, $P < 0.00001$) (Fig. 11).

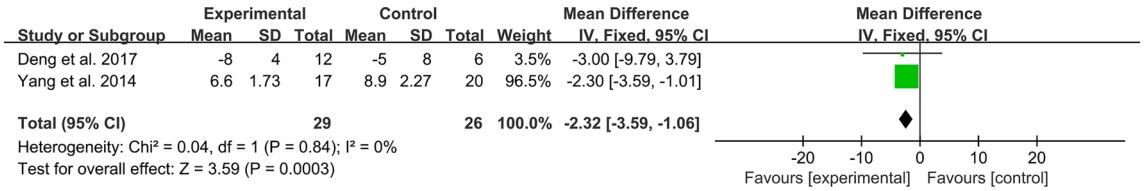

Fig. 10 SLEDAI of SLE after MSC therapy

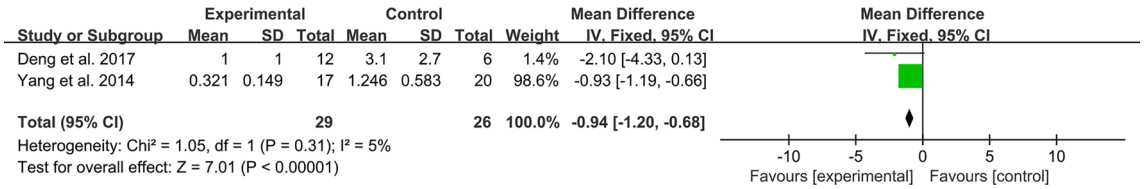

Fig. 11 Urine protein of SLE after MSC therapy

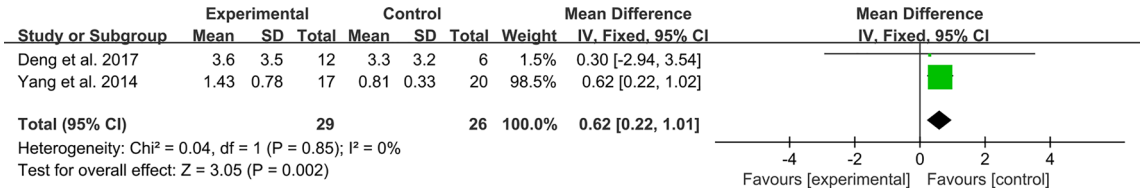

Fig. 12 Serum C3 of SLE after MSC therapy

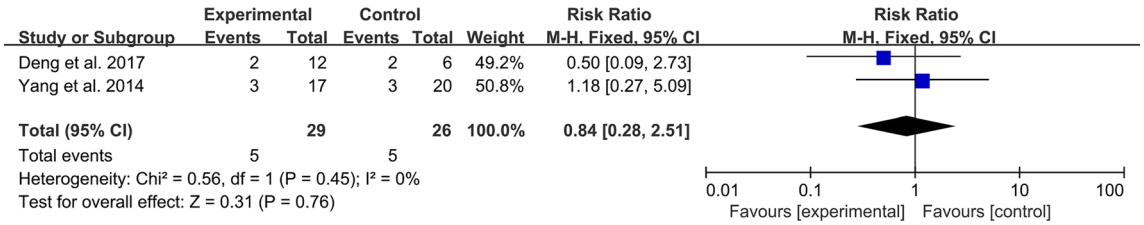

Fig. 13 Adverse events of MSC therapy for SLE

Serum C3

Two RCTs reported serum C3. The heterogeneity test indicated low heterogeneity, necessitating the use of a fixed effect model. The findings indicated that MSC treatment may increase C3 compared to the control group (SMD = 0.62, 95% CI 0.22 to 1.01, $P < 0.00001$) (Fig. 12).

Adverse events

Two RCTs reported serum adverse events. The heterogeneity test indicated low heterogeneity, necessitating the use of a fixed effect model. The findings indicated that MSC treatment does not increase the incidence of adverse events compared to the control group (RR = 0.83, 95% CI 0.28 to 2.51, $P = 0.76$) (Fig. 13).

Inflammatory bowel disease

Clinical efficacy

A total of 4 RCTs were included. The heterogeneity test indicated low heterogeneity, necessitating the use of a fixed effect model. The findings indicated that MSC treatment may decrease clinical efficacy compared to the control group (RR = 2.02, 95% CI 1.53 to 2.67, $P < 0.00001$) (Fig. 14).

Adverse events

A total of 4 RCTs were included. The heterogeneity test indicated low heterogeneity, necessitating the use of a fixed effect model. The findings indicated that MSC treatment does not increase the incidence of adverse events compared to the control group (RR = 0.99, 95% CI 0.81 to 1.22, $P = 0.96$) (Fig. 15).

Multiple sclerosis

Number of lesions and Volume of lesions

Two RCTs reported number and volume of lesions. For number of lesions, the heterogeneity test indicated low heterogeneity, necessitating the use of a fixed effect model. The findings indicated that the difference of number of lesions between two groups was of no statistical significance (WMD = 0.98, 95% CI-−4.18 to 6.14, $P = 0.71$) (Fig. 16).

For volume of lesions, the heterogeneity test indicated low heterogeneity, necessitating the use of a fixed effect model. The findings indicated that the difference of volume of lesions between two groups was of no statistical significance (WMD = −2.84, 95% CI− 7.23 to 1.54, $P = 0.20$) (Fig. 17).

Expanded disability status scale

Three RCTs reported EDSS data that could be extracted for meta-analysis. The heterogeneity test indicated high heterogeneity, necessitating the use of a random effect model. The findings indicated that the difference of EDSS between two groups was of no statistical significance (SMD = 0.12, 95% CI− 1.18 to 1.43, $P = 0.85$) (Fig. 18).

Adverse events

Two RCTs reported adverse events. The heterogeneity test indicated high heterogeneity, necessitating the use of a random effect model. The findings indicated that MSC treatment does not increase the incidence of adverse events compared to the control group (RR = 1.12, 95% CI 0.81 to 1.53, $P = 0.50$) (Fig. 19).

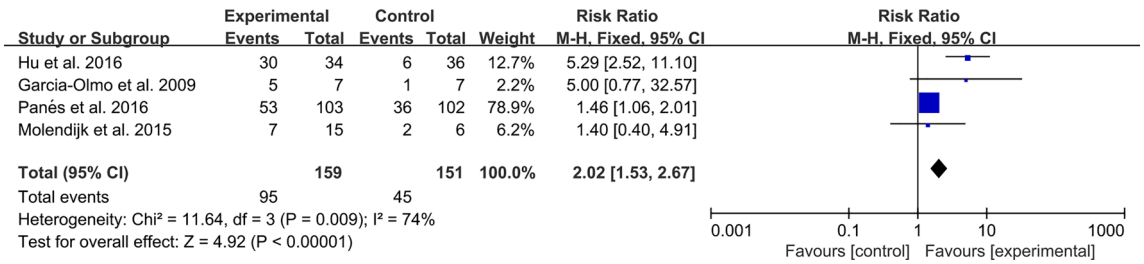

Fig. 14 Clinical efficacy of inflammatory bowel disease after MSC therapy

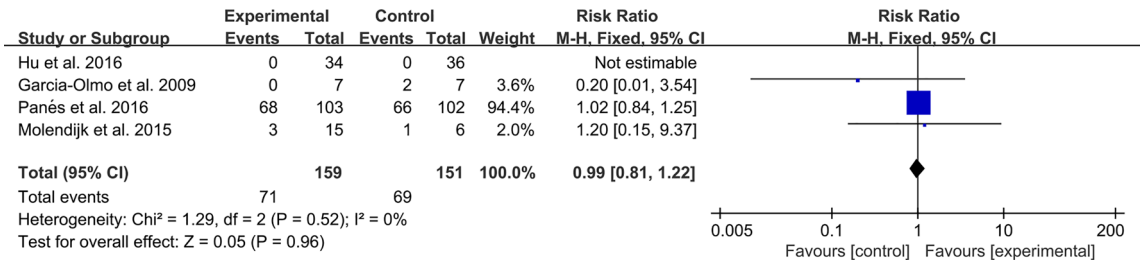

Fig. 15 adverse events of MSC therapy for inflammatory bowel disease

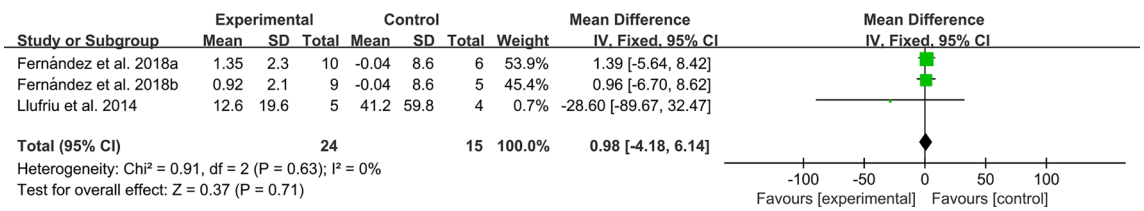

Fig. 16 Number of lesions of multiple sclerosis after MSC therapy

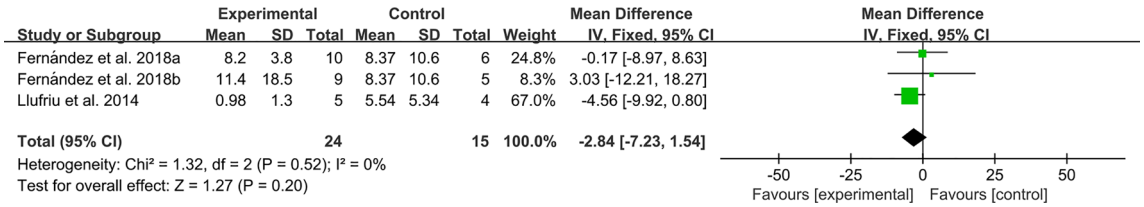

Fig. 17 Volume of lesions of multiple sclerosis after MSC therapy

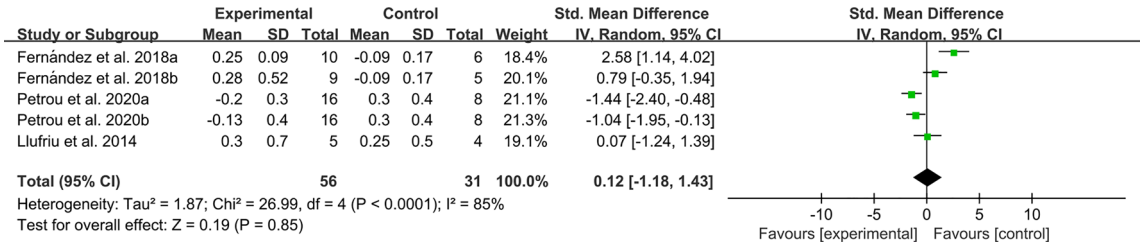

Fig. 18 Expanded disability status scale of multiple sclerosis after MSC therapy

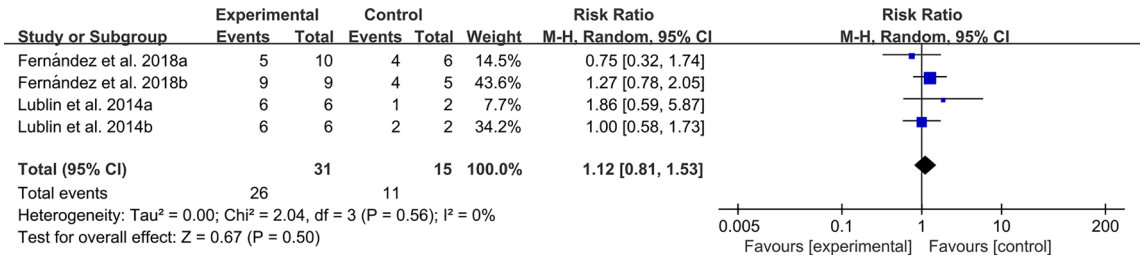

Fig. 19 Adverse events of MSC therapy for multiple sclerosis

PSS

Only 1 RCT examined the use of MSC in the treatment of PSS. In the study conducted by Li et al. in 2023, a total of 64 participants successfully completed the treatment and follow-up assessment. Significant improvements in salivary and lacrimal gland secretion were observed three months after treatment ($P<0.05$). Notably, significant improvements were also observed in ESSDAI and ESSPRI scores following ADSCs therapy ($P<0.05$). Furthermore, significant reductions in IgG, IgM, C3, C4, and ESR levels between the two groups were observed at certain follow-up time points ($P<0.05$).

Discussion

Therapeutic effect of MSCs on autoimmune and rheumatic immune diseases

Rheumatic immune diseases arise from disruptions in self-tolerance or aberrant regulation of autoimmune cells, triggered by a blend of genetic and environmental factors [88, 89]. Traditional treatment for autoimmune conditions heavily relied on immunosuppressive therapies, often leading to diverse side effects with prolonged use. Conventional immunosuppressants broadly diminish immune responses, hampering the body's ability to identify and eliminate foreign antigens, mutated cells, or aging cells, thereby elevating infection risks and potentially triggering malignancies [90, 91]. In contrast, Mesenchymal stem cells (MSCs) exhibit multi-faceted attributes surpassing mere mesodermal lineage differentiation for cell replacement. They boast unique immunomodulatory traits primarily achieved by orchestrating the release of diverse anti-inflammatory factors at an immunological level, fostering immune tolerance and homeostasis [92]. Furthermore, MSCs can elude detection by allogeneic T cells and natural killer (NK) cells, enabling prolonged survival in disparate hosts. Consequently, MSCs demonstrate scant immunogenicity and bidirectional immune modulation, distinguishing them from other adult stem cell variants [93, 94]. In regulating immunity and inflammation, MSCs exhibit regulatory effects on both innate and adaptive immune cells, rendering them versatile in immune response modulation [95]. They regulate inflammation through intricate mechanisms

involving adaptive and innate immune responses, including inhibiting T cell function and proliferation, promoting regulatory T cell subsets, suppressing dendritic cell maturation, halting B cell proliferation, differentiation, and immunoglobulin production, steering macrophages towards an anti-inflammatory state, and curbing natural killer cell activity [96]. The immune modulation by MSCs occurs through direct cell-to-cell interactions and the secretion of soluble factors induced by interferon-gamma (IFN-γ) from activated immune cells. These soluble factors comprise indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), prostaglandin E2 (PGE2), and interleukin-10 (IL-10) [97–99]. These mechanisms collectively aid in resolving inflammation in rheumatoid arthritis. Additionally, MSCs have showcased reparative and therapeutic effects on diverse tissues and organs by secreting a myriad of cytokines, extracellular vesicles containing microRNAs, and enhancing the microenvironment. They facilitate tissue repair by modulating pertinent signaling pathways like insulin-like growth factor-1 (IGF-1), transforming growth factor-beta (TGF-β), and Wnt [100].

In terms of regulating adaptive immunity, several studies have demonstrated the anti-inflammatory and negative regulatory effects of MSCs on T cell function. In vivo, besides inhibiting neutrophil apoptosis and prolonging neutrophil lifespan, MSCs aid in bacterial clearance. They promote the proliferation of T cell tolerance populations by inhibiting energy metabolism in T cell groups or inducing regulatory T cells, thus inhibiting T lymphocyte proliferation [101]. The suppressive effect of MSCs on T cells exhibits a dose-dependent relationship. MSCs also inhibit the proliferation of B lymphocytes by blocking the G0/G1 cell cycle phase instead of inducing cell apoptosis [102]. The mechanisms of MSCs' interaction with B cells resemble those with T cells, involving physical contact and the secretion of soluble factors. It has been reported that MSCs inhibit the function of B cells through direct interaction via PD-1/PD-L1 [103]. Furthermore, Rosado et al. demonstrated that MSCs inhibit B cell proliferation and antibody production [104].

Recent investigations have extensively explored MSC efficacy in treating varied rheumatic immune diseases. This study seeks to delve into MSC mechanisms in these conditions via systematic assessment and meta-analysis. Additionally, the research probes the feasibility of replacing conventional therapies with standardized cell preparations and manufacturing procedures, heralding novel avenues for cellular therapies and envisioning enhanced treatment prospects in autoimmune and rheumatic immune disorders (Fig. 20).

MSCs for spondyloarthritis

Spondyloarthritis is a progressive autoimmune condition distinguished by intermittent and recurrent morning stiffness, pain, and in severe instances, lumbar and sacroiliac joint stiffness, curtailing mobility and significantly impairing quality of life [105]. In the clinical management of spondyloarthritis, nonsteroidal anti-inflammatory drugs (NSAIDs) and immunosuppressive agents are mainstays. Despite their ability to alleviate inflammation, mitigate symptoms, and enhance patient well-being, these treatments often fall short in efficacy or entail notable side effects [105]. Studies have demonstrated a notable decline in the immunoregulatory potential of bone marrow-derived MSCs in patients with spondyloarthritis [106]. Reinstating normal MSC function in spondyloarthritis necessitates introducing healthy MSCs. Recent progresses in MSC research and methodologies offer novel paths for treating spondyloarthritis [107, 108]. Su et al. showcased through in vivo and in vitro assessments that bone marrow-derived mesenchymal stem cells (BMMSCs) engineered to overexpress KAT2A activation display enhanced bone repair and immunomodulatory capabilities compared to quiescent BMMSCs [109]. Li et al. found that MSC infusion therapy could ameliorate spondyloarthritis symptoms, leading to decreased lower back and joint pain in patients. MSC infusion also reduced inflammatory responses in spondyloarthritis individuals, evidenced by diminished inflammatory markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [110]. Wang et al. reported that by the 4th week, ASAS20 responders reached 77.4%, with an average relief duration of 7.1 weeks. The mean ASDAS-CRP score decreased from 3.6 ± 0.6 at baseline to 2.4 ± 0.5 by the 4th week, and subsequently rose to 3.2 ± 0.8 by the 20th week, with no adverse reactions observed in the study cohort [111].

This systematic review includes 1 RCT about MSC transplantation in the treatment of spondyloarthritis [36]. This RCT showed that there was a potential improvement in the overall effectiveness compared to treatment involving Fliximab [36]. However, to obtain definitive conclusions, further exploration in this field is warranted in the future.

MSCs for RA

Rheumatoid arthritis (RA) is a rheumatological immune disease characterized primarily by erosive arthritis. Pathologically, it manifests as synovitis and vasculitis, gradually leading to joint cartilage and bone destruction. Inevitably, this results in joint deformities, functional impairment, and potential complications such as pulmonary and cardiovascular diseases, malignancies, and depression [97].

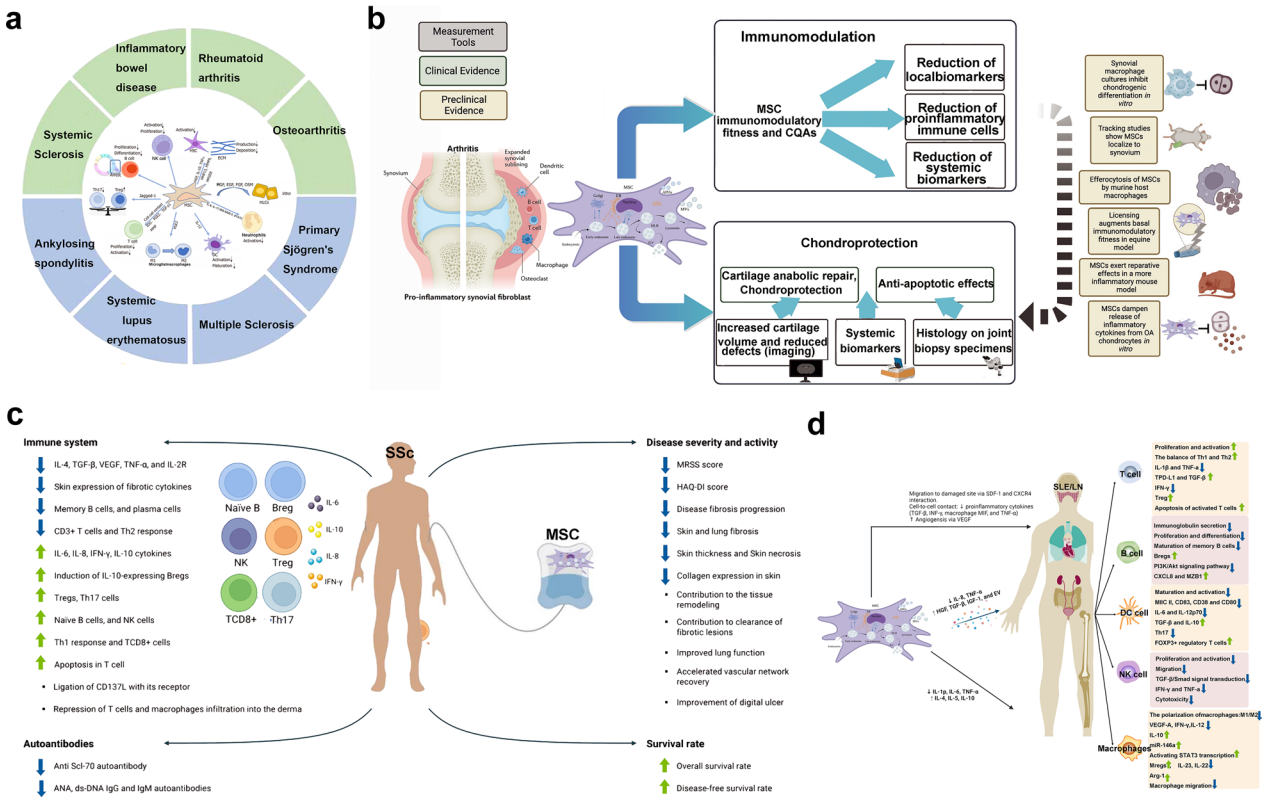

Fig. 20 Mechanisms of MSCs therapy on different diseases (**a**: on autoimmune and rheumatic immune diseases; **b**: on inflammatory arthritis **c**: on Ssc; on SLE and LN)

Current research highlights the potent anti-inflammatory and immunomodulatory properties of MSCs, along with their capacity to repair joint cartilage, offering a promising clinical approach for rheumatoid arthritis treatment [112]. Recent findings indicate that MSCs within joint tissues can differentiate and mend damaged tissues, exerting inhibitory influences on the inflammatory milieu. The mechanisms encompass differentiation and repair, where MSCs can transform into various mesenchymal cell types like osteoblasts, chondrocytes, and myocytes under specific inducements, actively engaging in tissue restoration. Further, immune regulation involves the secretion of immunoregulatory cytokines such as transforming growth factor-beta 1 (TGF-β1) and interleukin-10 (IL-10) to modulate T lymphocyte actions, suppress B lymphocyte functions, and mitigate dendritic cell maturation, natural killer cell activity, and cytokine production [113, 114]. MSCs also have the potency to generate regulatory T lymphocytes within inflamed areas, rein in T cell proliferation through contact inhibition, and diminish the immunosuppressive effects of cytokines [115]. Notably, MSCs can reduce pro-inflammatory cytokines like TNF-α and IL-17, while boosting anti-inflammatory cytokine levels such as IL-10 and IL-4 in RA patients, thereby exerting an anti-inflammatory impact [102, 116]. Studies indicate that MSCs can produce osteoprotegerin to impede osteoclast formation and fibroblast-like synoviocyte (FLS) proliferation. Additionally, under chemotactic influences, MSCs migrate to joint injury locations, differentiate into chondrocytes, and expedite joint repair [117–119].

This systematic review includes 3 RCTs about MSC transplantation in the treatment of RA. Those RCTs indicate that the utilization of bone marrow-derived mesenchymal stem cells (BM-MSCs) in patients with RA exhibits favorable tolerability and safety profiles. Notably, a considerable proportion of patients achieved significant outcomes, demonstrating reduced disease activity and comprehensive ACR responses. The administration of MSCs resulted in sustained enhancements in clinical symptoms, with remarkable effectiveness observed for up to 12 months, generating a clinical success rate of 54%. Furthermore, notable immunological alterations were observed, along with promising indications of alleviating knee pain and promoting functional amelioration.

MSCs for Ssc

SSc is an autoimmune disorder characterized by localized fibrosis of the skin or multiple organs throughout the body, including the skin, heart, lungs, kidneys, and digestive system. Damage to vital organs often leads to a higher mortality rate, significantly impacting patient prognosis [120]. The pathogenesis of SSc is complex and remains incompletely understood. Currently, symptomatic treatment is the main approach, as effective therapeutic drugs are still lacking. Medications such as hormones and immunosuppressants often fail to improve disease progression and prognosis, while presenting various adverse reactions [121]. The mechanisms of MSCs in SSc primarily involve two aspects: (1) replacement of damaged tissue through differentiation into various cell lineages and (2) modulation of immune responses through immunoregulatory functions. This is primarily achieved through various mechanisms, including (1) soluble regulatory factors, such as immune modulators, angiogenic factors, anti-apoptotic factors, and antioxidants; (2) paracrine effects; (3) cell–cell contact; (4) mitochondrial transfer; and (5) extracellular vesicles (exosomes), all contributing to immune response modulation [122–124].

This systematic review includes 1 RCT about MSC transplantation in the treatment of Ssc [40]. This RCT showed that ADRC treatment showed marginal enhancements in hand function compared to the placebo group, but statistical significance was not reached. However, in patients with diffuse cutaneous SSc (dcSSc), significant improvements in Cochin Hand Function Scale (CHFS) scores (6.3 points) and Health Assessment Questionnaire Disability Index (HAQ DI) scores (0.17 points) at 48 weeks were observed, with more than half of the dcSSc patients experiencing these improvements. The well-tolerated procedure involving small-volume adipose tissue extraction and ADRC therapy suggests the potential efficacy of ADRC treatment in dcSSc patients, warranting further clinical trials for investigation [40].

MSCs for OA

Osteoarthritis is considered a chronic and progressive degenerative disease of the cartilage, characterized by cartilage loss, subchondral bone remodeling, osteophyte formation, and synovial inflammation [125]. Its pathogenesis can be understood as the result of excessive mechanical pressure exerted on joint tissues, surpassing their load-bearing capacity and leading to an imbalance between tissue destruction and repair, consequently triggering the occurrence of osteoarthritis [126, 127]. Although various treatment approaches for OA exist, their effectiveness is limited to slowing the progression of knee osteoarthritis without the ability to reverse existing cartilage damage, ultimately necessitating knee joint replacement [128, 129]. However, the complications associated with knee joint replacement, such as infection, loosening, dislocation, and the high cost of surgery, impose physical and financial burdens on patients. Therefore, promoting cartilage regeneration and reversing the progression of knee osteoarthritis has been a hot topic in the fields of regenerative medicine and orthopedics [130, 131]. The emergence of mesenchymal stem cells (MSCs) provides a novel therapeutic approach. Due to their potential for chondrogenic differentiation and immunomodulatory effects, an increasing number of preclinical and clinical studies have indicated that intra-articular injection of MSCs can improve knee function, alleviate pain, and even facilitate cartilage repair and regeneration in patients with knee osteoarthritis [21, 132–134]. However, a relative number of studies have also suggested that intra-articular injection of MSCs has limited efficacy in cartilage regeneration. Therefore, this study adopts a meta-analysis approach, combining and analyzing the clinical findings of multiple related studies to evaluate the clinical efficacy and safety of intra-articular injection of MSCs in the treatment of knee osteoarthritis, aiming to provide new insights for the clinical management of this condition.

This systematic review and meta-analysis included a total of 25 RCTs. The meta-analysis findings demonstrated positive outcomes in terms of pain reduction (VAS decrease). Notably, the adipose subgroup exhibited significant improvements in WOMAC pain, WOMAC physical function, and total WOMAC scores. However, no significant improvements were observed in any subgroup for WOMAC stiffness. Moreover, the analysis revealed that the incidence rate of adverse events did not increase with the use of MSCs.

MSCs for SLE

SLE is a complex rheumatic autoimmune disease, and its underlying pathogenesis remains elusive. It arises from the interplay of various factors, including genetics, environment, race, sex hormones, immunity, and epigenetics, which collectively disturb immune homeostasis and lead to organ involvement and loss of self-tolerance [135, 136]. Currently, the conventional treatment methods for SLE mainly focus on controlling disease progression rather than achieving complete remission, and they often come with substantial toxicity and serious adverse reactions. Leveraging its advantages in immune modulation and tissue regeneration, MSCs have emerged as a new hope for SLE treatment, with immune suppression being one of the key mechanisms by which MSCs alleviate SLE symptoms [1, 31, 137]. MSCs have been found to inhibit the secretion of

pro-inflammatory cytokines, suppress immune cell proliferation, and induce the conversion of immune cell types into regulatory clones by secreting interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), and human leukocyte antigen-G (HLA-G) soluble anti-inflammatory factors [138]. Dendritic cells play a pivotal role in the pathogenesis of SLE. In in vitro studies, MSCs secrete prostaglandin E2 and IL-6, as well as cytokine inhibitors, to suppress monocyte differentiation into mature dendritic cells [139]. They inhibit the upregulation of CD1a, CD40, CD80, CD86, and HLA-DR-related surface antigens and maintain the immature status of dendritic cells, thereby hindering their effective activation of naive T cells and stimulation of T cell proliferation [140]. A study by Ye Ling et al. revealed that transplantation of adipose-derived MSCs can enhance the activity of dendritic cells, upregulate the ratio of regulatory T cells, suppress the differentiation of helper T cells into the Th2 subtype, inhibit the Th1 to Th2 shift, regulate the immune function of systemic lupus erythematosus mice, and improve immune dysfunction [141]. Other researchers have also found remarkable therapeutic effects when using umbilical cord MSCs in combination with rituximab to treat SLE patients [142]. Furthermore, as research progresses, MSCs have been found to exhibit pro-inflammatory effects in certain circumstances [143]. Different inflammatory microenvironments can induce two distinct types of MSCs with M1 and M2 characteristics, similar to macrophages, referred to as pro-inflammatory MSC1 and inflammatory MSC2, respectively [144]. It is evident that the immune regulatory capacity of MSCs exhibits bidirectionality.

Meanwhile, studies have shown that allogeneic MSCs can inhibit the proliferation of T cells in SLE patients [145]. Furthermore, compared to conventional cyclophosphamide regimens, the use of MSCs in treating MRL/lpr lupus mice has demonstrated superior therapeutic effects [146]. Additionally, MSCs exert immunosuppressive effects in SLE/LN by inhibiting the TNF family member BAFF, thus suppressing the overactivation of B lymphocytes [147]. The mechanism of action involves the suppression of BAFF, a member of the TNF family, thereby inhibiting excessive activation of B lymphocytes and exerting immunosuppressive effects. In terms of safety, MSCs have been successfully employed in critically ill and refractory SLE patients, yielding significant therapeutic outcomes without any transplant-related adverse effects [148].

This systematic review and meta-analysis includes 2 RCT about MSC transplantation in the treatment of SLE [66, 67]. This meta-analysis revealed significant differences in disease activity and renal involvement between the experimental and control groups. Notably, the experimental group exhibited a substantial reduction in SLEDAI scores and urine protein levels compared to the control group. Furthermore, the serum C3 levels in the MSC-treated group were significantly elevated compared to the control group. Regarding safety, the incidence of adverse events did not significantly differ between the MSC group and the control group, suggesting comparable safety profiles for both MSC treatment and the control interventions (placebo or traditional therapy). Overall, these results support the notion that MSC therapy can be considered as safe and effective as the control interventions.

MSCs for inflammatory bowel disease

IBD is a chronic, idiopathic autoimmune disease characterized by inflammation and pathological changes in the intestinal mucosa. It encompasses ulcerative colitis (UC), Crohn's disease, and other chronic forms of IBD. Historically, IBD predominantly affected young adults in developed Western countries, with a higher incidence among females [149, 150]. Immune factors represent the most direct and pivotal elements in IBD [151–153]. Excessive production of pro-inflammatory cytokines by T helper 1 and 17 cells has been implicated in the recruitment of inflammatory cells to the intestinal epithelium and the development of acute and chronic intestinal inflammation [152, 154]. Studies have demonstrated an increased secretion of pro-inflammatory cytokines by Th1 and Th17 cells in patients with Crohn's disease, while patients with UC exhibited excessive production of these cytokines by Th2 cells [154]. Furthermore, in both UC and Crohn's disease, there is a decreased level of infiltrating anti-inflammatory regulatory T cells in the intestinal tissues, which is also considered a contributing factor to the pathogenesis [155, 156]. The intimate relationship between the dysregulated immune response and the occurrence and progression of IBD provides a scientific basis for the therapeutic use of MSCs in the treatment of IBD.

The advantages of stem cell therapy for IBD include its notable treatment efficacy, durability of effects, reduced recurrence and occurrence of complications, as well as high patient satisfaction [157]. Literature reports indicate that compared to surgical treatment, MSC therapy for Crohn's disease-associated anal fistula not only demonstrates higher cure rates and fewer complications but also exhibits a more stable and reproducible treatment effect, leading to improved clinical outcomes. Early clinical trials have evaluated the short- and long-term efficacy of autologous or allogeneic MSC therapy for IBD [158]. Darvadstrocel, a stem cell therapy approved by the European Medicines Agency,

was evaluated in a multicenter, randomized, double-blind phase III clinical trial that assessed its efficacy in the treatment of refractory complex anal fistulas associated with Crohn's disease in 107 patients. The results showed that at the 52-week follow-up, 56.3% of patients in the treatment group achieved complete remission, compared to 38.6% in the control group ($P=0.010$) [159]. Recently, Furukawa et al. [159] completed an open-label phase III clinical trial of darvadstrocel and found no safety concerns or adverse reactions associated with MSC therapy. The 2019 European Crohn's and Colitis Organisation guidelines on Crohn's disease and colitis summarized the results of several clinical trials involving stem cell therapy, concluding that allogeneic MSC therapy is safe and effective for the treatment of complex anal fistulas associated with Crohn's disease. Subsequent clinical studies have focused on long-term follow-up data, revealing that over 50% of patients still experience treatment effectiveness at the 52-week follow-up after MSC therapy, and the clinical benefits can be maintained up to 156 weeks without potential adverse reactions such as tumor formation or ectopic tissue development [160]. Ciccozzi et al. [161] reported injecting autologous bone marrow-derived MSCs into Crohn's disease-related fistulas, and through follow-ups at 1, 2, and 4 years post-treatment, they found no recurrence in 88%, 50%, and 37% of patients, respectively, with no observed adverse events. A meta-analysis of 23 studies involving 696 participants, including four randomized controlled trials, demonstrated that 80% of patients undergoing MSC therapy achieved closure of Crohn's disease fistulas, with a closure rate of 64% in the MSC group compared to only 37% in the control group. The incidence of treatment-related adverse events in the MSC group was 13% (24% in the control group), and the recurrence rate was 0 [157]. These results suggest that local injection of MSCs in Crohn's disease fistula not only provides a safe approach but also holds promise for therapeutic efficacy.

This systematic review and meta-analysis included a total of 4 RCTs. The results of meta-analysis revealed improvements in patients' clinical efficacy. The incidence of adverse events between two groups were of no statistical significance.

MSCs for multiple sclerosis

MS is an autoimmune-mediated demyelinating disease of the central nervous system (CNS). The main pathological feature of demyelinating diseases is the loss of myelin with relative preservation of axons. Due to limited remyelination capacity, axonal damage can occur secondary to myelin loss, leading to severe consequences [162]. MS lesions involve white matter in different areas of the CNS, with local demyelination forming gliotic scars, resulting in the formation of multiple sclerosis plaques. These plaques show evident inflammatory cell infiltration within and around them, closely related to T-cell activation and cellular immune responses [163, 164]. Currently, approximately 2.5 million people worldwide are affected by MS, imposing a heavy burden on families and society [165]. Existing treatments for MS are primarily palliative and generally involve hormone therapy, immunomodulation, and symptomatic treatment measures [166, 167]. Mesenchymal stem cells (MSCs) are considered an optimal therapeutic approach as they possess significant immunomodulatory and inhibitory effects. Furthermore, their ability to regulate both the innate and acquired immune systems has been clinically validated, making them suitable for alleviating neurological impairments [168, 169]. Regarding the safety of MSCs in the treatment of MS, transplantation approaches include intravenous injection, arterial injection, and intrathecal injection [169]. In 2009, experts in the field of stem cell research reached a consensus on various standards for MSC transplantation in MS, which encompassed factors such as cell isolation and culture, transplantation protocols, and efficacy evaluation. These quantifiable requirements were proposed to guide clinical applications. Subsequently, several MS treatment centers in Europe and Canada conducted clinical trials on intravenous injection of MSCs, which demonstrated positive therapeutic effects in alleviating the course of MS and reversing neuronal damage [170]. Moreover, multiple MSC injections were considered necessary [171]. Studies also indicated that intrathecal injection could directly deliver MSCs into the cerebrospinal fluid, facilitating their rapid support and nourishment of demyelinated areas, thus alleviating lesion damage [172, 173]. Due to the lower plasticity and more stable differentiation of adult MSCs compared to embryonic or reprogrammed stem cells, the clinical application of adult MSCs is regarded as safe [174].

Most non-blinded clinical studies on the safety and feasibility of MSCs for MS have employed intravenous injection methods. In a phase I clinical trial conducted by Cohen et al. [175], MSC transplantation via intravenous injection was successful, meeting the safety and efficacy evaluation criteria without significant adverse effects. Yamout et al. [173] reported that out of 10 MS patients who received high-dose intravenous cell injection, only 1 patient experienced meningeal irritation. Bonab et al. [176] administered a single MSC injection therapy to 22 patients in the progressive stage of MS; during a one-year follow-up, no significant side effects were observed, and 70% of patients experienced symptom relief. The successful treatment of multiple sclerosis with umbilical cord mesenchymal stem cells (hUC-MSCs) was first

reported in 2009 when a patient with MS showed significant improvement in sensory function and muscle strength after hUC-MSC transplantation [177]. Clinical experiments conducted over a one-year observation period showed no significant adverse reactions in the hUC-MSC treatment group. Additionally, the relapse rate was lower in MS patients who received hUC-MSC treatment. Testing for inflammatory cytokines showed a shift in immune function from Th1 to Th2 in the treatment group, and there was an increase in HGF expression in the hUC-MSC treatment group [178]. Another report indicated that during a four-year period of BMSCs and hUC-MSCs treatment, clinical symptoms and radiological changes did not increase. Many lesions had regressed by the end of treatment, with no new lesions detected by magnetic resonance imaging [179]. Riordan et al. [180] conducted intravenous injection of hUC-MSCs in 20 patients and found that the symptoms improved, the number of lesions decreased, the EDSS score decreased, and the quality of life for patients significantly improved after hUC-MSC transplantation. These results fully demonstrate the efficacy and safety of hUC-MSCs in the treatment of multiple sclerosis, providing hope for their clinical application.

This systematic review and meta-analysis included a total of 5 RCTs. The current study shows that compared with the control group, MSC does not significantly improve the Number of lesions, Volume of lesions, and EDSS. Since the number of RCTs is too small, more RCTs are needed to confirm or revise these results.

MSCs for PSS

pSS is a chronic autoimmune disease characterized by lymphocytic proliferation and progressive impairment of exocrine glands. Approximately 30% of patients experience multi-organ involvement, such as skin, kidneys, lungs, and the nervous system, while about 5% develop malignant lymphomas, posing a threat to their lives [181]. Currently, treatment mainly focuses on symptomatic relief, with limited efficacy. Steroids and disease-modifying antirheumatic drugs (DMARDs), including biologics, are used to control inflammatory activity during systemic involvement [182–184]. However, these treatments increase the risk of infections and fail to provide satisfactory therapeutic outcomes. Therefore, there is an urgent need for a safe and effective treatment strategy.

Several studies have demonstrated the ability of MSCs to suppress abnormal T cell proliferation and secretion of multiple proinflammatory factors in SS patients and animal models, leading to reduced lymphocytic infiltration in salivary and lacrimal glands, restoration of exocrine gland function, and alleviation of dryness symptoms [185–187]. Research has shown that MSCs from different sources, such as bone marrow, umbilical cord, dental pulp, and labial gland, can increase salivary flow rate in SS animal models, improve dryness symptoms, and reduce lymphocytic infiltration in salivary and lacrimal glands [186, 188–193]. Studies by Liu, Yao, Shi, and others have shown that umbilical cord-derived MSCs can downregulate Th17 cells, induce Treg cell generation, restore Th17/Treg balance, and exert immunomodulatory effects [186, 190, 191]. Clinical studies by Xu and others have demonstrated that allogeneic MSC therapy can induce CD4+T cell differentiation towards Treg and Th2 cells while inhibiting differentiation towards Th17 and Tfh cells [194]. Genc, Matsumura-Kawashima, and others have shown that dental pulp and dental follicle MSCs promote Treg cell proliferation, exert immunosuppressive effects, reduce IFN-γ and IL-17-secreting cells in the spleen, and restore cellular homeostasis [193, 195, 196]. Studies by Du, Yang, and others have demonstrated that deciduous dental pulp MSCs upregulate Treg cells and downregulate Th1, Th17, and Tfh cells, thereby regulating immunity [197, 198]. Li and colleagues have shown that UCMSC-derived extracellular vesicles (UCMSC-EVs) promote M2 macrophage polarization, induce Treg cell generation, increase the proportion of Treg cells, and alleviate autoimmune dacryoadenitis [199]. Furthermore, Li and colleagues demonstrated that the proportion of Th17 cells is significantly increased, while the proportion of Treg cells is decreased in the peripheral blood of SS patients. Lip gland MSCs or lip gland MSC-derived exosomes can suppress CD4+T cell differentiation into Th17 cells and induce Treg cell proliferation [189]. In summary, consistent with previous studies, the results of this experimental study indicate that UCMSC-EV intervention can downregulate Th1 and Th17 cells, upregulate Th2 and Treg cells, restore Th1/Th2 and Th17/Treg ratios, consistently mirroring the effects of UCMSC intervention.

Our previous research has revealed a novel mechanism for the clinical application of mesenchymal stem cells (MSCs) in primary Sjögren's syndrome (pSS). It was found that MSCs improve the symptoms of pSS by promoting dendritic cells to secrete interleukin IL-27 [190]. In our clinical study, we observed a significant improvement in the Visual Analog Scale (VAS) scores of patients after MSC treatment at 2 weeks. Among the 11 patients with dryness of mouth and eyes, there was a remarkable improvement in salivary flow rate at 2 weeks after MSC treatment, which doubled at 1 month. With the exception of 3 patients who had concomitant neurological damage and showed poor response to treatment, the remaining patients with

severe complications experienced varying degrees of improvement. One month after MSC transplantation, the serum titers of anti-SSA and anti-SSB antibodies in patients significantly decreased, with a 50% reduction observed in anti-SSB titers, and no adverse reactions were reported. Moreover, the salivary flow rate increased significantly after transplantation ($P<0.05$). During the follow-up at 2 weeks, 1 month, and 3 months, both the VAS scores and the Total Estimation of Symptom Severity (TESS) scores showed significant reductions. Sialography demonstrated improved exocrine gland filling and emptying function at 12 months after transplantation. Furthermore, MSC transplantation showed significant improvement in liver function impairment and hematological system damage in patients with pSS. One month after MSC transplantation, the levels of anti-SSA/Ro antibodies decreased significantly [pre-transplantation levels: (84.76 ± 62.19) kU/L; 1 month: (0.51 ± 0.22) kU/L, $P<0.01$]. Likewise, the levels of anti-SSB/La antibodies also decreased significantly [pre-transplantation levels: (146.62 ± 83.08) kU/L; 1 month: (52.61 ± 38.67) kU/L, $P<0.001$]. Additionally, the serum levels of immunoglobulins decreased significantly [194].

This systematic review included 1 RCTs about MSCs in the treatment of PSS. In Li et al.'s 2023 study, 64 participants completed the treatment and assessment. Three months after treatment, significant improvements were seen in salivary and lacrimal gland secretion, as well as ESSDAI and ESSPRI scores ($P<0.05$). Additionally, there were significant reductions in IgG, IgM, C3, C4, and ESR levels between the two groups at specific follow-up time points ($P<0.05$) [77].

Recommendations and challenges in the treatment of autoimmune and rheumatic diseases with MSC

Our research group has conducted extensive clinical research on mesenchymal stromal cell (MSC) therapy for autoimmune diseases such as SLE, PSS, and SSc [200–202], and MSCs have gained regulatory approval in several countries [203, 204]. However, a key issue persists: the efficacy of MSC therapy remains inconsistent across studies, reflecting varied MSC sources, cultivation techniques, and treatment protocols. Our meta-analysis indicates significant differences in clinical outcomes due to these inconsistencies.

Based on these findings and our clinical experience, we offer recommendations: (1) MSC therapy should be combined with other treatments for maximum benefit, rather than being solely relied upon; (2) the optimal MSC dose is approximately (1–2)×10^6 cells/kg, with a maximum of 2×10^6 cells/kg; (3) early intervention with MSC therapy is preferable, as efficacy decreases in advanced disease stages; (4) further clinical research is needed to refine MSC protocols for different autoimmune diseases; (5) multiple doses may be more effective than a single application; (6) treatment protocols should be patient-specific rather than standardized; and (7) MSC therapy is not limited by age. While MSCs have shown safety and efficacy, further large-scale randomized controlled trials are essential to fully establish their therapeutic potential.

Conclusion

MSC transplantation may have the potential to treat autoimmune and rheumatic immune diseases. Moreover, MSC transplantation appears to be relatively safe and could be considered as a viable alternative treatment option for autoimmune and rheumatic immune diseases. However, more RCTs are needed to determine the efficacy and safety of MSCs in the treatment of RA, AS, SSc, and other autoimmune and rheumatic immune diseases.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13287-025-04184-x.

Additional file 1.

Additional file 2.

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Author contributions

Liuting Zeng and Lingyun Sun are responsible for the study concept and design. Liuting Zeng, Chang Liu, Yang Wu, Shuman Liu, Yaru Zheng, Wensa Hao, Dandan Wang, Lingyun Sun are responsible for the data collection, data analysis and interpretation; Liuting Zeng drafted the paper; Lingyun Sun supervised the study; all authors participated in the analysis and interpretation of data and approved the final paper.

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Availability of data and materials

The data used to support the findings of this study are included within the article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
We declare no competing interests.

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