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Therapeutic Potential of Mesenchymal Stromal Stem Cells in Rheumatoid Arthritis: a Systematic Review of In Vivo Studies

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Abstract

Standard treatment options for rheumatoid arthritis (RA) often fail to deliver a long-term therapeutic outcome and in many cases cause intractable adverse events leading to treatment discontinuation or readjustment. Treatment with mesenchymal stem cells (MSCs) has been recently studied in RA due to its immunomodulatory and anti-inflammatory capacities. Thus, this study aims at systematically search and review the literature for randomized or non-randomized clinical trials comparing interventions of MSCs with placebo in RA patients. Electronic searches were conducted on PubMed, SCOPUS, Cochrane-CENTRAL, registries of clinical trials and grey literature. Selected studies were estimated for risk of bias with the Cochrane RoB tool 2 or the ROBINS-I tool. Four trials met the eligibility criteria and entered the review process. Identified MSCs treatments varied from allogeneic to autologous or umbilical cord-derived cells. Enrolled patients had an active RA and had poor responses to previous standard medications. In general, the safety evaluation revealed that treatment with MSCs was safe and well tolerated. Regarding the efficacy measurements, modest improvements were found in RA symptoms and RA-related indices. Significant decreases were found in inflammatory molecules such as C-reactive protein, tumor necrosis factor alpha and interleukin 6. However, clinical response criteria related to RA were achieved by a low-to-moderate percentage of patients. In conclusion, treatment of RA with MSCs appears to have a short-term therapeutic effect. Better-designed randomized trials with sufficient follow-up periods are needed so that the long-term safety and efficacy interventions with MSCs would be elucidated.

Keywords Rheumatoid arthritis · Cell therapy · Stem cells · Mesenchymal · Bone marrow · Umbilical

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting the joints by causing deformity and disability [1–4]. Hand deformities, swelling of the metacarpophalangeal and proximal interphalangeal joints with ulnar deviation of the fingers are observed. The disease process causes initially inflammation of the synovial membrane and then spreads to all other parts of the joint (cartilage/bone damage) [1, 4–6], as fibroblast-like synoviocytes adopt an aggressive and invasive phenotype. The immune responses mediate the joint destruction through the joint fibroblast activation and pro-inflammatory cytokine induction [7, 8]. Additionally, pro-inflammatory cytokines are produced, such as tumor necrosis factor alpha (TNF-a), and interleukins IL-6, IL-1, and IL-17 [5, 9].

Traditionally, RA has been treated with disease-modifying anti-rheumatic drugs (DMARDs) along with non-steroidal

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anti-inflammatory drugs (NSAIDs) and glucocorticoids [4]. Lately, efforts were made for new target therapies that include biological agents, TNF-a inhibitors and B cell-depleting therapies. These treatments seem to ameliorate disease activity and repair bone erosions in some patients [3, 5]. The need for a treatment that guarantees safety and efficacy is of paramount importance in this disease, as few patients achieve long-term drug-free clinical remission [2, 4, 10] and the possibility of adverse effects, high cost [9] and unresponsiveness is present [7].

The Food and Drug Administration (FDA) can grant a fast track designation on regenerative medicine therapies which aim to unmet medical needs in serious conditions based on clinical data or evidence from in vitro or animal models [11]. Relevant clinical trials with multiple sites can be considered by the FDA if they intent to share their combined data and adhere to common manufacturing and quality testing practices [11]. Determination of clinically meaningful endpoints is also a matter of importance for the FDA in clinical trials of regenerative medicine therapies [11].

Early-development stem cells, which have been described by many investigators and assigned different names, are probably overlapping populations of similar cells. Very small embryonic-like stem cells (VSELs) are on the top of hierarchy of all these cells. VSELs could probably be a link between early-development stages and stem cell compartments in adulthood [12]. A recent review highlights a trend for the investigation of tissue remodeling and repair involving mesenchymal stem cells [13].

Mesenchymal stem cells (MSCs) are multipotent nonhematopoietic stromal cells that are able to differentiate into tissues such as bone, cartilage, adipose, muscle, ligament and tendon [1, 5, 9, 14, 15]. MSCs can be easily isolated from bone marrow or adipose tissue as well as placenta, peripheral blood, umbilical cord or synovium and rapidly expanded in culture [1, 4, 8, 10, 16]. MSCs have also been shown to have immuno-suppressive and healing properties, improve angiogenesis and prevent fibrosis [3, 17]. Their contribution to autoimmune and inflammatory disorders' treatment is major, as they release paracrine factors, alter the cytokine secretion and potently modulate immune responses, showing antiproliferative and anti-inflammatory capacities [1–3, 10].

Clinical benefits of MSCs are possibly the result of anti-inflammation, immune-modulatory and immune tolerance induction [5]. Additionally, the regenerative potential of MSCs depends on patient's age, which reinforces the accumulation of oxidative stress and the increase of epigenetic alterations [18]. Mesenchymal stem cell transplantation (MSCT) enhances the clinical characteristics of various autoimmune diseases, such as multiple sclerosis and systemic lupus erythematosus [7, 9, 19]. MSCs' properties concerning regenerative potential could play a role in visual impairment, as innovative prospects for therapy of human retinal diseases come to the fore [20]. On the other hand, type 2 diabetes and metabolic syndrome limit MSCs' therapeutic properties [21].

Moreover, treatment with MSCs reduced the inflammatory response of peripheral blood mononuclear cells (PBMCs) in patients with RA [3]. Additionally, expanded adipose-derived stem cells (eASCs) diminish the production of inflammatory cytokines [16]. The secretome's extracellular vesicles (exosomes, microvesicles, particles, peptides, cytokines) play a pivotal role in stem cell-based therapies of degenerative, autoimmune or inflammatory diseases [22]. As a result, MSCs have been characterized as promising for the treatment of RA [10, 17, 23, 24]. A previous narrative review pointed out that allogeneic mesenchymal stem cells might be effective in RA and, so far, the use of MSCs in a clinical level has been directed towards patients suffering from RA resistant to standard treatments [25]. To our knowledge, this is the first attempt to systematically review the evidence from in vivo studies concerning the therapeutic potential of MSCs in RA patients.

Methods

A systematic search of the literature was conducted following the PRISMA statement guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses) and consulting the center for reviews and dissemination's guidance for undertaking reviews in health care (CRD) [26]. The research question was defined with the PICO format as: P = patients diagnosed with RA, I = administration of MSCs, C = placebo or similar neutral/inactive treatment, O=Safety and efficacy-related outcomes.

In more detail, the outcome variables used for safety evaluation were the presence of adverse events and for the efficacy evaluation were the improvement of symptoms (such as reported pain, physical strength, pain free walking distance, standing time), the reduction of other treatments, the extent of immune restoration and the possible relapse. The secondary outcome variables were the following: DAS28 (disease activity score 28), ESR (erythrocyte sedimentation rate), VAS (visual analogue scale), low disease activity (DAS28-ESR < 3.2), HAQ (health assessment questionnaire), WOMAC scales (Western Ontario and McMaster Universities Arthritis Index), SF-36 (short-form 36 health questionnaire), EULAR response criteria (European league against rheumatism criteria) and ACR20/50/70 criteria (American College of Rheumatology 20/50/70 criteria).

Eligibility Criteria

Randomized and non-randomized clinical trials were included in this review. Furthermore, an eligible trial had to have defined rheumatoid arthritis according to 2010 ACR/EULAR

criteria and have recruited adult patients. With regard to treatment groups, studies were considered if they had interventions with post-natal or adult or somatic stem cells, stromal or mesenchymal and autologous or allogeneic cells. Eligible control groups were administered with placebos or neutral, inactive substances. Studies with conventional co-treatments were eligible if they were distributed in both intervention and control groups. Conventional therapies included disease-modifying anti-rheumatic drugs (DMARDs), corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).

Exclusion criteria were 1) studies with participants having diseases other than RA, such as other autoimmune joint diseases, or RA in remission were excluded, 2) articles published in a language other than English, 3) interventions with hematopoietic, totipotent, pluripotent, induced pluripotent, fetal, and embryonic cells, 4) studies with an epidemiologic design (such as cohorts, cross-sectional, case-controls) or trials not with a control group and 5) studies on animals.

Search Strategy

A literature search was performed in the electronic databases of MEDLINE, SCOPUS, and Cochrane CENTRAL. Additional searches were conducted on ClinicalTrials.gov, ICTRP of the World Health Organization, ISRCTN registry, in EULAR journals (annals of the rheumatic diseases) and in grey literature. The PROSPERO database was searched to confirm that no systematic reviews were being conducted based on the specific research question. The search terms used were the following keywords: mesenchymal cells, stem or stromal cells and rheumatoid arthritis. The preliminary search string used, based on the MESH controlled vocabulary, was: {(stem OR stromal OR mesenchymal) cells} AND rheumatoid arthr* AND (human OR man). The search was restricted to records published in the English language from inception up to December 2018. Records identified through the databases were managed using the software Mendeley, in which the duplicates were removed, and were screened for eligibility by two authors (Alexia K and DA) with disagreements being resolved through discussion with another author (Aristeidis K).

Study Selection

All retrieved titles/abstracts were screened against inclusion and exclusion criteria by two authors (Alexia K and DA) and studies that did not meet all eligibility criteria were excluded. Full-text publications of all remaining sources were obtained and screened against eligibility criteria. Disagreements among the reviewers were resolved by discussion with the primary author (Aristeidis K). Publications that met all inclusion criteria were included in this review.

Assessment of Risk of Bias and Methodological Quality

Eligible trials were assessed for their risk of bias and methodological quality by two authors (Alexia K and KG) and disagreements were resolved by a third author (Aristeidis K). Risk of bias for RCTs was assessed via the Cochrane Risk of Bias (RoB) tool 2.0 [27]. According to RoB tool 2.0, the studies were assessed for risk of biases arising due to randomization process, deviations from indented interventions, missing outcome data, measurement of the outcome and in selection of the reported results and their overall bias was also noted as being low risk, high risk or with some concerns. Furthermore, for the non-randomized trial of Wang et al. (2013) [5] the risk of bias was assessed by the Cochrane Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool. This trial was assessed on the risk of biases caused by confounding, selection of participants, classification of interventions, deviations from Intended interventions, missing data, measurement of outcomes, selection of the reported result and overall judgment which is analogous to the judgment of the aforementioned categories. Finally, methodological quality was assessed via the modified Jadad scale based on the description of the randomization scheme, blinding method, drop-outs or withdrawals, presentation of inclusion and exclusion criteria, adverse events and statistical analysis [28].

Data Extraction

Data extraction was performed independently by two reviewers (Alexia K and AB) and supervised by the primary author (Aristeidis K). The extracted data included information about the registry of protocol, study location, design and masking of interventions, types of MSCs and placebos, sample size, treatment groups allocation, participant characteristics (age, gender and duration of illness), duration of intervention and follow-up periods, previous poor medication response, co-therapies, and outcomes of interest. All data were extracted on predefined forms.

Results

Study Selection

Initially, 1135 records were identified through electronic searches on databases and trial registries. After removal of duplicates, 1117 records were screened and 44 full-text studies were assessed for eligibility (Fig. 1). 40 studies were excluded for not meeting the inclusion criteria, mainly due to intervention with other types of cells, and finally, four trials [2, 5, 16, 29] entered the review.

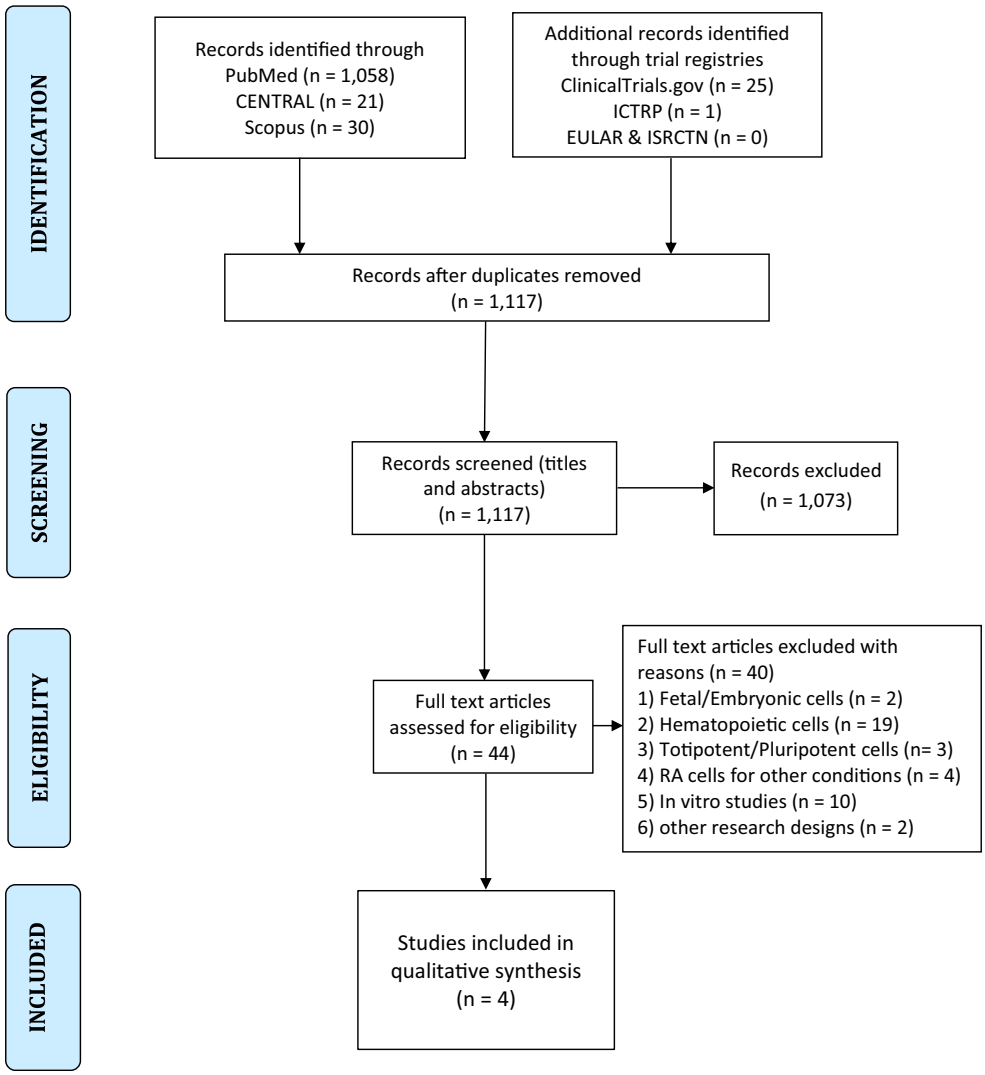

Fig. 1 PRISMA flowchart of stages in study selection

Study Characteristics

Three studies used a randomized scheme to allocate participants in their interventions [2, 16, 29] and one had a non-randomized design [5]. All studies were conducted from 2010 up to 2017 and Table 1 summarizes their basic characteristics. The range of the intervention period varied from one day (single dose intervention) up to eight months and follow-up periods lasted up to one year after first enrollment. Only the trial of Wang et al. (2013) [5] enrolled patients at a different period; first in the intervention groups and two years later in the control group. MSC types used in intervention groups were allogeneic adipose-derived MSCs [16], autologous bone marrow-derived stromal MSCs [29] and umbilical cord-derived MSCs [2, 5]. In all studies, participants' mean age was above 40 years and their vast majority of patients were women. Furthermore, all studies enrolled patients who had active RA and had poor responses to standard RA medications.

Risk of Bias and Quality Assessment

Assessment of risk of bias of RCTs is presented in Fig. 2. The study of Alvaro-Garcia et al. (2017) [16] was judged as being in high risk of overall bias and having high risk of bias in missing outcome data and measurement of the outcome. The RCT of Yang et al. (2018) [2] was also in high risk of overall bias due to measurement of the outcome, and in the trial of Shadmanfar et al. (2018) [29] its risk of overall bias was met with some concerns. Furthermore, assessment of risk of bias in the non-randomized CT of Wang et al. (2013) [5] was conducted according to the ROBINS-I tool and is presented in Table 2. This trial was judged as having a serious risk of bias mainly due to potential confounding, which can be present in trials lacking randomization. A serious risk of bias judgment was also noted in the domain of "selection of the reported result" due to incongruence in the list of outcome measures presented in its protocol and its publication. Finally, a moderate bias was judged in the domain of the "selection of

Table 1 Characteristics of included studies

First author, year	Alvaro-Garcia, 2017	Shadmanfar, 2018	Yang, 2018	Wang, 2013
Registry	NCT01663116	AC/91/1133 (Royan Institute EthicsCommittee); NCT01873625	ChiCTR-ONC-16008770	NCT01547091
Study period	2011–13	2011–13	2016–17	2010 (Treatment group) – 2012 (control group)
Location	Spain	Iran	China	China
Design	RCT	RCT	RCT	Non-randomized CT
MSC type	Allogeneic adipose-derived	Autologous BM-derived	Umbilical cord	Umbilical cord
Sample size (n)	53	30	105	172
Treatment groups	*Cohort A* (n = 20): 1×10^6 cells/kg *Cohort B* (*n* = 20): 2×10^6 cells/kg *Cohort C* (*n* = 6): 3×10^6 cells/kg	MSC (n = 15)	MSC: 1×10^6 cells/kg *After 12 weeks evaluation*; • Response group (*n* = 28) • Non-response group (*n* = 24)	MSC: 4×10^7 cells/kg; • *Group 1* (*n* = 76): 3 months • *Group 2* (*n* = 45): 6 months • *Group 3* (*n* = 15): 8 months
Control groups	Ringer's lactate solution (n = 7)	normal saline (n = 15)	physiological saline (*n* = 53)	stem cell solvent (*n* = 36)
Duration	• Treatment: 15 days • Follow-up: 6 months	• Treatment: 1 dose • Follow-up: 12 months	• Treatment: 12 weeks • Follow-up: 12 months	Treatment: 3–8 months
Blinding	Single blind for safety, Double blind for efficacy	Triple blind	No	No
Females (%)	91%	87%	79%	74%
Mean age (years)	*Cohort A*: 54.15 *Cohort B*: 57.40 *Cohort C*: 50.33 *Placebo*: 58.43	*MSC: 50.4* *Placebo: 48.1*	*Response group: 50.7* *Non-response group: 51.2* *Control: 49.8*	*Group 1: 47.0* *Group 2: 44.6* *Group 3: 46.2* *Control: NR*
RA duration (years)	*Cohort A*: 14.36 *Cohort B*: 13.07 *Cohort C*: 20.25 *Placebo*: 22.73	NR	*Response group:* 4 *Non-response group:* 3.94 *Control*: 3.89	>5 years: • *Group 1: 58%* • *Group 2: 67%* • *Group 3: 73%* • *Control*: NR
Study population (inclusion criteria)	• diagnosis of RA for >6 months • 4 tender and 4 swollen joints • DAS28-ESR ≥3.2 • treated with at least one non biological agent (mean number 2,98)	• knee symptoms medium to severe, confirmed diagnosis of RA with knee involvement • no previous uncontrolled chronic diseases other than RA or diseases resulted in knee malformations, no injections into the studied knee in the last 3 months	• active RA • no other autoimmune or systemic diseases	• active RA • >3 painful joints • joint swelling • tenderness • ESR > 45 mm/h • CRP > 15 mg/dl • morning stiffness: at least 1 h
Previous poor medication response	Yes	Yes	Yes	Yes
Other co-therapies	• Kept stable: non biological DMARDs, NSAIDs, glucocorticoids, • rescue therapy after the third month with any DMARD including biologics	• Allowed: DMARDs • Not allowed: NSAIDs	Allowed and reduced based on disease improvement: DMARDs, NSAIDs, steroids and biologics	Allowed at small doses: MTX and/or leflunomide and/or hydroxychloroquine

BM: bone marrow; DAS28: disease activity score 28; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; MTX: methotrexate; MSC: mesenchymal stem cells; NR: not reported; NSAIDs: nonsteroidal anti-inflammatory drugs; RA: rheumatoid arthritis; RCT: randomized clinical trial

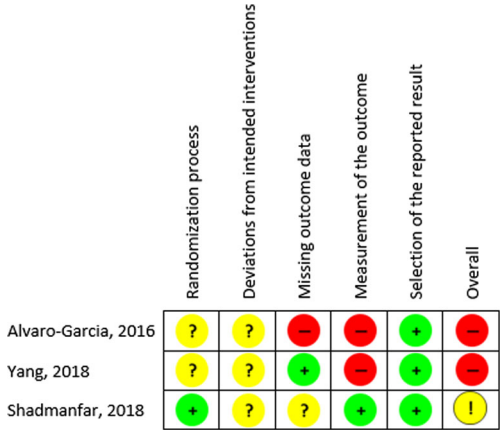

Fig. 2 Risk of bias assessment of included RCTs according to Cochrane RoB tool 2.0. Green circles: low risk of bias, yellow circles: some concerns and red circles: high risk of bias

participants into the study" due to different enrollment periods used in the intervention and control groups.

The methodological quality of all studies based on the Jadad scale are illustrated in Table 3. Among the included RCTs only the trial of Shadmanfar et al. (2018) [29] scored the maximum and the non-randomized trial of Wang et al. (2013) [5] had the lowest score.

Safety Evaluation

MSCs administration was generally safe and well tolerated in all studies (Table 4). Mild adverse events such as chills and/or fever were noted in two studies with short duration. Specifically, in the study of Wang et al. (2013) [5] they were manifested in 6 patients and lasted for two hours, and in the study of Yang et al. (2018) [2] they concerned three patients and disappeared within three hours. On the other hand, Shadmanfar et al. (2018) [29] found that post-injection pain and/or articular swelling were present within one month after transplantation which were resolved with NSAIDs.

Finally, Alvaro-Gracia et al. (2017) [16] described 141 adverse events, with 85% (Cohort A), 75% (Cohort B), 100% (Cohort C) and 57% (placebo group) having at least one adverse event. The most frequent of them were fever, respiratory infections, headache, systemic infections, urinary tract infections, nausea, arthralgia, asthenia, malaise and vomiting. Moreover, 133 adverse events were mild or moderate and 8 were severe. The severe adverse events included lacunar infarction, diarrhea, tendon rupture, rheumatoid nodule and arthritis in cohort A, sciatica and RA in cohort B, and asthenia in the placebo group. As far as lacunar infarction is concerned, it was considered as a dose limiting toxicity and it occurred 8 days after the second treatment administration. The patient with this complication was the only one who discontinued the study because of adverse events.

Efficacy Evaluation

Efficacy of MSCs administration was evaluated based on their potential to 1) lead to improvements of symptoms, 2) reduce the doses of other co-administered medicines, 3) improve immune-related biomarkers, and 4) improve RA-related indices. Table 4 presents extracted information on the aforementioned outcomes.

Improvement of Symptoms

In the study of Alvaro-Gracia et al. (2017) [16],there was no clinical benefit after 3 months follow-up and the therapeutic effect tended to wane or fluctuate. There was clearly an implication for a constant need of administration [16]. On the other hand, in the study of Shadmanfar et al. (2018) [29], there was a distinct superiority of the MSCT group concerning a clinical improvement at the first month, which was maintained until 12 months. The clinical parameters involved pain-free walking distance, time to jelling (not significant improvement) and standing time (significant improvement). At the end of this study, improved physical and mental subscales were reported in the MSC group. However, this improvement was not statistically important.

In addition, the study of Yang et al. (2018) [2] showed that the MSC group had enhanced clinical symptoms and low disease activity during the 12 weeks of follow-up. The improvement in disease status maintained for most of the patients for 12 months, with a general clinical response rate at 54%. Two patients of the response group (8%) experienced pain and swelling at 24 weeks and their ESR-CRP levels were increased.

A rapid clinical response occurred after the administration of umbilical cord-derived stem cells in the study of Wang et al. (2013) [5]. Specifically, there was a significant positive impact on joint pain and swelling, which started 12 h after

Table 2 Risk of bias assessment in the non-randomized trial of Wang, 2013 according to Cochrane ROBINS-I tool

1. Bias due to confounding	2. Bias caused by selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended interventions	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall judgement
Serious	Moderate	Low	Moderate	Low	Moderate	Serious	Serious

Table 3 Scores of methodological quality based on the modified Jadad scale

Study	1. was the research described as randomized?	2. was the randomization appropriate?	3. was the research described as blinded?	4. was the approach of blinding appropriate?	5. was there a description of drop-outs or withdrawals?	6. was there a presentation of inclusion/ exclusion criteria?	7. was the approach used to assess adverse events described?	8. was the approach of statistical analysis described?	Total score
Alvaro-Garcia, 2017	Yes	Not described	Yes	No	Yes	Yes	Yes	Yes	5
Shadmanfar, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Yang et al.,2018	Yes	Not described	No	Not described	Yes	Yes	Yes	Yes	5
Wang, 2013	No	Not described	No	Not described	No	Yes	Yes	Yes	3

A point is assigned to a "Yes", a point is subtracted to a "No" for the 2nd and the 4th question. Otherwise, no points count

intervention and was maintained throughout the study. Moreover, the number of joints affected with tenderness and swelling was reduced and diet, sleep and physical strength were enhanced as early as two weeks after treatment with MSC.

Reductions in Co-Administrated Medicines

In all studies there was a co-administration of medicines (Table 1). Two studies described a dose reduction or cease of other therapies during MSC intervention. More specifically, Shadmanfar et al. (2018) [29] mentioned that MSCs implantation was responsible for reductions in methotrexate and prednisolone intake at the first 6 months, but not after 1 year. Moreover, the study of Yang et al. (2018) [2] refers to a stepwise reduction of prednisone acetate in 23 patients after MSCs administration.

Immune Evaluation

Two of the included studies [2,5] demonstrated an increased percentage of CD4 + CD25 + Foxp3 + Tregs and in one study [2] there was a decreased percentage of CD4 + IL17A + Th17 cells after MSCs administration. Wang et al. (2013) [5] found decreased levels of rheumatoid factor (RF), IL-6, TNF-a and increased levels of IL-4 in the group receiving MSCs treatment, which was associated with the decreased ratio of Th1/ Th2 cells. Yang et al. (2018) [2] put emphasis on the low Treg/ Th17 ratio before MSC treatment, which points to an imbalance in the immune system and significant inflammation after MSC administration. Moreover, in the response group of this study, significant increases in hemoglobin and albumin levels and decreases in platelet levels were observed after 48 weeks. On the other hand, a decrease in IL-6, TNF-a levels was distinct 4 weeks after MSC intervention and remained statistically significant after 24 and 48 weeks of follow-up. RF and anti-CCP levels were decreased, but this was not significant. On the contrary, IL-10 levels (immunosuppressive cytokine by Treg cells) were increased at 4 weeks.

Regarding CRP, minimum changes were found in the study of Shadmanfar et al. (2018) [29]. Moreover, Alvaro-Gracia et al. (2017) [16] pointed out that CRP tended to decrease in cohorts A and C but not in cohort B or placebo. Finally, Yang et al. (2018) [2] mentioned that CRP levels waned at a significant level 12 weeks after MSCT and this persisted for 48 weeks without repeated administration for most of the patients.

Evaluation of RA Indices

With regard to the index of DAS28, significant decreases were noted in two trials [2, 5] followed treatment with MSCs. The trial of Shadmanfar et al. (2018) [29] which enrolled RA

Table 4 Summary of outcomes in included studies

Outcomes / Studies	Alvaro-Garcia, 2017	Shadmanfar, 2018	Yang, 2018	Wang, 2013
Safety evaluation				
Mild AE	Reported along with moderate AE	Post-injection pain and/or articular swelling within 1 month	Chills or fever in 3 patients	Chill and/or fever for 2 h maximum in 6 patients
Moderate AE	133 AE; No relevant vital signsabnormalities other than those associated with the reported AEs, normal laboratory values	NR	NR	NR
Severe AE	8 AE in 6 patients; • *Cohort A*: 5 AE • *Cohort B*: 2 AE • *Placebo*: 1 AE	NR	NR	NR
Dose reduction	NR	MTX and prednisolone intake at first 6 months. Not after 1 year	Stepwise reduction of prednisone	NR
Improvement of symptoms	Clinical benefits reduced in time, decreased or fluctuated treatment effect after 3 months (no persistent improvement)	• pain free walking distance • time to jelling • standing time	• Improved clinical symptoms in 28 patients • 54% clinical response rate	• Improvement of sleep, diet and physical strength as early as 2 weeks • Alleviation of joint pain and swelling within 12 h • Reduction of the number of joints affected
Immune evaluation	• Non-significant clinical consequences of eASC-specific anti-HLA- I antibodies in 19% or patients • anti-HLA-II antibodies: not found • T cells: not significantly different among groups • CRP: decreasing trend in cohorts A and C, but not in cohort B or placebo	• CRP: minimum changes • ESR: no differences	Response group: • Increased percentage of CD4 + CD25 + Foxp3 + Tregs and Treg/Th17 ratio • Decreased percentage of CD4 + IL-17A + Th17 cells • Decreased levels of IL-6/ TNF-α and increased IL-10 levels at 4 weeks • Decreased levels of IL-6, TNF-α at 24 & 48 weeks • Decreased CRP levels at 12 weeks • Decreased anti-CCP, RF levels	• Decreased: CRP, RF, IL-6, TNF-a • Increased: CD4 + CD25 + Foxp3 + T regulatory cells (by 25% in 3 months, by 34% in 6 months and by 14% in 8 months), IL-4
Indices evaluation				
DAS28	NR	No differences	Decrease	Decrease
DAS28-ESR	decreasing tendency	NR	NR	NR
Low disease activity (DAS28-ESR < 3,2)	• Cohort A: 20% • Cohort C: 33.3% • Other groups: 0%	NR	NR	NR
VAS	NR	Knee Pain: decrease >50%	NR	NR
WOMAC	NR	No differences	NR	NR
SF-36	No improvement	No improvement	NR	NR
HAQ	NR	NR	Decrease persisted in the follow-up	No difference

Table 4 (continued)

Outcomes / Studies	Alvaro-Garcia, 2017	Shadmanfar, 2018	Yang, 2018	Wang, 2013
EULAR response criteria	At 3 months: • *Cohort A*: 20% • *Cohort C*: 33.3% • *Other groups*: 0%	NR	NR	NR
ACR20/50/70 responses	ACR20 at month 3: • *Cohort A*: 25% • *Cohort B*: 15% • *Cohort C*:17% • *Placebo*: 0% ACR50: greater for cohorts A, B& C ACR70: very low responses	NR	NR	ACR20/50/70: • *Group 1*: 36%, 28% and 12%, respectively • *Group 2*: 47%, 20% and 4%, respectively • *Group 3*: 33%, 7% and 7%, respectively

AE: adverse events; ACR20/50/70: American College of Rheumatology responses; anti-CCP: antibodies directed to cyclic citrullinated peptides; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; HAQ: health assessment questionnaire; IL: interleukin; MTX: methotrexate; NR: not reported; RF: rheumatoid factor; SF-36: short form-36 health questionnaire; TNF-a: tumor necrosis factor alpha; VAS: pain visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index

patients with knee involvement found a greater than 50% decrease in knee pain. Furthermore, health-related quality of life as measured by the SF-36 questionnaire did not demonstrated any improvement in two trials [16, 29] and the function-related HAQ questionnaire showed mixed results in the trials in which it was evaluated [2, 5]. The composite measure of ACR 20/50/70 responses were reached by a moderate percentage of patients with less patients meeting the increased 50 or 70% improvement levels [5, 16]. Analogous results were found for the EULAR response criteria which were assessed in one trial [16].

Discussion

MSCs administration was found a safe and well-tolerated therapeutic option in the selected studies. There are encouraging indications for its therapeutic potential, which are based on the anti-inflammatory, immune modulation and immune tolerance induction [2]. Specifically, MSCs administration can ameliorate the immune function, the clinical symptoms and the evaluation indices. For example, DMARDs plus MSCs administration led to a significant disease activity reduction for a long period in patients with refractory RA [5].

A great variability was noted in the evaluation of clinical efficacy outcomes and the beneficial results tended to wane or fluctuate after a period of treatment and an additional administration was required as soon as relapse symptoms emerged [2, 5, 16]. The increased level of T regulatory cells was associated with the improvement in disease status and was considered an important clinical index for the efficacy of UC-MSCs. Moreover, the UC-MSCs administration alleviated DMARDs side effects and, consequently, contributed to compliance to this conventional treatment [5].

Adipose or bone marrow derived MSCs tested for regenerative and immunomodulatory capabilities in different autoimmune diseases and animal model inflammatory arthritis verify these findings [30, 31]. However, the precise mechanism concerning the therapeutic potential of MSCs is still under investigation [7]. MSCs affect the immune responses involving immune function modulation and immune tolerance induction [2, 7, 10, 32]. They function as auxiliary antigen-presenting cells (APC) contributing to the development of a regulatory APC population with T cell- modulating capabilities [32]. Also, MSCs regulate the adaptive and the innate response through the induction of CD4 + CD25 + FoxP3 + T regulatory cells, the suppression of dendritic cell maturation, the adoption of an anti-inflammatory phenotype by the macrophages and the suppression of NK cells [10, 13, 25, 33]. They produce many immunomodulatory cytokines and growth factors, hindering monocyte maturation and T cell proliferation [6, 7, 10].

Furthermore, MSCs obstruct the pro-inflammatory cytokines and limit the expression of Th17 cells while evidence points to the relationship between Th17 and T regulatory cells [7, 10]. To be specific, several studies suggested that adipose-derived or bone marrow MSCs have the capability to reduce the catastrophic Th1/Th2 response and enhance the T regulatory cells activation, whereas others showed no improvement with MSC treatment [13].

MSCs have an immunosuppressive, anti-inflammatory and paracrine effect on joint disease processes. Also, they contribute to tissue repair. It is likely that synovial stromal cells (FLSs and MSCs) could regulate the homeostasis of the immune system and that failure of such immunomodulation within the joint is the first event in RA development [13].

Treatments fail to almost a third of RA patients and clinical remission does not necessarily entail the cessation of joint damage [13]. Despite the fact that in physiological conditions the synovium promotes the joint homeostasis, in RA it has a catastrophic effect on the inflammatory/immune cells of the joint and the resident fibroblast-like synoviocytes (FLSs). Normal FLSs play an important role in joint well-being by obstructing T cell proliferation and dendritic cells production from monocytes. RA FLSs though, function as antigen-presenting cells leading to T cell activation and proliferation [34]. Moreover, RA FLSs are able to augment B-cells and contribute to their survival and function. On the other hand, the relationship between FLS and MSCs is indistinct. They might represent the same cell type with functional differentiation, or they could stand for different developmental status of the same cell lineage [13]. It has been stated that MSCs can obstruct the proliferation of fibroblast-like synoviocytes and suppress osteoclastogenesis by producing osteoprotegerin [32]. In an in vitro study, UC-MSCs had a significant inhibitory effect on the proliferation and the responses of FLSs to inflammation, obstructed T cell activation and induced T cells upregulation [34].

In RA, MSCs/FLSs are incompetent to control inflammation due to the interaction between inflammatory and immune cells and, on the contrary, they end up intensifying the inflammation process. Aberrant crosstalk between FLSs/MSCs and immune cells could create a vicious cycle maintaining and intensifying RA progression. Thus, the use of MSCs as cell-therapy for autoimmune diseases needs to include the targeting of the inflammatory factors within the synovium [6].

Mesenchymal stromal cells offer many opportunities for novel RA treatments. So far, the use of MSCs at a clinical level involves RA patients resistant to common therapies. Most likely it is preferable to give MSC treatment at early stages of the condition aiming at immune system modulation through the induction of regulatory networks. Therefore, clinical studies selection criteria for RA patients are of paramount importance [25]. It is controversial whether BM-derived MSCs constitute the ideal source for novel treatments in RA. It is suggested that adipose-derived MSCs may provide a more reliable source of cells [31]. It is appealing to consider that MSC treatment could determine disease course (due to mesenchymal cells' anti-inflammatory and immunosuppressive properties) and joint tissue repair by preventing tissue damage from triggering inflammation [13]. The ultimate goal is to consolidate joint homeostasis. Undoubtedly, MSCs' capability to induce immune tolerance is very promising [24, 25, 35].

The small number of patients in the existing studies did not provide the necessary clinical evidence for a statistically significant superiority of MSCs in RA treatment. So, the limited population was the main issue in evaluating the clinical efficacy [7]. On the other hand, the follow-up periods varied significantly, so that the safety estimation would not be determinant. Due to this, it is not clear if the repetitive administration is safe. Moreover, the ideal route of administration, frequency of MSC therapy and cell source of MSCs for treating RA are yet unknown. The appropriate therapeutic dosage of MSCs is still undefined and is related to the therapeutic application [36]. Cells of different sources seem to have a plethora of differentiation potential [37, 38]. Additionally, another aspect of variability was the different methods of cell production and dosage determination found in the included studies. As a result, a solid conclusion cannot be reached.

Future research has to put emphasis on safety while determining the appropriate MSCs dosage and carefully implementing the re-administration periods. Safety needs to be verified by conducting studies with a large follow-up period and repetitive administration. As far as therapeutic potential is concerned, future research should focus on multicenter randomized clinical trials with sufficient sample sizes, proper selection criteria of RA patients and longer follow-up periods for a valid efficacy evaluation. In addition, joint imaging data should be considered, along with the appropriate patient profile for the right kind and dosage of MSCs used. Furthermore, due to the substantial variety in clinical efficacy outcomes, biomarkers that predict the MSCT response are needed. According to the Yang et al. (2018), IFN-levels could be used as a biomarker for clinical efficacy prediction and RA patients selection [2]. Finally, the regeneration of a near natural cartilage or bone tissue will demand a proper combination of MSCs, biodegradable and chondroinductive scaffolds, and specific factors of anti-inflammation and differentiation [39].

Conclusion

MSCs immunosuppressive and anti-inflammatory functions as well as joint tissue repair capabilities render RA treatment with the use of these cells very promising. Clinical studies are at an early stage and are restricted to patients who could not achieve clinical remission with the use of other therapies. A

challenging goal is to induce remission via permanent immune tolerance, protect against structural damage and repair existing damage. The identification of RA patients most likely to respond to MSC treatment will be crucial. Our data show that the therapeutic effect of MSCs is a short-term one. However, this picture is subject to change depending on future well-designed clinical trials.

Author's Contributions Alexia K and Aristeidis K: conceive the study. Alexia K: systematic search, screening for eligibility, data extraction, bias and quality assessment, and drafting of the manuscript. DA: systematic search, screening for eligibility and drafting the manuscript. AB: data extraction and drafting the manuscript. KG: bias and quality assessment, and drafting the manuscript. Aristeidis K: systematic search, screening for eligibility, data extraction, bias and quality assessment, and drafting the manuscript. All authors: contribution in the design of the work, interpretation of data, critical revision for important intellectual content, approval of the final version of the manuscript to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Usha Shalini, P., Vidyasagar, J. V. S., Kona, L. K., Ponnana, M., & Chelluri, L. K. (2017). In vitro allogeneic immune cell response to mesenchymal stromal cells derived from human adipose in patients with rheumatoid arthritis. *Cellular Immunology, 314*, 18–25. https://doi.org/10.1016/j.cellimm.2017.01.008.
2. Yang, Y., He, X., Zhao, R., Guo, W., Zhu, M., Xing, W., Jiang, D., & Liu, C. (2018). Serum IFN - γ levels predict the therapeutic effect of mesenchymal stem cell transplantation in active rheumatoid arthritis. *Journal of Translational Medicine, 16*, 1–9. https://doi.org/10.1186/s12967-018-1541-4.
3. Oshita, K., Yamaoka, K., Udagawa, N., Fukuyo, S., Sonomoto, K., Maeshima, K., Kurihara, R., Nakano, K., Saito, K., Okada, Y., Chiba, K., & Tanaka, Y. (2011). Human mesenchymal stem cells inhibit osteoclastogenesis through osteoprotegerin production. *Arthritis and Rheumatism, 63*(6), 1658–1667. https://doi.org/10.1002/art.30309.
4. Zeng, J., Wang, F., & Mao, M. (2016). Co-culture of fibroblast-like synoviocytes with umbilical cord-mesenchymal stem cells inhibits expression of pro-inflammatory proteins, induces apoptosis and promotes chondrogenesis. *Molecular Medicine Reports, 14*(4), 3887–3893. https://doi.org/10.3892/mmr.2016.5721.
5. Wang, L., Wang, L., Cong, X., Liu, G., Zhou, J., Bai, B., Li, Y., Bai, W., Li, M., Ji, H., Zhu, D., Wu, M., & Liu, Y. (2013). Human Umbilical Cord Mesenchymal Stem Cell Therapy for Patients with Active Rheumatoid Arthritis: Safety and Efficacy (Vol. 22). https://doi.org/10.1089/scd.2013.0023.
6. El-Jawhari, J. J., El-Sherbiny, Y. M., Jones, E. A., & McGonagle, D. (2014). Mesenchymal stem cells, autoimmunity and rheumatoid arthritis. *Qjm, 107*(7), 505–514. https://doi.org/10.1093/qjmed/hcu033.
7. Jaroughi, N., Azimian, V., Mardpour, S., Kakroodi, F. A., Bolurieh, T., & Hosseini, S. E. (2018). Intra-articular knee implantation of autologous bone marrow – derived involvement : Results of a randomized , triple-blind , placebo-controlled. Cytotherapy, (79). https://doi.org/10.1016/j.jcyt.2017.12.009.
8. Tso, G. H. W., Law, H. K. W., Tu, W., Chan, G. C. F., & Lau, Y. L. (2010). Phagocytosis of apoptotic cells modulates mesenchymal stem cells osteogenic differentiation to enhance IL-17 and RANKL expression on CD4+ T cells. *Stem Cells, 28*(5), 939–954. https://doi.org/10.1002/stem.406.
9. Baharlou, R., Ahmadi-Vasmehjani, A., Faraji, F., Atashzar, M. R., Khoubyari, M., Ahi, S., Erfanian, S., & Navabi, S. S. (2017). Human adipose tissue-derived mesenchymal stem cells in rheumatoid arthritis: Regulatory effects on peripheral blood mononuclear cells activation. *International Immunopharmacology, 47*, 59–69. https://doi.org/10.1016/j.intimp.2017.03.016.
10. Rheumatology, D. (2018). *Intravenous infusion of umbilical cord blood- derived Mesenchymal stem cells in rheumatoid arthritis : A phase 1a clinical trial, 1–7*. https://doi.org/10.1002/sctm.18-0031.
11. FDA, & CBER (2019). Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry. Retrieved from http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
12. Ratajczak, M. Z., Marycz, K., Poniewierska-Baran, A., Fiedorowicz, K., Zbucka-Kretowska, M., & Moniuszko, M. (2014, September 1). Very small embryonic-like stem cells as a novel developmental concept and the hierarchy of the stem cell compartment. *Advances in Medical Sciences. Medical University of Bialystok*. https://doi.org/10.1016/j.advms.2014.08.001.
13. De Bari, C. (2015). Are mesenchymal stem cells in rheumatoid arthritis the good or bad guys? *Arthritis Research & Therapy, 17*(1), 113. https://doi.org/10.1186/s13075-015-0634-1.
14. Ham, O., Lee, C. Y., Song, B., Lee, S., Kim, R., Park, J., Lee, J., Seo, H., Lee, C. Y., Chung, Y., Maeng, L., Lee, M. Y., Kim, J., Hwang, J., Woo, D. K., & Chang, W. (2014). Upregulation of miR-23b Enhances the Autologous Therapeutic Potential for Degenerative Arthritis by Targeting PRKACB in Synovial Fluid-Derived Mesenchymal Stem Cells from Patients., *37*(6), 449–456.
15. Gonzalez-Rey, E., Gonzalez, M. A., Varela, N., O'Valle, F., Hernandez-Cortes, P., Rico, L., Büscher, D., & Delgado, M. (2010). Human adipose-derived mesenchymal stem cells reduce inflammatory and T cell responses and induce regulatory T cells in vitro in rheumatoid arthritis. *Annals of the Rheumatic Diseases, 69*(1), 241–248. https://doi.org/10.1136/ard.2008.101881.
16. Álvaro-Gracia, J. M., Jover, J. A., García-Vicuña, R., Carreño, L., Alonso, A., Marsal, S., Blanco, F., Martínez-Taboada, V. M., Taylor, P., Martín-Martín, C., DelaRosa, O., Tagarro, I., & Díaz-González, F. (2017). Intravenous administration of expanded allogeneic adipose-derived mesenchymal stem cells in refractory rheumatoid arthritis (Cx611): Results of a multicentre, dose escalation, randomised, single-blind, placebo-controlled phase Ib/IIa clinical trial. *Annals of the Rheumatic Diseases, 76*(1), 196–202. https://doi.org/10.1136/annrheumdis-2015-208918.
17. Zheng, Z. H., Li, X. Y., Ding, J., Jia, J. F., & Zhu, P. (2008). Allogeneic mesenchymal stem cell and mesenchymal stem cell-differentiated chondrocyte suppress the responses of type II collagen-reactive T cells in rheumatoid arthritis. *Rheumatology, 47*(1), 22–30. https://doi.org/10.1093/rheumatology/kem284.
18. Kornicka, K., Marycz, K., Marędziak, M., Tomaszewski, K. A., & Nicpoń, J. (2017). The effects of the DNA methyltranfserases inhibitor 5-Azacitidine on ageing, oxidative stress and DNA methylation of adipose derived stem cells. *Journal of Cellular and Molecular Medicine, 21*(2), 387–401. https://doi.org/10.1111/jcmm.12972.
19. Wang, Q., Li, X., Luo, J., Zhang, L., Ma, L., Lv, Z., & Xue, L. (2012). The allogeneic umbilical cord mesenchymal stem cells regulate the function of T helper 17 cells from patients with rheumatoid

arthritis in an in vitro co-culture system. *BMC Musculoskeletal Disorders, 13*(1), 249–247. https://doi.org/10.1186/1471-2474-13-249.

20. Cislo-Pakuluk, A., & Marycz, K. (2017). A promising tool in retina Regeneration: Current Perspectives and Challenges When Using Mesenchymal Progenitor Stem Cells in Veterinary and Human Ophthalmological Applications. *Stem Cell Reviews and Reports*. Humana Press Inc. https://doi.org/10.1007/s12015-017-9750-4, .
21. Kornicka, K., Houston, J., & Marycz, K. (2018). Dysfunction of Mesenchymal stem cells isolated from metabolic syndrome and type 2 diabetic patients as result of oxidative stress and autophagy may limit their potential therapeutic use. *Stem Cell Reviews and Reports*. Humana Press Inc. https://doi.org/10.1007/s12015-018-9809-x.
22. Tay, J., Allan, D. S., Le, Y., Fergusson, D., Akyurekli, C., & Richardson, R. B. (2014). A systematic review of preclinical studies on the therapeutic potential of Mesenchymal stromal cell-derived microvesicles. *Stem Cell Reviews and Reports, 11*(1), 150–160. https://doi.org/10.1007/s12015-014-9545-9.
23. Kim, K., Kim, H. J., Kim, B., Kwon, Y., Kim, H., & Kim, Y. (2018). Epigenetic modification of mesenchymal stromal cells enhances their suppressive effects on the Th17 responses of cells from rheumatoid arthritis patients, 1–10.
24. Kastrinaki, M., & Papadaki, H. A. (2009). Mesenchymal stromal cells in rheumatoid arthritis : Biological proper- ties and clinical applications, 61–69.
25. Ansboro, S., Roelofs, A. J., & De Bari, C. (2017). Mesenchymal stem cells for the management of rheumatoid arthritis. *Current Opinion in Rheumatology, 29*(2), 201–207. https://doi.org/10.1097/BOR.0000000000000370.
26. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, T. P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine, 6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097.
27. Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., et al. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed.), 366*, l4898. https://doi.org/10.1136/bmj.l4898.
28. Oremus, M., Wolfson, C., Perrault, A., Demers, L., Momoli, F., & Moride, Y. (2001). Interrater reliability of the modified Jadad quality scale for systematic reviews of Alzheimer's disease drug trials. *Dementia and Geriatric Cognitive Disorders, 12*(3), 232–236. https://doi.org/10.1159/000051263.
29. Shadmanfar, S., Labibzadeh, N., Emadedin, M., Jaroughi, N., Azimian, V., Mardpour, S., Kakroodi, F. A., Bolurieh, T., Hosseini, S. E., Chehrazi, M., Niknejadi, M., Baharvand, H., Gharibdoost, F., & Aghdami, N. (2018). Intra-articular knee implantation of autologous bone marrow–derived mesenchymal stromal cells in rheumatoid arthritis patients with knee involvement: Results of a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial. *Cytotherapy, 20*(4), 499–506. https://doi.org/10.1016/j.jcyt.2017.12.009.
30. Tyndall, A., & Van Laar, J. M. (2010). Stem cells in the treatment of inflammatory arthritis. *Best Practice and Research: Clinical Rheumatology, 24*(4), 565–574. https://doi.org/10.1016/j.berh.2010.01.008.
31. MacFarlane, R. J., Graham, S. M., Davies, P. S., Korres, N., Tsouchnica, H., Heliotis, M., Mantalaris, A., & Tsiridis, E. (2013). Anti-inflammatory role and immunomodulation of mesenchymal stem cells in systemic joint diseases: Potential for treatment. *Expert Opinion on Therapeutic Targets, 17*(3), 243–254. https://doi.org/10.1517/14728222.2013.746954.
32. Liang, J., Li, X., Zhang, H., Wang, D., Feng, X., Wang, H., Hua, B., Liu, B., & Sun, L. (2012). Allogeneic mesenchymal stem cells transplantation in patients with refractory RA. *Clinical Rheumatology, 31*(1), 157–161. https://doi.org/10.1007/s10067-011-1816-0.
33. Bouffi, C., Djouad, F., Mathieu, M., Noel, D., & Jorgensen, C. (2009). Multipotent mesenchymal stromal cells and rheumatoid arthritis: Risk or benefit? *Rheumatology, 48*(10), 1185–1189. https://doi.org/10.1093/rheumatology/kep162.
34. Liu, Y., Mu, R., Wang, S., Long, L., Liu, X., Li, R., et al. (2010). Therapeutic potential of human umbilical cord mesenchymal stem cells in the treatment of rheumatoid arthritis. *Arthritis Research & Therapy, 12*(6), R210. https://doi.org/10.1186/ar3187.
35. Kobelt, G., Jennifer Eriksson, G. P., & J. B. (2017). The burden of multiple sclerosis 2015: Methods of data collection, assessment and analysis of costs, quality of life and symptoms. *Multiple Sclerosis Journal, 23*(2s), 153–156. https://doi.org/10.1177/https.
36. Perdisa, F., Gostyńska, N., Roffi, A., Filardo, G., Marcacci, M., & Kon, E. (2015). Adipose-derived Mesenchymal stem cells for the treatment of articular cartilage: A systematic review on preclinical and clinical evidence. *Stem Cells International, 2015*. https://doi.org/10.1155/2015/597652.
37. Mazor, M., Lespessailles, E., Coursier, R., Daniellou, R., Best, T. M., & Toumi, H. (2014). Mesenchymal stem-cell potential in cartilage repair: An update. *Journal of Cellular and Molecular Medicine, 18*(12), 2340–2350. https://doi.org/10.1111/jcmm.12378.
38. Maumus, M., Guérit, D., Toupet, K., Jorgensen, C., & Noël, D. (2011). Mesenchymal stem cell-based therapies in regenerative medicine: Applications in rheumatology. *Stem Cell Research & Therapy, 2*(2), 14. https://doi.org/10.1186/scrt55.
39. Djouad, F., Bouffi, C., Ghannam, S., Noël, D., & Jorgensen, C. (2009). Mesenchymal stem cells: Innovative therapeutic tools for rheumatic diseases. *Nature Reviews Rheumatology, 5*(7), 392–399. https://doi.org/10.1038/nrrheum.2009.104.