Indonesian Journal of Rheumatology
Journal Homepage: https://journalrheumatology.or.id/index.php/IJR

Efficacy and Safety of Stem Cell Transplantation in Rheumatoid Arthritis: A Systematic Review of Trials

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ARTICLE INFO

Keywords:
Hematopoietic stem cell
Mesenchymal stem cell
Rheumatoid arthritis
Stem cell transplantation

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/IJR.v15i1.241

A B S T R A C T

Background: Rheumatoid arthritis (RA) is an autoimmune disorder that deteriorates the quality and function of the synovium membrane, resulting in chronic inflammation, pain, and progressive joint destruction. Based on previous clinical research, stem cell transplantation has shown a promising therapeutic effect for RA based on its anti-inflammatory, immunomodulatory, and regenerative properties. This systematic review aims to evaluate the efficacy and safety of stem cell transplantation for rheumatoid arthritis therapy. **Methods:** A literature search was performed via PubMed, ProQuest, EBSCOHost, EMBASE, SCOPUS, Cochrane, DOAJ, and clinicaltrial.gov databases, selecting studies that evaluated the effect of stem cells on rheumatoid arthritis from inception to April 7, 2023. The Cochrane Risk of Bias was used to assess randomized controlled trials and ROBINS-I was used to assess clinical trials. **Results:** 7 randomized controlled trials (RCTs) and 12 non-randomized studies involving 682 subjects were included in this review. Stem cell transplantation was related with better outcomes based on significant improvement of the DAS28 score, HAQ score, ACR score, and laboratory parameters. There were no significant changes in safety parameters compared to the baseline value and control group. Fever, flu-like symptoms, nausea, and vomiting were the most frequently reported adverse effects. Nevertheless, this review revealed a moderate risk of bias and high heterogeneity of the efficacy outcomes of RCTs. **Conclusion:** Stem cell-based therapies provide clinical benefits for rheumatoid arthritis patients with satisfactory safety measures.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder that deteriorates the quality and function of the synovium membrane, resulting in chronic inflammation, pain, and progressive joint destruction.[1] This chronic systemic disease is estimated to affect approximately 0.24 to 1 per cent of the population and is twice as common in women compared to men.[2] Articular and systemic manifestations in RA can lead to poor long-term outcomes such as disability and death. Current conventional treatments by steroid drugs, antirheumatic drugs, and biological agents are being applied in clinical practice. However, long-term use of these drugs causes side effects, and some RA patients may develop resistance to these drugs. Currently, many treatments such as stem cell transplantation, biological preparations, and novel botanical preparations are being studied to manage patients and improve their quality of life.[1] Based on previous clinical research, stem cell transplantation has shown a promising therapeutic effect for RA based on its anti-inflammatory, immunomodulatory, and regenerative properties. It is considered safe and has a long-term potential to cure autoimmune diseases.[3]

Two stem cell lines that have been studied for RA therapy, including mesenchymal stem cell (MSC) and hematopoietic stem cell (HSC). In addition to their ability to differentiate into multiple cell lines, MSCs can modulate innate and adaptive immune responses

by alleviating the proinflammatory phenotype, particularly by decreasing populations of DCs, macrophages, NK cells, B and T cells, and promoting anti-inflammatory phenotype.[3] The HSC acts by " resetting" the dysregulated immune system of a patient with immuno-ablative therapy and allows the outgrowth of a non-aggressive immune system from reinfused hematopoietic stem cells, either from the patient (autologous HSCT) or a healthy donor (allogeneic HSCT).[4] This review aims to evaluate the efficacy and safety of stem cell transplantation for rheumatoid arthritis therapy.

2. Methods

Literature search strategy

This systematic review was created based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA). Relevant studies were retrieved from PubMed, ProQuest, EBSCOHost, EMBASE, SCOPUS, Cochrane, DOAJ, ClinicalTrials.gov from inception to April 14, 2023, with search terms as follows : (("mesenchymal stem cell transplantation"[MeSH Terms]) OR ("stem cell transplantation/therapeutic use"[MeSH Terms]) OR ("hematopoietic stem cells"[MeSH Terms])) AND ("arthritis, rheumatoid"[MeSH Terms]). The search included randomized controlled trials and clinical trials with no language restrictions applied. However, studies included in this review were restricted to English and Bahasa Indonesia, which were the only languages readable by the reviewers.

Inclusion and exclusion criteria

The inclusion criteria for the included studies were: (1) study design: randomized controlled trials (RCT) and clinical trials; (2) language: English; (3) comparison and intervention: stem cell as main treatment; and (4) outcome parameter: efficacy (DAS28, HAQ, ACR20, ACR50, ACR70, ESR, CRP, RF, anti-CCP) and safety (adverse events, Hb, Hct, RBC count, WBC count, platelet count, AST, ALT, albumin, BUN, creatinine, blood glucose, uric acid, total cholesterol, triglyceride). Furthermore, the exclusion criteria included (1) no extractable data and (2) irretrievable full-text articles.

Study selection

The selection process for the included studies in the systematic review is shown in Figure 1. The initial search yielded 3645 studies, of which 991 were duplicates, and 2635 were excluded after screening the title and/or abstract. Furthermore, the excluded studies were based on no relevance to the predefined inclusion criteria. Thus, 19 studies were included in this systematic review, of which seven were RCT and twelve were non-randomized studies.

Data extraction and quality assessment

Three independent reviewers (EF, GK, and PA), Literature search and data extraction was performed by and disagreements were resolved through discussion. The following information was extracted from each study: author and publication year, study design, study location, follow-up duration, treatment arm and additional treatment, number of patients, age of patients, gender of patients, duration of disease, number of joints pain, number of joints swelling, morning stiffness, pre-treatment DAS28, pre-treatment HAQ, pre-treatment ESR, pre-treatment CRP, pre-treatment RF, pre-treatment anti-CCP, DAS28, HAQ, ACR20, ACR50, ACR70, ESR, CRP, RF, anti-CCP, adverse events, Hb, Hct, RBC count, WBC count, platelet count, AST, ALT, albumin, BUN, creatinine, blood glucose, uric acid, total cholesterol, triglyceride.

The three reviewers (EF, GK and PA) assessed the included studie's quality. To evaluate the perceived risk of bias within the randomized controlled trials, the Cochrane Risk of Bias for Randomized Controlled Trials tool was used, while the non-randomized studies were evaluated using the Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) tool.

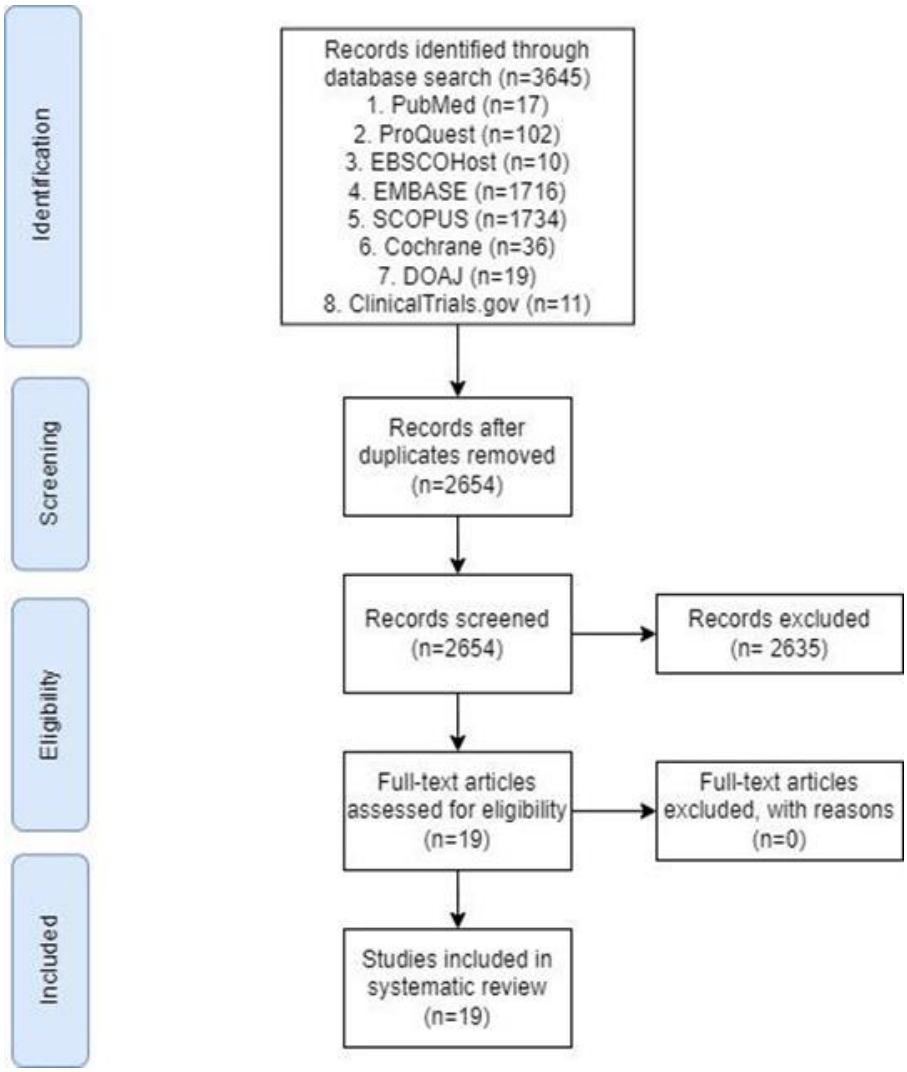

Figure 1. Literature search strategy.

3. Results

Search results

The literature searching and screening process is shown in Figure 1. Initially, 3645 studies were obtained from 8 databases. 991 duplicates removed and 2635 studies excluded after the title and abstract screening. There was no study excluded after the full text and eligibility assessment. Finally, only 19 studies were included in this review.

Study characteristics and critical appraisal

There were 7 RCT[5-11] and 12 non-randomized CT[12-23] published from 1999 to 2022, with a total of 682 samples included in this review. There were 12 studies[5,7-11,14-18,23] using mesenchymal stem cells (MSC) and 7 studies[6,12,13,19–22] using hematopoietic stem cells (HSC) as the treatment. The majority of samples were female, with mean age ranging from 37.3 to 58.43 years old. Duration of disease ranged from 3.89 to 42.7 years. Pre-treatment Disease Activity Score-28 (DAS28) and Health Assessment Questionnaire (HAQ) ranged from 4.53 to 7.0 and 0.69 to 2.51, respectively. A detail of included studies' characteristics and results is shown in Table 1. All included studies' on the risk of bias assessment showed moderate risk of bias and high heterogeneity as shown in Figure 2 for RCT and Figure 3 for non-randomized CT.

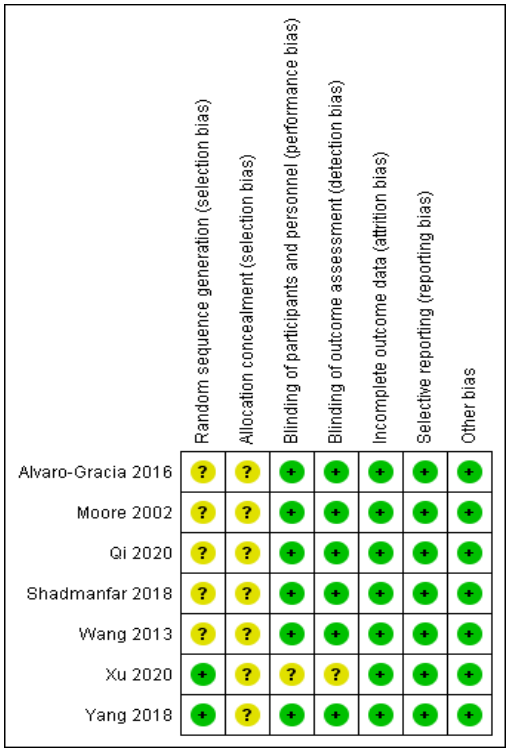

Figure 2. Risk of bias assessment for RCT.

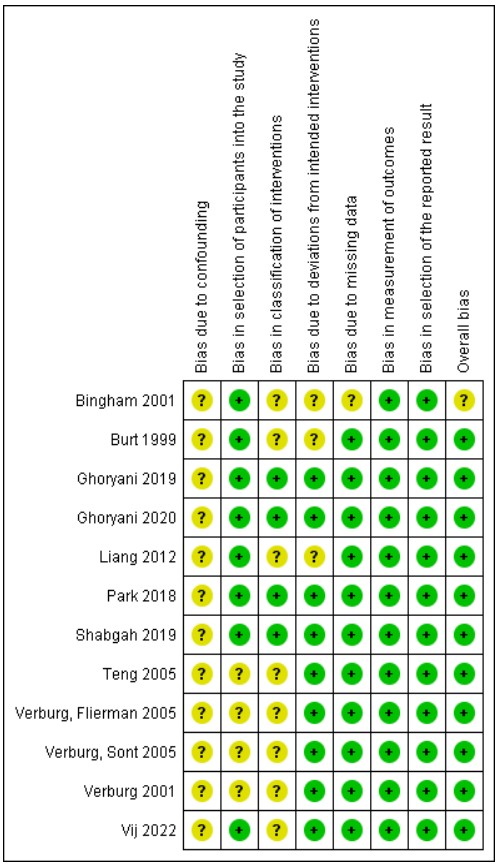

Figure 3. Risk of bias assessment for non-randomized studies.

Study outcome

The summary of included studies' outcomes is shown in Table 2.

Disease activity score-28 (DAS28)

There were significant improvements in DAS28 compared to the baseline reported by 11 studies.[5,7,8,10,14–18,20–22] Study by Alvaro-Gracia et al. (2016) showed a reduction from mean DAS28 of 6.16 to 3.2 and 2.0 after 1 month and 3 months of 4 million/kg MSC transplantation.[5] Ghoryani et al. (2019) and Ghoryani et al. (2020) reported a reduction of mean DAS28 of 5.02 to 4.45 and 4.25, and 5.56 to 5.04 and 4.72, respectively, after 1 month and 12 months of MSC transplantation.[14,15] Study by Liang et al. (2012) showed a mean DAS28 improvement of 1.7 in the first month and 2.1 in the sixth month after MSC transplantation.[16] Park et al. (2018) reported mean DAS28 reduction from 4.53 to 2.93 after 1 month, while Qi et al. (2020) reported a mean DAS28 reduction from 5.82 to 3.96 after 3 months of MSC transplantation.[7,17]Shabgah et al. (2019) reported a reduction from a mean DAS28 of 5.56 to 5.04 and 4.72 after 1 month and 12 months of MSC transplantation.[18] Meanwhile, Shadmanfar et al (2018) reported a DAS28 reduction of 0.4 after 12 months of MSC transplantation.[8] Verburg, Flierman et al. (2005), Verburg, Sont et al. (2005) and Verburg et al. (2001) reported DAS28 improvement from 5.42 to 2.63, 5.41 to 2.39 and 5.39 to 2, respectively, after 3 months HSC transplantation.[20–22] Study by Xu et al. (2020) showed a DAS28 reduction of 0.69 and 1.28 after 1 month and 12 months of MSC transplantation, respectively.[10]

Health assessment questionnaire (HAQ)

Four studies reported significant improvements in HAQ compared to baseline.[7,10,17,19] Study by Park et al. (2018) showed HAQ improvement from 0.69 to 0.54 after 1 month of MSC transplantation.17 Teng et al. (2005) reported HAQ reduction from 1.59 to 0.97 after 3 months of HSC transplantation.[19] Meanwhile, Xu et al. (2020) reported HAQ reduction of 0.17, 0.37 and 0.40 after 1 month, 3 months and 12 months of MSC transplantation, respectively.[10] However, Qi et al. (2020) reported HAQ increasing from 2.51 to 3.45 after 3 months of MSC transplantation.[7]

American College Rheumatology (ACR) score

Eleven studies did not report the American College of Rheumatology (ACR) score. Alvaro-Gracia et al. (2016) reported 3 patients achieving ACR70 until the third month after 4 million/kg MSC transplantation.[5] Bingham et al. (2001) reported 1 patient reaching ACR50 and 2 patients reaching ACR70 after HSC transplantation at the end of the study.[12] Study by Burt et al. (1999) showed 1 patient achieving ACR50 in 6 months, 3 patients achieving ACR70 in 3 months, and 1 patient achieving ACR70 in 9 months after HSC transplantation.[13] Study by Moore et al. (2002) showed 23 patients, 15 patients and 13 patients reaching ACR20, ACR50 and ACR70, respectively, after HSC transplantation in the end of the study.[6] Verburg et al. (2005) and Verburg et al. (2001) reported 5 patients reaching ACR20 and ACR50, and 2 patients reaching ACR70 12 months after HSC transplantation.[21,22] Wang et al. (2013) reported 14 patients achieving ACR20 and 3 patients achieving ACR50 and ACR70 in 6 months after MSC transplantation.[9] Meanwhile, Xu et al. (2020) reported 15 patients, 6 patients and 1 patient achieving ACR20, ACR50 and ACR70, respectively, in 12 months after MSC transplantation.[10]

Laboratory markers

All studies reported improvements in ESR, CRP, RF and anti-CCP parameters. Six studies reported a reduction of ESR after MSC transplantation.[5,7,8,14,17,18] Seven studies reported reduced CRP after MSC transplantation, and one study reported reduced CRP after HSC transplantation.[5,7,8,14,17,18,21,23] Two studies reported a reduction of RF and anti-CCP after MSC transplantation.[7,14]

Safety

Three studies reported no adverse event after MSC transplantation.[14–16] Four other studies did not report adverse events.[7,10,18,20] Alvaro-Gracia et al. (2016), Wang et al. (2013), and Yang et al. (2018) reported 9 patients, 6 patients and 3 patients with fever, respectively, after MSC transplantation.[5,9,11] Moore et al. (2002) reported 29 patients with fever, while Bingham et al. (2001) reported 3 patients with neutropenic sepsis and 1 patient with fever of unknown origin after HSC transplantation.[6,12] Alvaro-Gracia et al. (2016) reported 2 patients with influenza-like illness and 8 patients with respiratory tract infection, while Shadmanfar et al. (2018) reported 12 patients with influenza after MSC transplantation.[5,8] Alvaro-Gracia et al. (2016) also reported 5 patients with nausea and 3 with vomiting after MSC transplantation.[5] Meanwhile, Burt et al. (1999), Moore et al. (2002), Teng et al. (2005), Verburg et al. (2005) and Verburg et al. (2001) reported 4 patients, 17 patients, 8 patients, 8 patients and 12 patients with nausea and vomiting, respectively, after HSC transplantation.[6,13,19,21,22] In addition, only 5 studies reported laboratory safety parameters showing significant changes.[7,9,11,17,23]

4. Discussion

Stem cell therapeutic mechanisms in rheumatoid arthritis

Currently, promising therapeutic management of rheumatoid arthritis (RA) lies in cellular therapy, specifically stem cell transplantations. Recently studied stem cell lines for the therapeutic management of RA are mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs). Both stem cell lines have their therapeutic mechanisms in RA. MSCs are known for their self-renewal capacity, tissue and organ regeneration, and ability to modulate immune inflammatory dysregulation. On the other hand, HSCs are known for their immune reset capability but require the help of chemotherapy.

The mechanism of MSCs to self-renew, and regenerate tissues and organs and the ability to modulate inflammation makes them a potential candidate for RA management. MSCs can modulate inflammation through the alleviation of an inflammatory phenotypes. In the presence of inflammatory environment, MSCs secrete a variety of soluble factors, such as growth factors, cytokines, and enzymes, including indoleamine-2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), nitric oxide (NO), transforming growth factor-β1 (TGF-β1), hepatocyte growth factor (HGF), hemoxygenase (HO), COX-2, IL-6 and IL-10. The presence of IDO converts the essential amino acid tryptophan to kynurenine which ultimately leads to the suppression of T- cell proliferation. Moreover, IDO induces the generation of regulatory T cells (Tregs) and dendritic cells into a tolerogenic state. Furthermore, MSCs also produce nitric oxide synthase (iNOS), which induces the production of NO from macrophages leading to the inhibition of T-cell proliferation, secretory, and cytolitic function .[3] Aside from the secretion of soluble factors, the immunomodulatory effect of MSCs lies in cell-cell interaction. In the presence of an inflammatory milieu where cytotoxic cells are present, MSCs undergo caspase activation leading to apoptosis which macrophages will engulf. The engulfment of apoptotic MSCs leads to the production of IDO, which suppresses both the innate and adaptive immune system.[24]

Contrastingly, the mechanism of HSCs as therapeutic management of RA lies in the “immune reset”. HSCs, as stem cell lines that form blood and immune cells can reset self-reactive lymphocytes. The mechanism of immune reset requires the help of immuno-ablation chemotherapy, which eliminates all self-reactive immune cells, followed by the infusion of HSCs. The infusion of HSCs resets the natural course of RA autoimmunity from the complete removal of self-reactive immune cells and replacement by new immune cells from HSC differentiation.[25]

Clinical efficacy and safety of stem cell transplantation in rheumatoid arthritis

All included studies in this review exhibited

improvement in efficacy parameters and reported no significant adverse events. This result corresponds to a systematic review by Zeng et al. (2021) which showed that MSC transplantation is associated with reduced disease activity and clinical symptom improvement.[26] Although HSC transplantation is associated with overall clinical improvement and minor adverse events, a systematic review by Muthu et al. (2021) showed that the improvement effects only significantly last 2 years.[27] Several studies included in this review even demonstrated that combining a dditional therapy may enhance the efficacy of stem cell transplantation in rheumatoid arthritis. For instance, Xu et al. (2020) showed better improvement of DAS28, HAQ and ACR score in a combination with IFN-γ and MSC transplantation compared to MSC transplantation alone as IFN-γ may induce the immunosuppressive effects of MSC.[10] Another study by Qi et al. (2020) using Lugua polypeptides, traditional Chinese medicine, in combination with MSC therapy demonstrated better improvement of DAS28, HAQ and laboratory parameters compared to MSC therapy alone.[7] However, the safety outcome was not reported in both combination therapeutic studies and still must be confirmed in further research.

Applicability in clinical practice

As stated by Sarsenova et al. (2021), MSC-based therapy is widely used in clinical practice to treat various diseases. Its potent immunomodulatory properties make it highly effective in autoimmune disorders.[3] Several clinical trials have proven the efficacy and safety of stem cell therapy for RA.[28] According to the National Institutes of Health, more than 350 clinical studies on MSC-based therapy are ongoing, and about 10 are associated with RA therapy.[3]

Stem cell therapy for RA has a strong potential in Indonesia because it offers good remission outcomes with few side effects. Stem cell treatment in Indonesia is currently growing in the domain of therapeutic research. However, the number of stem cell treatment clinics in Indonesia still needs to grow. According to Regulation No. 32/2018 issued by the Indonesian Health Ministry, 11 hospitals in Indonesia are authorized to provide stem cell therapy.[29] Another limitation of the use of therapy in clinical practice is the relatively high cost of treatment.

Strengths and limitations of the study

This review includes updated clinical study results to assess the efficacy and safety of stem cell therapy in the treatment of RA. We included both randomized and non-randomized clinical trials to get as much information as possible regarding the therapeutic efficacy of stem cell therapy. The findings of this study can be utilized to make suggestions regarding the importance of stem cell research and development as a treatment option for RA. Nevertheless, the follow-up period varied widely, making it impossible to determine the safety estimation accurately. The ideal administration route, frequency, dosage, and safe repetition of MSC treatment are currently undefined. Studies with a long follow-up time and repeated administration are required to confirm safety.

Table 1. Study characteristics results.

No	Study (year)	Study Design	Study location or registry	Follow up duration	Treatment arm (with cell count)	Additional treatment (with doses)	No. of patients	Age (years)	Gender		Duration of disease (years)	Joints pain number	Joints swelling number	Morning stiffness	Other clinical characteristics	Pretreatment DAS28	Pretreatment HAQ	Pretreatment ESR (mm/hour)	Pretreatment CRP (mg/dl)	Pretreatment RF (IU/ml)	Pretreatment Anti-CCP (IU/ml)
									Male (n)	Female (n)											
1	Álvaro-Gracia (2016)	RCT	Spain	1, 2, 3 months	MSC Cx611 (1 million/kg)	N/A	20	54.14 ± 7.79	2	18	14.36 ± 6.60	29.15 ± 18.17	13.85 ± 9.24	N/A	N/A	6.24 ± 1.21	1.84 ± 0.66	37.80 ± 26.66	1.72 ± 2.27	N/A	N/A
					MSC Cx611 (2 million/kg)		20	57.40 ± 11.01	2	18	13.07 ± 9.36	11.00 ± 8.01	34.05 ± 19.92	N/A	N/A	5.78 ± 1.18	1.56 ± 0.53	34.05 ± 19.92	1.33 ± 1.41	N/A	N/A
					MSC Cx611 (4		6	50.33 ±	0	6	20.25 ± 8.12	11.50 ±	48.00 ±	N/A	N/A	6.16 ± 1.35	1.88 ± 0.51	48.00 ± 40.08	1.86 ± 1.75	N/A	N/A

					million/kg)			15.62				4.72	40.08							
					Placebo (ringer lactate)		7	58.43 ± 14.25	1	6	22.73 ± 22.65	7.14 ± 4.30	41.71 ± 19.53	N/A	N/A	5.77 ± 0.75	1.73 ± 0.74	41.71 ± 19.53	0.88 ± 0.95	N/A	N/A
2	Bingham (2001)	CT	United of Kingdom	Mean (SD): 20 (7.4) months	Autologous CD34+ cells (2 x 10^6/kg)	IV cyclophosphamide (200 mg/kg) for 4 days; mesnal antiemetic; allopurinol	6	37.3 ± 11.57	3	3	6.8 ± 5.2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3	Burt (1999)	CT	America	Unclear	Combination of CD34+, CD 3+ and CD19+ cells (various dose)	IV cyclophosphamide (200 mg/kg) for 4 days; antithymocyte globulin (90 mg/kg) for 3 days; methylprednisolone (1 gm) for 3 days	4	46.25 ± 2.68	1	3	6 ± 1.22	27 ± 7.64	32 ± 7.68	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4	Ghoryani (2019)	CT	Iran	1, 6, 12 months	Autologous bone marrow-derived MSC (1 x 10^6/kg)	Sulfasalazine (< 1-2 g/day), prednisolone (< 10-15 mg/day), methotrexate (7.5-25 mg/week, hydroxychloroquine (< 400 mg/day)	9	44.66 ± 6.50	0	9	12.87 ± 4.73	N/A	N/A	N/A	N/A	5.02 ± 0.45	N/A	11.75 ± 2.75	9.71 ± 5.03	88.13 ± 19.05	218.73 ± 41.37
5	Ghoryani (2020)	CT	Iran	1, 6, 12 months	Autologous bone marrow-derived MSC (1 x 10^6/kg)	Sulfasalazine (< 1-2 g/day), prednisolone (< 10-15 mg/day), methotrexate (7.5-25 mg/week, hydroxychloroquine (< 400 mg/day)	13	44 ± 7.50	0	13	12.16 ± 4.08	N/A	N/A	N/A	N/A	5.56 ± 0.40	N/A	N/A	N/A	N/A	N/A
6	Liang (2012)	CT	China	Mean (range): 19 (7-29) months	Bone marrow derived or umbilical cord derived MSC (1 x 10^6/kg)	Corticosteroid (with tapering off)	4	45.2 ± 7.2	0	4	42.7 ± 13.5	20 ± 4.0	15.7 ± 8.8	N/A	N/A	7.0 (0.8)	N/A	N/A	N/A	N/A	N/A
7	Moore (2002)	RCT	Australia	Monthly up to 12 months	HSCT with CD34-selected cells (2 x 10^6 cells/kg)	N/A	18	35 (22-61)	6	12	1-20	32 (9-50)	12.5 (6-34)	N/A	VAS 4.2 (2.5-8.3)	N/A	1.1 (0.7-2.0)	35 (10-97)	2.5 (0.5-14.8)	89% positive	N/A
					HSCT with unmanipulated cells (2 x 10^6 cells/kg)	N/A	15	42 (23-63)	3	12	1-20	31 (9-66)	19 (10-59)	N/A	VAS 6.5 (1.6-9.1)	N/A	1.2 (0.4-2.1)	35 (9-95)	1.85 (0.6-14.1)	80% positive	N/A
8	Park (2018)	CT	Korea	4 weeks	hUCB-MSCs 2.5 x 10^7, 5 × 10^7 , or 1 × 10^8 cells for 30 minutes	DMARD (MTX)	9	57.4 ± 10	0	9	9.5 ± 8.7	11.8 ± 16.7	2.4 ± 2.7	N/A	VAS 6.48 ± 2.02	4.53 ± 1.35	0.69 ± 0.63	23.3 ± 12	0.81 ± 1.12	66.7% positive	44.4% positive
9	Qi (2020)	RCT	China	3 months	UC-MSC cells	DMARD (MTX), leflunomide	60	44 (18-65)	7	53	10 (0.5-33)	4 (3-9)	N/A	3.1 (2-5)	N/A	5.82 ± 1.4	2.51 ± 2.01	65.07 ± 32.87	51.44 ± 37.09	251.09 ± 65.98	251.04 ± 89.98
					Cervus and cucumis peptide + UC-MSC cells	DMARD (MTX), leflunomide	59	43 (16-64)	6	53	10 (0.5-35)	4 (3-10)	N/A	3.3 (2-5)	N/A	6.05 ± 1.7	1.99 ± 1.17	52.22 ± 45.12	33.16 ± 25.37	323.01 ± 95.42	356.03 ± 112.03
10	Shabgah (2019)	CT	Iran	1, 6, 12 months	Autologous bone marrow-derived MSCs (1 x 10^6 cells/kg)	Sulfasalazine (<1-2 g/day), prednisolone (<10-15 mg/day), and/or hydroxychloroquine (<400 mg/ day), and/or methotrexate (7.5-25 mg/week)	15	44 ± 7.50	0	15	12.16 ± 4.08	N/A	N/A	N/A	VAS 7.92 ± 0.54	5.56 ± 0.40	N/A	23.75 ± 7.73	14.12 ± 5.09	N/A	N/A
11	Shadmanfar (2018)	RCT	Iran	1, 3, 6, 12 months	Autologous bone marrow-derived MSCs (42 ± 4 × 10^6 cells in 5 mL of normal	DMARD (MTX)	13	50.4 ± 8.5	0	13	N/A	N/A	0.4 ± 0.64	N/A	VAS for affected knee 3.3 (0.6); WOMAC pain 62.8 (14.0); WOMAC function	N/A	N/A	N/A	N/A	N/A	N/A

					saline)										64.2 (9.6); WOMAC stiffness 50.0 (26.6); WOMAC total 62.7 (10.4); MTX 16.2 (11.9)						
					Placebo (normal saline)	DMARD (MTX)	15	48.1 ± 10.8	2	13	N/A	N/A	0.4 ± 0.7	N/A	VAS for affected knee 3.8 (0.7); WOMAC pain 52.3 (22.1); WOMAC function 54.2 (18.7); WOMAC stiffness 35.8 (34.3); WOMAC total 52.4 (18.4); MTX 14.4 (13.0)	N/A	N/A	N/A	N/A	N/A	N/A
12	Teng (2005)	CT	Netherlands	3, 6, 9, 12, 18, 24, 60 months	Autologous CD34+ cells (2 x 10^6/kg)	IV cyclophosphamide (200 mg/kg), filgrastim (granulocyte colony-stimulating factor) (10 ug/kg/day), leukapheresis, minimal dose NSAID, corticosteroid with tapering off	8	Mean 43 (35-51)	1	7	Mean 13 (7-20)	N/A	N/A	N/A	Arthritis impact VAS (5.14 ± 0.81), general health score (50.6 ± 4.17), health change score (37.5 ± 11.6), functional status (44.6 ± 9.73)	Mean 5.4 (3.82-7.24)	1.59 ± 0.27	N/A	N/A	100% positive	N/A
13	Verburg, Flierman (2005)	CT	Netherlands	3, 12 months	Autologous CD34+ cells (2 x 10^6/kg)	IV cyclophosphamide (200 mg/kg), filgrastim (granulocyte colony-stimulating factor) (10 ug/kg/day), leukapheresis, minimal dose NSAID, corticosteroid with tapering off	7	Mean 49 (35-55)	N/A	N/A	Mean 12 (7-20)	N/A	N/A	N/A	N/A	5.42	N/A	N/A	N/A	N/A	N/A
14	Verburg, Sont (2005)	CT	Netherlands	3, 6, 12, 15, 18, 24 months	Autologous CD34+ cells (2 x 10^6/kg)	IV cyclophosphamide (200 mg/kg), filgrastim (granulocyte colony-stimulating factor) (10 ug/kg/day), leukapheresis, minimal dose NSAID, corticosteroid with tapering off	8	Mean 48 (35-55)	N/A	N/A	Mean 12.8 (7-20)	N/A	N/A	N/A	Progression of joint damage (8.9 points/year)	Mean 5.41 (3.82-7.24)	N/A	N/A	Mean 56 (0-129)	N/A	N/A
15	Verburg (2001)	CT	Netherlands	7-21 months	Autologous HSC (6.9x10^6 CD34+ cells/kg (range 4.8–11.1)	IV cyclophosphamide (200 mg/kg), filgrastim (granulocyte colony-stimulating factor) (10 ug/kg/day), leukapheresis, minimal dose NSAID, corticosteroid with tapering off	14	Mean 43 (22-55)	3	11	Mean 10 (2-20)	Mean 25 (11-49)	Mean 24 (7-39)	N/A	VAS pain (Mean 6.6 (2.2-9.7))	Mean 5.39 (3.82-7.24)	Mean 1.8 (1-2.5)	Mean 56 (12-100)	Mean 59 (6-129)	85% positive	N/A
16	Vij (2022)	CT	Texas, USA	4, 12, 26, 52 months	Adipose-derived mesenchymal stem cells (2 x 10^8 cells)	DMARD, glucocorticoid, NSAID (Unknown dose)	15	Median 52 (IQR 38-61)	1	14	Median 11.4 (IQR 6.2-26.4)	Median 20.0 (IQR 11.0–36.0)	Median 12.0 (IQR 8.0–19.0)	N/A	IL-6 (Median 4.90 (IQR 2.90–12.1)), TNF-α (Median 1.45 (IQR 0.88–3.23))	N/A	N/A	Median 43.0 (IQR 33.0–55.0)	Median 10.0 (IQR 4.50–18.1)	N/A	N/A
17	Wang (2013)	RCT	China	1 week, 3, 6, 8	Umbilical cord MSC (4.0×10^7 cells)	DMARD (Methotrexate at 7.5-10 mg/week,	172	Mean 46.1	9	127	≤2 year, n: 202–5	N/A	N/A	N/A	N/A	5.64	0.67	N/A	N/A	N/A	N/A

				months		and/or leflunomide at 10 mg/day, and/or hydroxychloroquine at 200 mg/day), NSAID (Unknown dose)					year, n: 31 >5 year, n: 85											
18	Xu (2020)	RCT	China	1, 2, 3, 4, 8, 12, 24, 48 weeks	Human umbilical cord MSC (1 x 10^6/kg) + IFN gamma	DMARDS, NSAID	30	48.3	5	25	4.21 ± 2.5	N/A	N/A	N/A	N/A	5.74 ± 0.49	1.61 ± 0.20	46.24 ± 7.70	23.78 ± 6.12	96.9% positive	93.8% positive
					Human umbilical cord MSC (1 x 10^6/kg)		30	47.8	4	26	3.93 ± 2.7	N/A	N/A	N/A	N/A	5.70 ± 0.62	1.64 ± 0.22	47.69 ± 8.58	23.04 ± 5.97	97% positive	93.9% positive
19	Yang (2018)	RCT	China	1, 2, 3, 4, 12, 24, and 48 weeks	Umbilical cord MSC (1×10 cells/kg)	DMARD, glucocorticoid, NSAID (Unknown dose, with tapering off based on status improvement)	52	Response group (50.7), non-response group (51.2)	Response group (7), non-response group (5)	Response group (21), non-response group (19)	Response group (4±2.75), non-response group (3.94±2.79)	N/A	N/A	N/A	N/A	Response group (5.45±0.54), non-response group (5.9±0.79)	Response group (1.62±0.17), non-response group (1.68±0.23)	N/A	N/A	N/A	N/A
					50 mL of 1% albumin in physiological saline		53	49.8	10	43	3.89±2.52	N/A	N/A	N/A	N/A	5.63±0.87	1.59±0.21	N/A	N/A	N/A	N/A

Table 2. Summary of study outcomes.

No.	Study (year)	Treatment arm (with cell count)	Efficacy										Safety															
			DAS28	HAQ	ACR20 (n)	ACR50 (n)	ACR70 (n)	ESR (mm/hour)	CRP (mg/dl)	RF (IU/ml)	Anti-CCP (IU/ml)	Other	Adverse event	Hb	Hct	RBC count	WBC count	Platelet count	AST	ALT	Albumin	BUN	Creatinine	Blood glucose	Uric acid	Total cholesterol	Triglyceride
1	Álvaro-Gracia (2016)	MSC (1 million/kg)	Month 1: 5.2 ± 1.6 Month 2: 5.3 ± 1.5 Month 3: 4.9 ± 1.7	N/A	Month 1: 9 Month 2: 5 Month 3: 5	Month 1: 4 Month 2: 2 Month 3: 3	Month 1: 1 Month 2: 0 Month 3: 1	N/A	Month 1: 1.0 ± 0.9 Month 2: 1.2 ± 1.2 Month 3: 1.3 ± 1.2	N/A	N/A	N/A	Fever (2), malaise (1), UTI (3), respiratory tract infection (6), ear infection (2), gastroenteritis (2), rash (2), muscular weakness (2), headache (2), nausea (4), vomiting (2), diarrhea (2), dental caries (2), anemia (1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		MSC (2 million/kg)	Month 1: 5.4 ± 1.2 Month 2: 4.7 ± 1.1 Month 3: 5.1 ± 1.1	N/A	Month 1: 4 Month 2: 6 Month 3: 3	Month 1: 0 Month 2: 3 Month 3: 1	Month 1: 0 Month 2: 1 Month 3: 0	N/A	Month 1: 1.7 ± 1.7 Month 2: 1.4 ± 1.5 Month 3: 1.7 ± 1.8	N/A	N/A	N/A	Fever (6), malaise (2), influenza-like illness (2), UTI (1), respiratory tract infection (1), headache (3), nausea (1), vomiting (1), anemia (2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		MSC (4 million/kg)	Month 1: 3.2 ± 3.0 Month 2: 3.6 ± 2.5 Month 3: 2.0 ± 0.7	N/A	Month 1: 2 Month 2: 1 Mo	Month 1: 1 Month 2:	Month 1: 1 Month 2: 1 Mo	N/A	Month 1: 1.1 ± 1.2 Month 2: 0.7 ±	N/A	N/A	N/A	Fever (1), UTI (2), respiratory tract infection (1), headache (1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

					nth 3: 1	1 Month 3: 1	nth 3: 1		0.5 Month 3: 0.7 ± 0.5																		
		Placebo	Month 1: 4.8 ± 1.0 Month 2: 6.0 ± 2.2 Month 3: 5.8 ± 0.4	N/A	Month 1: 2 Month 2: 1 Month 3: 0	Month 1: 1 Month 2: 0 Month 3: 0	Month 1: 0 Month 2: 0 Month 3: 0	N/A	Month 1: 1.0 ± 1.1 Month 2: 1.7 ± 2.7 Month 3: 1.3 ± 0.9	N/A	N/A	N/A	No adverse event	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2	Bingham (2001)	Autologous CD34+ cells (2 x 10^6/kg)	N/A	N/A	0	1	2	N/A	N/A	N/A	N/A	N/A	Neutropenic sepsis (3), bilateral pleural efufusion (1), fever of unknown origin (1), pancytopenia (1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3	Burt (1999)	Combination of CD34+, CD 3+ and CD19+ cells (various dose)	N/A	N/A	N/A	Month 6: 1	Month 1 and 3: 3 Month 9: 1	N/A	N/A	N/A	N/A	N/A	Nausea (4), vomiting (4), hair loss (4), uncomplicated bacteremia (1),	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4	Ghoryani (2019)	Autologous bone marrow-derived MSC (1 x 10^6/kg)	Month 1: 4.45 ± 0.52 Month 6: 4.74 ± 0.45 Month 12: 4.25 ± 0.66	N/A	N/A	N/A	N/A	Month 1: 7.00 ± 1.19 Month 6: 16.62 ± 4.93 Month 12: 11.62 ± 4.65	Month 1: 9.40 ± 4.59 Month 6: 7.74 ± 2.35 Month 12: 9.07 ± 4.55	Month 1: 77.51 ± 19.53 Month 6: 59.58 ± 21.10 Month 12: 65.68 ± 18.79	Month 1: 228.11 ± 43.64 Month 6: 209.83 ± 39.15 Month 12: 162.41 ± 32.83	N/A	No adverse event	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
5	Ghoryani (2020)	Autologous bone marrow-derived MSC (1 x 10^6/kg)	Month 1: 5.04 ± 0.44 Month 6: 5.06 ± 0.34 Month 12: 4.72 ± 0.50	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No adverse event	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6	Liang (2012)	Bone marrow derived or umbilical cord derived MSC (1 x 10^6/kg)	Month 1 mean improvement: 1.7 Month 6 mean improvement: 2.1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No adverse event	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7	Moore (2002)	HSCT with CD34-selected cells (2 x 10^6 cells/kg)	N/A	N/A	23	15	13	N/A	N/A	N/A	N/A	N/A	Fever (15); mucositis (7); diarrhea (12); nausea/vomiting (10); musculoskeletal pain (16); rash (8); headache (14); hypotension (4); elevated liver enzyme (2); anxiety (5)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

		HSCT with unmanipulated cells (2 x 10^6 cells/kg)	N/A	N/A				N/A	N/A	N/A	N/A		Fever (14); mucositis (7); diarrhea (8); nausea/vomiting (7); musculoskeletal pain (11); rash (11); headache (10); hypotension (3); elevated liver enzyme (1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
8	Park (2018)	2.5 x 10^7, 5 × 10^7 , or 1 × 10^8 cells of hUCB-MSCs for 30 minutes	Month 1: 2.93 ± 1.22	Month 1: 0.54 ± 0.58	N/A	N/A	N/A	Month 1 changes: -7.9 ± 10.4	Month 1 changes: -0.37 ± 1.09	N/A	N/A	Month 1: 46.9 (29.1)	Joint pain (1)	N/A	Baseline 38.54.3; week 4 38.94.8	N/A	Baseline 7.992.68; week 4 8.233.30	Baseline 292.172.6; week 4 281.6778.8	Baseline 20.25.3; week 4 23.569.7	Baseline 17.04.9; week 4 20.5610.6	Baseline 4.210.14; week 4 4.190.13	Baseline 11.92.6; week 4 13.23.9	Baseline 0.660.06; week 4 0.640.09	Baseline 108.212.9; week 4 104.68.3	Baseline 3.631.11; week 4 4.161.19	Baseline 179.030.5; week 4 186.327.3	Baseline 100.929.6; week 4 126.854.0
9	Qi (2020)	UC-MSC cells	Month 3: 3.96 ± 1.09	Month 3: 3.45 ± 1.21	N/A	N/A	N/A	Month 3: 45.97 ± 22.91	Month 3: 27.153 ± 23.02	198.08 ± 95.50	204.82 ± 84.05	N/A	N/A	N/A	N/A	Baseline: 4.07 ± 0.88; month 3 4.16 ± 0.74	Baseline: 7.01 ± 3.02; month 3: 6.95 ± 2.46	Baseline: 190.02 ± 56.55; month 3: 190.20 ± 55.76	Baseline: 30.28 ± 4.97; month 3: 32.06 ± 11.75	Baseline: 21.07 ± 5.77; month 3: 19.88 ± 11.05	Baseline: 120.51 ± 12.76; month 3: 117.50 ± 10.54	Baseline: 4.20 ± 1.66; month 3: 4.89 ± 2.04	N/A	N/A	N/A	Baseline: 40.55 ± 10.89; month 3: 42.11 ± 9.57	Baseline: 43.11 ± 12.08; month 3: 43.39 ± 10.89
		Cervus and cucumis peptide + UC-MSC cells	Month 3: 3.55 ± 1.40	Month 3: 1.11 ± 1.29	N/A	N/A	N/A	Month 3: 21.89 ± 14.53	Month 3: 18.67 ± 19.01	239.07 ± 85.58	280.22 ± 110.01	N/A	N/A	N/A	N/A	Baseline: 3.72 ± 0.44; month 3: 3.83 ± 0.59	Baseline: 6.31 ± 2.07; month 3: 6.02 ± 2.55	Baseline: 182.36 ± 70.46; month 3: 182.20 ± 65.02	Baseline: 29.42 ± 5.44; month 3: 29.79 ± 12.26	Baseline: 20.42 ± 5.40; month 3: 19.79 ± 10.36	Baseline: 108.58 ± 12.52; month 3: 110.50 ±11.89	Baseline: 4.39 ± 1.55; month 3: 4.80 ± 1.47	N/A	N/A	N/A	Baseline: 43.11 ± 11.36; month 3: 43.12 ± 10.55	Baseline: 42.31 ± 11.26; month 3: 43.52 ± 11.79
10	Shabgah (2019)	Autologous bone marrow-derived MSCs (1 x 10^6 cells/kg)	Month 1: 5.04 ± 0.44; month 6: 5.06 ± 0.34; month 12: 4.72 ± 0.50	N/A	N/A	N/A	N/A	Month 1: 14.58 ± 4.62; month 6: 14.58 ± 3.69; month 12: 15.41 ± 3.74	Month 1: 9.63 ± 3.64; month 6: 8.53 ± 2.03; month 12: 9.71 ± 3.64	N/A	N/A	VAS (month 1: 6.67 ± 0.56; month 6: 6.67 ± 0.56; month 12: 5.61 ± 0.70)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
11	Shadmanfar (2018)	Autologous bone marrow-derived MSCs (42 ± 4 × 106 cells in 5 mL of normal saline)	Month 12 mean improvement: -0.4 (-0.7--0.1)	N/A	N/A	N/A	N/A	-5.9 (-14.5-2.7)	-0.2 (-0.5-0.2)	N/A	N/A	Month 12 mean improvement: VAS -2.2 (-3.6--0.9); WOMAC pain -16.5 (-30.5--2.6); WOMAC function -16.5 (-30.4--2.6); WOMAC stiffness -8.6 (-26.4-9.1); WOMAC total -16.1 (-27.7--4.4); MTX -2.4 (-6.9-2.1)	Pain (9); migraine (2); influenza (12); rhinitis (10); sleepiness (5); allergic reaction (2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	Month 12 mean improvement: -0.4 (-0.8--	N/A	N/A	N/A	N/A	-6.1 (-17.0-4.7)	-0.3 (-0.6--0.1)	N/A	N/A	Month 12 mean improvement: VAS -1.7 (-	Pain (10); influenza (14); rhinitis (13)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

			0.1)									4.0-0.6); WOMAC pain -6.7 (-20.3-6.9); WOMAC function -9.6 (-20.8-1.6); WOMAC stiffness 3.3 (-14.1-20.8); WOMAC total -6.9 (-17.7-3.9); MTX -0.8 (-10.9-9.3)																
12	Teng (2005)	Autologous CD34+ cells (2 x 10^6/kg)	N/A	Month 3: 0.97 ± 0.18 Month 60: 1.25 ± 0.18	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Arthritis impact VAS (2.09 ± 0.88 in month 3), general health score (63.1 ± 5.90 in month 6), health change score (70.9 ± 5.81 in month 6), functional status (65.5 ± 7.03 in month 9)	Nausea (8), vomitting (8), alopecia (8), WHO grade 3 toxicity (1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
13	Verburg, Flierman (2005)	Autologous CD34+ cells (2 x 10^6/kg)	Month 3: 2.63 Month 6: 3.31	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
14	Verburg, Sont (2005)	Autologous CD34+ cells (2 x 10^6/kg)	Month 3: 2.39 (0.89-4.36) Month 24: 3.42 (1.16-4.98)	N/A	Month 12: 5 Month 24: 4	Month 12: 5 Month 24: 3	Month 12: 2 Month 24: 1	N/A	Month 3: 14 (2-24) Month 24: 40 (0-88)	N/A	N/A	Progression of joint damage (1.3 points /year in month 12; 2.7 points /year in month 24)	Nausea (8), vomitting (8), alopecia (8), thrombosis of subclavian vein (1), hydradenitis (1), metrorrhagia (1), herpes zoster (1), pseudomembranous enterocolitis (1), pneumothorax (1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
15	Verburg (2001)	Autologous HSC (6.9x10^6 CD34+ cells/kg (range 4.8–11.1)	Month 3, n: 2 Month 6, n: 3 Month 12, n: 1	N/A	Month 3: 8 Month 6: 8 Month 12: 5 Month 15: 3	Month 3: 6 Month 6: 7 Month 12: 5 Month 15: 3	Month 3: 3 Month 6: 2 Month 12: 2 Month 15: 2	N/A	N/A	N/A	N/A	N/A	Nausea (12), vomitting (12), alopecia (12), thrombosis of subclavian vein (1), hydradenitis (1), metrorrhagia (1), herpes zoster (2), pseudomembranous enterocolitis (1), pneumothorax (1), and febrile neutropenia (7), WHO grade 3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

												toxicity (3)														
16	Vij (2022)	Adipose-derived mesenchymal stem cells (2 x 10^8 cells)	N/A	N/A	N/A	N/A	N/A	Week 52: 34.5 (23.8 – 62.8)	Week 52: 6.00 (3.00– 12.0)	N/A	N/A	Tender joint counts (1.00 (0.00–4.00) in week 52), swollen joint counts (1.00 (0.00–3.00) in week 52), IL-6 (4.60 (2.75–13.9) in week 52), TNF-α (1.15 (0.73–2.28) in week 52)	Hematuria and right eyelid pruritis (1), anemia (1), thrombocytopenia (1)	Week 4: 12.4 (11.5-12.9) Week 12: 12.4 (12.0-13.1) Week 26: 12.5 (11.8-13.3) Week 52: 12.8 (11.9-13.4)	Week 4: 38.8 (37.2-40.4) Week 12: 39.4 (38.8-40.6) Week 26: 39.5 (37.6-40.8) Week 52: 40.6 (38.2-42.6)	Week 4: 4.2 (4.1-4.3) Week 12: 4.3 (4.1-4.6) Week 26: 4.4 (4.1-4.6) Week 52: 4.4 (4.1-4.7)	Week 4: 6.8 (5.9-8.7) Week 12: 6.5 (5.7-8.2) Week 26: 7.5 (5.7-10.1) Week 52: 7.2 (5.0-8.5)	Week 4: 291.5 (231.0-317.5) Week 12: 283.0 (230.0-348.0) Week 26: 320.0 (269.0-353.3) Week 52: 289.0 (254.0-328.0)	Week 4: 20.0 (16.0 - 26.3) Week 12: 17.0 (14.0 - 22.0) Week 26: 18.0 (16.0 - 24.0) Week 52: 19.0(15.0-23.5)	Week 4: 22.0 (17.8-24.5) Week 12: 19.0 (14.0-21.0) Week 26: 16.5 (13.8-22.3) Week 52: 18.0 (13.5-25.0)	Week 4: 4.3 (4.1-4.5) Week 12: 4.3 (4.1-4.5) Week 26: 4.3 (4.0-4.4) Week 52: 4.3 (4.1-4.7)	Week 4: 15.0 (11.0 - 22.0) Week 12: 15.0 (12.0 - 20.0) Week 26: 14.5 (11.0 - 16.5) Week 52: 12.0 (10.0 - 16.5)	Week 4: 0.7(0.6-0.9) Week 12: 0.8 (0.6-1.0) Week 26: 0.8 (0.6-0.9) Week 52: 0.7 (0.7-0.8)	Week 4: 85.5 (78.8 - 90.5) Week 12: 91.0 (86.0 - 96.0) Week 26: 85.5 (81.0 - 91.0) Week 52: 92.0 (86.5 -103)	N/A	N/A	N/A
17	Wang (2013)	Umbilical cord MSC (4.0×10^7 cells) + DMARD	N/A	N/A	Month 6: 14 (58%)	Month 6: 3 (13%)	Month 6: 3 (13%)	N/A	N/A	N/A	N/A	N/A	Fever (6)	112.09 ±14.50	N/A	N/A	6.00 ±2.18	222.88 ±97.23	N/A	N/A	36.69 ±4.95 g/L	5.39 ±1.73 mM	50.72 ±16.11 uM	4.66 ±0.90 mM	N/A	4.37± 0.97 mM	1.51± 0.77 mol/L
		Medium + DMARD	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	103.56 ±16.39	N/A	N/A	5.96 ±1.04	241.25 ±65.75	N/A	N/A	37.61 ±4.22 g/L	5.15 ±1.51 mM	49.57 ±8.38 uM	4.81 ±0.80 mM	N/A	4.19± 1.21 mM	1.49± 0.76 mol/L
18	Xu (2020)	Human umbilical cord MSC (1 x 10^6/kg) + IFN gamma	Month 1 difference: -2.14 ± 0.60 Month 3 difference: -2.51 ± 0.58 Month 12 difference: -2.54 ± 0.60	Month 1 difference: -0.59 ± 0.28 Month 3 difference: -0.73 ± 0.24 Month 12 difference: -0.87 ± 0.27	Month 1: 26 Month 3: 28 Month 12: 28	Month 1: 10 Month 3: 11 Month 12: 11	Month 1: 3 Month 3: 4 Month 6: 4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Human umbilical cord MSC (1 x 10^6/kg)	Month 1 difference: -0.69 ± 0.64 Month 3 difference: -1.05 ± 0.95 Month 12 difference: -1.28 ± 1.03	Month 1 difference: -0.17 ± 0.29 Month 3 difference: -0.37 ± 0.24 Month 12 difference: -0.40 ± 0.26	Month 1: 7 Month 3: 16 Month 12: 15	Month 1: 2 Month 3: 6 Month 12: 6	Month 1: 1 Month 3: 1 Month 12: 1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
19	Yang (2018)	Umbilical cord MSC (1×10 cells/kg)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Fever (3)	Response (113.46 ± 16.62), non-response (103.24 ± 19.21)	N/A	N/A	Response (5.59 ± 1.47), non-response (5.78 ± 1.26)	Response (223.19 ± 65.87), non-response (262.31 ± 72.78)	N/A	N/A	Response (40.63 ± 3.25), on-response (32.57 ± 3.54)	N/A	Response (45.25 ± 14.21), non-response (45.36 ± 12.38)	Response (4.75 ± 0.86), non-response (4.84 ± 0.96)	N/A	Response (4.28 ± 1.93), non-response (4.23 ± 1.53)	Response (1.43 ± 0.58), non-response (1.49 ± 0.83)
		50 mL of 1% albumin in physiological saline	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

5. Conclusion

Stem cell transplantation in rheumatoid arthritis is associated with an improvement in efficacy parameters and no significant changes in safety parameters.

6. References

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