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Original Article

Analysis of efficacy and safety of mesenchymal stem cell and hematopoietic stem cell transplantation in rheumatoid arthritis: a systematic review and meta analysis of trials

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Objective: Rheumatoid arthritis (RA) is an inflammatory condition that causes persistent inflammation by deteriorating the quality and function of the synovium. Prior clinical studies on stem cell transplantation demonstrated promising anti-inflammatory, immunomodulatory, and regenerative benefit for RA. The goal of this study is to assess the efficacy and safety of stem cell transplantation for the management of RA.

Methods: Literature searching was conducted using PubMed, EMBASE, Scopus, Cochrane, ProQuest and EBSCOHost databases, including papers evaluating the efficacy of stem cells on RA. Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) was used to analyze clinical trials and the Cochrane Risk of Bias tool was used for randomized controlled trials (RCTs).

Results: This meta-analysis includes 7 RCTs and 12 non-randomized clinical trials involving 682 individuals. Stem cell transplantation was associated with improved efficacy outcomes based on significant improvements in the 1, 3, 6, and 12 months of Disease Activity Score-28 (DAS28); 1 and 3 months of erythrocyte sedimentation rate; 6 and 12 months of C-reactive protein. The most often reported side effects were fever, flu-like symptoms, nausea, and vomiting. Nonetheless, this meta-analysis found a moderate risk of bias with high heterogeneity in all included studies.

Conclusion: Stem cell transplantation offers clinical advantages for RA patients with acceptable safety measures.

Keywords: Hematopoietic stem cells, Mesenchymal stem cells, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that causes a decline in the physiological function of the synovial membrane, characterized by persistent inflammation, tenderness, and gradual joint impairment [1]. With an estimated prevalence of 0.24 to 1 percent of the population, this condition affects female twice as much as males [2]. Articular and systemic signs of RA can result in long-term consequences such as disability and mortality. In clinical practice, current standard treatments such as steroid medications, antirheumatic medicines, and biological agents are used. Nevertheless, prolonged use RA medications generates unfavorable effects, and some drug resistance may occur. Many treatments are now being researched to treat the disease and enhance patient's quality of life, including biological preparations, stem cell transplantation, and innovative plant preparations [1]. Prior clinical studies revealed a promising regenerative, immunomodulatory, and

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anti-inflammatory effects of stem cell transplantation for RA. Stem cell therapy has good safety profile with the potential to treat autoimmune diseases in the future [3].

Hematopoietic stem cell (HSC) and mesenchymal stem cell (MSC) are types of stem cell that have been investigated as RA treatment. The MSCs modulate immune responses by attenuating the proinflammatory components, as well as supporting anti-inflammatory processes [3]. The HSCs functions through dysregulated immune system reset, thus permitting the regrowth of non-aggressive immune cells from HSCs [4]. The purpose of this study is to assess the effectiveness and safety profile of stem cell transplantation as RA treatment.

MATERIALS AND METHODS

Ethical statement

This study being a systematic review and meta-analysis did not require formal ethical approval as per the policy of the Cipto Mangunkusumo Hospital-Faculty of Medicine, University of Indonesia ethical committee.

Literature search strategy

Our systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We conducted comprehensive searches across multiple databases, including PubMed, Cochrane, ProQuest, EMBASE, EBSCOHost, and Scopus. The search encompassed studies from the inception of these databases up to April 2023. Our search query included the following keywords: ((("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]). We did not apply any language restrictions, but randomized controlled trials (RCTs) and clinical trials filter was used in literature searching.

Inclusion and exclusion criteria

For our study selection, we established specific inclusion criteria: (1) study design: randomized and non-randomized trials; (2) articles in English; (3) comparison and intervention: studies focusing on stem cell therapy as the primary treatment; (4) outcome parameters: efficacy (using parameters such as Disease Activity Score-28 [DAS28], Health Assessment Questionnaire [HAQ], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) and safety (adverse events). The exclusion criteria of this study: (1) studies with no available data for extraction and (2) articles with irretrievable full-text.

Study selection

Figure 1 illustrates the process of selecting studies for inclusion in our systematic review. Initially, our search yielded a total of 3,645 studies, with 991 duplicates. After the initial screening of titles and/or abstracts, 2,635 studies were excluded as they did not meet the predefined inclusion criteria. The excluded studies were not relevant to our study objectives. Consequently, we included 19 studies in our systematic review, comprising seven RCTs and twelve non-randomized trials.

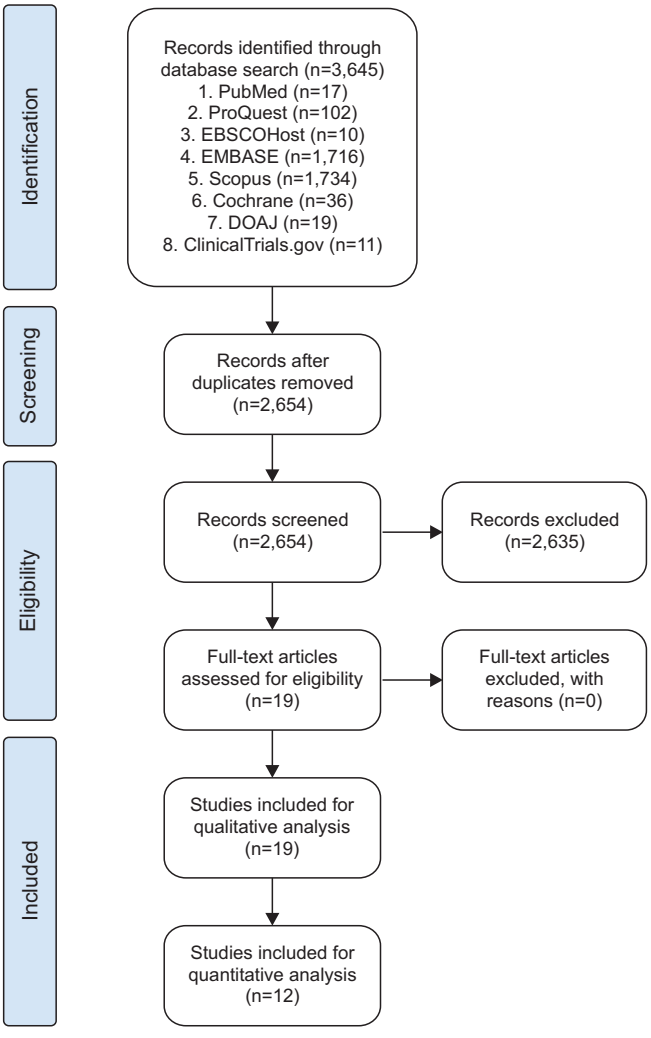


Figure 1. Literature search strategy.

Data selection, extraction and quality assessment

A team of four independent reviewers (EF, GK, PA, and KK) conducted the literature searching, data selection, and extraction. Any disagreements among reviewers were settled through discussion. The information extracted from the selected studies included details such as author names, year of publication, study design, location of trials, duration of follow-up, treatment protocols, patient demographics, disease characteristics, and various outcome measures (e.g., DAS28, HAQ, ESR, CRP, rheumatoid factor, anti-cyclic citrullinated peptide, and adverse events).

Quality assessment of included studies was carried out by the same four independent reviewers (EF, GK, PA, and KK). We used the Cochrane Risk of Bias for Randomized Controlled Trials tool to evaluate the perceived risk of bias in RCTs. Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) tool was employed to assess the perceived risk of bias of non-randomized trials.

Quantitative analysis

Mean difference of DAS28, HAQ, ESR, and CRP were analyzed by comparing before and after stem cell transplantation. Analysis was done using RevMan ver 5.4.1 with 95% confidence interval (CI) calculating pooled mean difference from mean and standard deviation before and after treatment. Random effect analysis model was used for all parameters as studies included were heterogenous. Subgroup analysis was performed to separate mesenchymal stem cell transplantation (MSCT) studies from hematopoietic stem cell transplantation (HSCT) studies whenever possible. Data distribution was assessed by calculating indexes of heterogeneity (Chi^2, I^2, and tau^2).

RESULTS

Search results

Literature searching from 8 databases yielded 3,645 articles. After removing 991 duplicates and excluding 2,635 for title and abstract screening, there were 19 studies included in systematic review. Only 12 studies were included for quantitative synthesis. Figure 1 illustrated the flowchart of literature screening process.

Study characteristics and critical appraisal

This review included 7 RCT [5-11] and 12 non-randomized

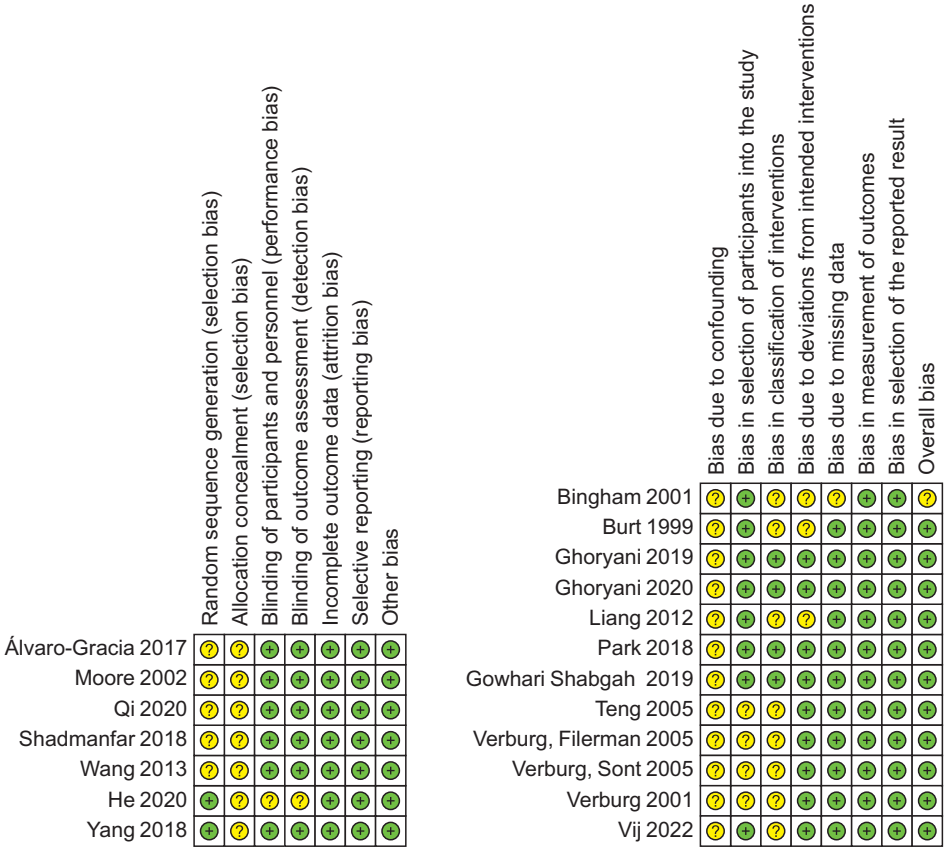
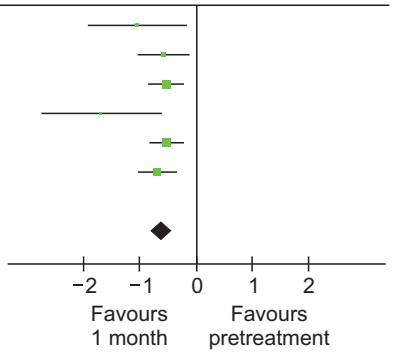


Figure 2. Risk of bias assessment of clinical trials (left) and non-randomized studies (right).

A

Study or subgroup	Favours 1 month Mean	SD	Total	Pretreatment Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Álvaro-Gracia 2017	5.2	1.6	20	6.24	1.21	20	4.3%	−1.04 [−1.92, −0.16]
Ghoryani 2019	4.45	0.52	9	5.02	0.45	9	14.9%	0.57 [−1.02, −0.12]
Ghoryani 2020	5.04	0.44	13	5.56	0.4	13	25.9%	−0.52 [−0.84, −0.20]
Liang 2012	5.3	0.75	4	7	0.8	4	2.9%	−1.70 [−2.77, −0.63]
Gowhari Shabgah 2019	5.04	0.44	15	5.56	0.4	15	29.0%	−0.52 [−0.82, −0.22]
He 2020	5.01	0.75	30	5.7	0.62	30	23.0%	−0.69 [−1.04, −0.34]
Total (95% CI)			91			91	100.0%	−0.62 [−0.81, −0.44]

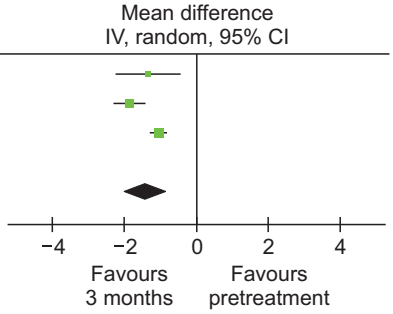
Heterogeneity: Tau^2=0.01; Chi^2=5.74, df=5 (p=0.33); I^2=13%
Test for overall effect: Z=6.61 (p<0.00001)



B

Study or subgroup	3 months Mean	SD	Total	Pretreatment Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Álvaro-Gracia 2017	4.9	1.7	20	6.24	1.21	20	22.1%	−1.34 [−2.25, −0.43]
Qi 2020	3.96	1.09	60	5.82	1.4	60	36.0%	−1.86 [−2.31, −1.41]
He 2020	4.65	0.2636	30	5.7	0.62	30	41.9%	−1.05 [−1.29, −0.81]
Total (95% CI)			110			110	100.0%	−1.41 [−2.01, −0.80]

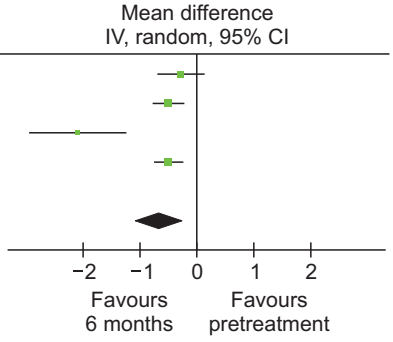
Heterogeneity: Tau^2=0.21; Chi^2=9.76, df=2 (p=0.008); I^2=80%
Test for overall effect: Z=4.57 (p<0.00001)



C

Study or subgroup	6 months Mean	SD	Total	Pretreatment Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Ghoryani 2019	4.74	0.45	9	5.02	0.45	9	25.8%	−0.28 [−0.70, 0.14]
Ghoryani 2020	5.06	0.34	13	5.56	0.4	13	29.8%	−0.50 [−0.79, −0.21]
Liang 2012	4.9	0.376	4	7	0.8	4	13.9%	−2.10 [−2.97, −1.23]
Gowhari Shabgah 2019	5.06	0.34	15	5.56	0.4	15	30.4%	−0.50 [−0.77, −0.23]
Total (95% CI)			41			41	100.0%	−0.67 [−1.08, −0.25]

Heterogeneity: Tau^2=0.13; Chi^2=14.10, df=3 (p=0.003); I^2=79%
Test for overall effect: Z=3.12 (p=0.002)



D

Study or subgroup	12 months Mean	SD	Total	Pretreatment Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Ghoryani 2019	4.25	0.66	9	5.02	0.45	9	16.3%	−0.77 [−1.29, −0.25]
Ghoryani 2020	4.72	0.5	13	5.56	0.4	13	25.3%	−0.84 [−1.19, −0.49]
Gowhari Shabgah 2019	4.72	0.5	15	5.56	0.4	15	26.9%	−0.84 [−1.16, −0.52]
He 2020	4.42	0.3825	30	5.7	0.62	30	31.4%	−1.28 [−1.54, −1.02]
Total (95% CI)			67			67	100.0%	−0.97 [−1.23, −0.70]

Heterogeneity: Tau^2=0.04; Chi^2=6.91, df=3 (p=0.07); I^2=57%
Test for overall effect: Z=7.18 (p<0.00001)

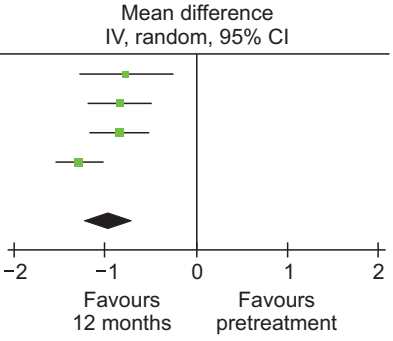


Figure 3. Forest plot of Disease Activity Score-28 (DAS28) after 1-, 3-, 6-, and 12-month of mesenchymal stem cell transplantation (A~D) and 3-month of hematopoietic stem cell transplantation (E). SD: standard deviation, CI: confidence interval.

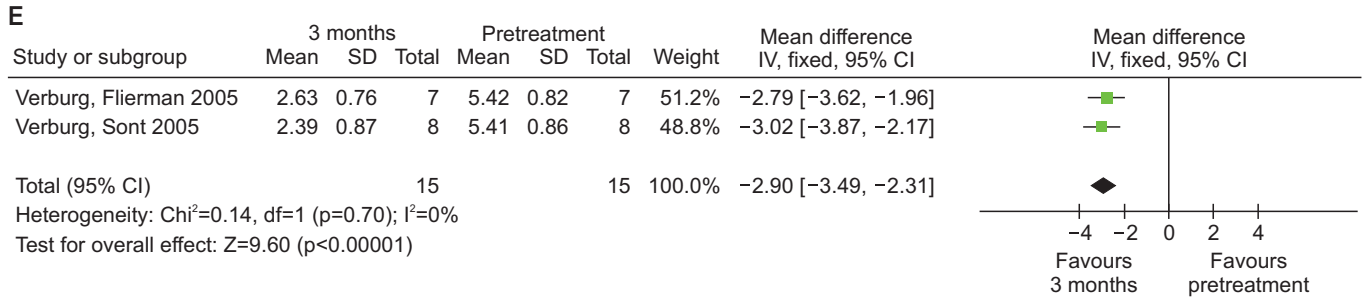


Figure 3. Continued.

CT [12-23] which were published from 1999 to 2022. There were 12 studies [5,7-11,14-18,23] performing MSCT and 7 studies [6,12,13,19-22] performing HSCT. A total of 682 samples have mean age ranged from 37.3 to 58.43 years old which majority were female with mean disease duration ranged from 3.89 to 42.7 years. Mean of pretreatment DAS28 ranged from 4.53 to 7.0, while mean of pretreatment HAQ ranged from 0.69 to 2.51. Further information of studies baseline characteristics can be seen in Supplementary Table 1. Risk of bias assessment revealed moderate risk of bias for both clinical trials and non-randomized studies as shown in Figure 2.

Study outcome

1) Disease Activity Score-28

Our analysis showed considerable improvement of DAS28 on 1, 3, 6, and 12 months after MSC transplantation and 3 months following HSC transplantation, as depicted in Figure 3. Mean difference of DAS28 after 1, 3, 6, and 12 months MSCT compared to pretreatment were −0.62 (95% CI [−0.81, −0.44], p<0.00001); −1.41 (95% CI [−2.01, −0.80], p<0.00001); −0.67 (95% CI [−1.08, −0.25], p=0.002); and −0.97 (95% CI [−1.23, −0.70], p<0.00001), as shown in Table 1. After 3 months and 6 months HSCT, mean difference was −2.90 (95% CI [−3.49, −2.31], p<0.00001) and −2.11 (95% CI [−2.62, −1.60], p<0.00001), respectively.

2) Health Assessment Questionnaire

This meta-analysis revealed an improvement of HAQ score 3 months after stem cell transplantation compared to pretreatment state, although not statistically significant (Figure 4). Overall, HAQ score mean difference was −0.09 (95% CI [−0.71, 0.53], p=0.19) with MSCT HAQ score mean difference of 0.26 (95% CI [−1.03, 1.54], p=0.69) and HSCT HAQ score mean difference of −0.62 (95% CI [−0.84, −0.40], p<0.00001), as shown in Table 1.

Laboratory parameters

Decrease of ESR mean was found after 1, 3, 6, and 12 months MSCT, however, loss of statistical significancy of ESR mean difference was noted in 6 and 12 months MSCT as depicted in Figure 5. Table 1 showed ESR mean difference of −6.43 (95% CI [−9.57, −3.30], p<0.0001); −19.10 (95% CI [−29.24, −8.96], p=0.0002); −2.10 (95% CI [−15.86, 11.66], p=0.76) and −4.69 (95% CI [−11.64, 2.27], p=0.19) after 1, 3, 6, and 12 months MSCT, respectively.

CRP mean value was reduced 1, 3, 6, and 12 months following stem cell transplantation, although it was only statistically significant starting 6 and 12 months after stem cell transplantation as illustrated in Figure 6. Table 1 showed CRP mean difference of −1.21 (95% CI [−2.75, 0.32], p=0.12); −11.70 (95% CI [−35.05, 11.66], p=0.33); −3,98 (95% CI [−7.50, −0.45], p=0.03); and −3.27 (95% CI [−5.64, −0.89], p=0.007) after 1, 3, 6, and 12 months MSCT, respectively.

Safety

Four studies did not mention any adverse event after stem cell transplantation [7,10,18,21], meanwhile three studies revealed no adverse event after MSCT [14-16]. Mild adverse events such as fever and nausea/vomiting were the most common adverse event by the included studies. Hair loss, headache, and musculoskeletal problems were reported as other common adverse event by several studies [5,6,8,13,19,20,22]. Table 2 summarizes adverse events found in the studies.

DISCUSSION

Therapeutic mechanisms of stem cell in rheumatoid arthritis

Stem cell transplantation is one of a few promising management approaches for RA. The research about MSCs and HSCs

Table 1. Efficacy of included studies

No.	Study (year)	Treatment arm (with cell count)	Efficacy					
			DAS28	HAQ	ESR (mm/hour)	CRP (mg/dL)	RF (IU/mL)	Anti-CCP (IU/mL)
1	Álvaro-Gracia (2017) [5]	MSC (1×10^6/kg)	Month I: 5.2 (1.6) Month II: 5.3 (1.5) Month III: 4.9 (1.7)	N/A	N/A	Month I: 1.0 (0.9) Month II: 1.2 (1.2) Month III: 1.3 (1.2)	N/A	N/A
		MSC (2×10^6/kg)	Month I: 5.4 (1.2) Month II: 4.7 (1.1) Month III: 5.1 (1.1)	N/A	N/A	Month I: 1.7 (1.7) Month II: 1.4 (1.5) Month III: 1.7 (1.8)	N/A	N/A
		MSC (4×10^6/kg)	Month I: 3.2 (3.0) Month II: 3.6 (2.5) Month III: 2.0 (0.7)	N/A	N/A	Month I: 1.1 (1.2) Month II: 0.7 (0.5) Month III: 0.7 (0.5)	N/A	N/A
		Placebo	Month I: 4.8 (1.0) Month II: 6.0 (2.2) Month III: 5.8 (0.4)	N/A	N/A	Month I: 1.0 (1.1) Month II: 1.7 (2.7) Month III: 1.3 (0.9)	N/A	N/A
2	Bingham (2001) [12]	Autologous CD34+ cell (2×10^6/kg)	N/A	N/A	N/A	N/A	N/A	N/A
3	Burt (1999) [13]	Combination of CD34+, CD3+ and CD19+ cells (various dose)	N/A	N/A	N/A	N/A	N/A	N/A
4	Ghoryani (2019) [14]	Autologous bone marrow-derived MSC (1×10^6/kg)	Month I: 4.45 (0.52) Month VI: 4.74 (0.45) Month XII: 4.25 (0.66)	N/A	Month I: 7.00 (1.19) Month VI: 16.62 (4.93) Month XII: 11.62 (4.65)	Month I: 9.40 (4.59) Month VI: 7.74 (2.35) Month XII: 9.07 (4.55)	Month I: 77.51 (19.53) Month VI: 59.58 (21.10) Month XII: 65.68 (18.79)	Month I: 228.11 (43.64) Month VI: 209.83 (39.15) Month XII: 162.41 (32.83)
5	Ghoryani (2020) [15]	Autologous bone marrow-derived MSC (1×10^6/kg)	Month I: 5.04 (0.44) Month VI: 5.06 (0.34) Month XII: 4.72 (0.50)	N/A	N/A	N/A	N/A	N/A
6	He (2020) [10]	Human umbilical cord MSC (1×10^6/kg)+IFN-γ	Month I difference: −2.14 (0.60) Month III difference: −2.51 (0.58) Month XII difference: −2.54 (0.60)	Month I difference: −0.59 (0.28 Month III difference: −0.73 (0.24) Month XII difference: −0.87 (0.27)	N/A	N/A	N/A	N/A
		Human umbilical cord MSC (1×10^6/kg)	Month I difference: −0.69 (0.64) Month III difference: −1.05 (0.95) Month XII difference: −1.28 (1.03)	Month I difference: −0.17 (0.29) Month III difference: −0.37 (0.24) Month XII difference: −0.40 (0.26)	N/A	N/A	N/A	N/A

Table 1. Continued 1.

No.	Study (year)	Treatment arm (with cell count)	Efficacy					
			DAS28	HAQ	ESR (mm/hour)	CRP (mg/dL)	RF (IU/mL)	Anti-CCP (IU/mL)
7	Liang (2012) [16]	Bone marrow-derived or umbilical cord-derived MSC (1×10^6/kg)	Month I mean improvement: 1.7 Month VI mean improvement: 2.1	N/A	N/A	N/A	N/A	N/A
8	Moore (2002) [6]	HSC with CD34-selected cell (2×10^6/kg)	N/A	N/A	N/A	N/A	N/A	N/A
		HSC with unmanipulated cell (2×10^6/kg)	N/A	N/A	N/A	N/A	N/A	N/A
9	Park (2018) [17]	hUCB-MSC (2.5×10^7/kg, 5×10^7/kg, 1×10^8/kg)	Month I: 2.93 (1.22)	Month I: 0.54 (0.58)	Month I difference: −7.9 (10.4)	Month I difference: −0.37 (1.09)	N/A	N/A
10	Qi (2020) [7]	UC-MSC	Month III: 3.96±1.09	Month III: 3.45±1.21	Month III: 45.97±22.91	Month III: 27.153±23.02	198.08±95.50	204.82±84.05
		Cervus and cucumis peptide+UC-MSC	Month III: 3.55±1.40	Month III: 1.11±1.29	Month III: 21.89±14.53	Month III: 18.67±19.01	239.07±85.58	280.22±110.01
11	Gowhari Shabgah (2019) [18]	Autologous bone marrow-derived MSCs (1×10^6/kg)	Month I: 5.04±0.44 Month VI: 5.06±0.34 Month XII: 4.72±0.50	N/A	Month I: 14.58±4.62 Month VI: 14.58±3.69 Month XII: 15.41±3.74	Month I: 9.63±3.64 Month VI: 8.53±2.03 Month XII: 9.71±3.64	N/A	N/A
12	Shadmanfar (2018) [8]	Autologous bone marrow-derived MSCs ($42\pm4\times10^6$ cells in 5 mL of normal saline)	Month XII mean improvement: −0.4 (−0.7 to −0.1)	N/A	−5.9 (−14.5~2.7)	−0.2 (−0.5~0.2)	N/A	N/A
		Placebo	Month XII mean improvement: −0.4 (−0.8 to −0.1)	N/A	−6.1 (−17.0~4.7)	−0.3 (−0.6 to −0.1)	N/A	N/A
13	Teng (2005) [19]	Autologous CD34+ cell (2×10^6/kg)	N/A	Month III: 0.97±0.18 Year V: 1.25±0.18	N/A	N/A	N/A	N/A
14	Verburg (2005) [20]	Autologous CD34+ cell (2×10^6/kg)	Month III: 2.63 Month VI: 3.31	N/A	N/A	N/A	N/A	N/A
15	Verburg, (2005) [21]	Autologous CD34+ cell (2×10^6/kg)	Month III: 2.39 (0.89~4.36) Year II: 3.42 (1.16~4.98)	N/A	N/A	Month III: 14 (2~24) Year II: 40 (0~88)	N/A	N/A
16	Verburg (2001) [22]	Autologous HSC (6.9×10^6 CD34+ cells/kg)	Month III, n: 2 Month VI, n: 3 Month XII, n: 1	N/A	N/A	N/A	N/A	N/A

Table 1. Continued 2.

No.	Study (year)	Treatment arm (with cell count)	Efficacy					
			DAS28	HAQ	ESR (mm/hour)	CRP (mg/dL)	RF (IU/mL)	Anti-CCP (IU/mL)
17	Vij (2022) [23]	Adipose-derived MSC (2×10^8/kg)	N/A	N/A	Year I: 34.5 (23.8~62.8)	Year I: 6.00 (3.00~12.0)	N/A	N/A
18	Wang (2013) [9]	Umbilical cord MSC (4.0×10^7/kg)+DMARD	N/A	N/A	N/A	N/A	N/A	N/A
		Medium+DMARD	N/A	N/A	N/A	N/A	N/A	N/A
19	Yang (2018) [11]	Umbilical cord MSC (1×10^6/kg)	N/A	N/A	N/A	N/A	N/A	N/A
		50 mL of 1% albumin in physiological saline	N/A	N/A	N/A	N/A	N/A	N/A

DAS28: Disease Activity Score-28, HAQ: Health Assessment Questionnaire, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RF: rheumatoid factor, CCP: cyclic citrullinated peptide, MSC: mesenchymal stem cell, HSC: hematopoietic stem cell, UK: United of Kingdom, DMARD: disease-modifying antirheumatic drug, hUCB: human umbilical cord blood-derived, UC-MSC: umbilical cord mesenchymal stem cells, N/A: not available.

roles in RA therapy keep progressing, with these two stem cell lines having different mechanism in the management of RA. Self-renewal ability, tissue and organ revitalization, and modulation of inflammatory dysregulation are known to be MSCs therapeutic mechanisms. Meanwhile, immune reset capability with the help of chemotherapy is specifically known to be HSCs therapeutic mechanisms [24,25].

The MSCs have the ability to self-regenerate and modulate inflammation, thus presenting itself to be a potential candidate in the management of RA. The MSCs modulates inflammation through the alteration of the secretion of growth factors, cytokines, and enzymes, such as indoleamine-2,3-dioxygenase (IDO), nitric oxide (NO), prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), hemoxygenase (HO), cyclooxygenase-2 (COX-2), transforming growth factor-β1 (TGF-β1), interleukin (IL)-6, and IL-10. Secretion of IDO allows the suppression of T cells proliferation through the convertion of essential amino acid tryptophan to kynurenine. Furthermore, IDO is able to generate regulatory T cells (Tregs) and causes tolerogenic dendritic cells. Moreover, the production of nitric oxide synthase (iNOS) inhibits the secretory, proliferation, and cytolytic function of T cells through the production of NO by macrophages [3]. Cell-cell interaction also plays a role in the immunomodulatory mechanism of MSCs. With the presence of cytotoxic cells, the inflammatory milieu causes caspase activation of MSCs leading to their apoptosis and engulfment by macrophages. The engulfment of MSCs produces IDO which suppresses the immune system [26].

On the other hand, HSCs rely on the "immune reset" mechanism for the therapeutic management of RA. As old self-reactive cells are removed, HSCs form new blood and immune cells which renews the patient's cells. The removal of self-reactive cells uses the immune-ablation chemotherapy. Once the cells have been eliminated, HSCs were obtained from the patient (autologous) or healthy donor (allogeneic) and infused to replace it with new healthy differentiated immune cells [25].

The efficacy and safety of stem cell transplantation in rheumatoid arthritis

Overall, improvements in efficacy parameters were found without any notable adverse events reported. Decreased disease activity and improvements in clinical symptoms after MSC transplantation have been reported by Zeng et al. (2022) [27].

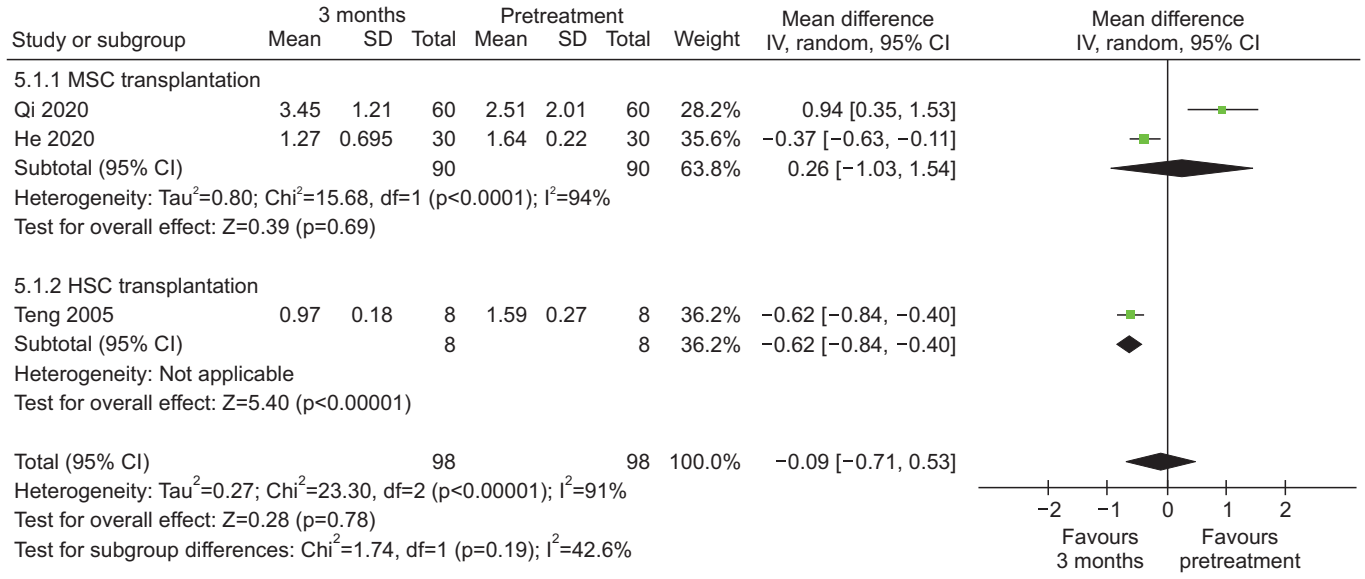


Figure 4. Forest plot of Health Assessment Questionnaire (HAQ) after 3 months stem cell transplantation. MSC: mesenchymal stem cell, HSC: hematopoietic stem cell, SD: standard deviation, CI: confidence interval.

A study by Muthu et al. (2021) [28] have reported the effect lasted significantly for 2 years. Moreover, studies demonstrated the combination of additional treatment may strengthen the efficacy of stem cell transplantation in RA patients. A study by He et al. (2020) [10] reported better improvements of DAS28, ACR, and HAQ score using MSCT combined with IFN-γ compared to MSCT alone due to the induction of immunosuppressive effects of IFN-γ towards MSCs. Another report by Qi et al. (2020) [7] demonstrated better improvements of HAQ, DAS28, and laboratory parameters with traditional Chinese medicine called Lugua polypeptides in combination with MSCT compared to MSCT alone. Although the efficacy of combination therapy was reported, both studies did not report the safety regarding the combined treatment, thus further studies regarding the safety are needed.

The DAS28 is a widely used evaluation tool for RA activity that includes clinical joint symptoms, overall health, and laboratory markers [29]. This meta-analysis showed that the DAS28 score was significantly lower 1, 3, 6, and 12 months following MSC transplantation compared to the baseline state. The majority of studies revealed a moderate response of DAS28 to stem cell therapy in accordance with The European League Against Rheumatism response criteria [30]. Additionally, the majority of the studies that were included discovered that DAS28 continued to improve during the follow-up period. MSCs have the capacity to reduce inflammation both through paracrine processes and interactions with immune system cells. MSCs decreased pro-inflammatory cytokines such as IL-1β and IL-6 significantly, whereas the level of anti-inflammatory cytokine (IL-10) is increased [3]. In the Wang et al. (2013) [9] study, the treatment of UC-MSCs substantially increased the amount of regulatory T cells in peripheral blood as well as IL-4 expression released by Th2 cells. The elevated level of regulatory T cells was positively connected with the improvement in disease state.

According to some studies, MSCs may inhibit immune cells in vitro in a dose-dependent way [31]. Recently, in a more focused research, Zheng et al. (2008) [32] demonstrated that collagen-type II-stimulated T cell proliferation and activation may be inhibited by allogeneic MSCs in a dose-dependent manner, proving substantial dosages of MSCs are required for the treatment. On the other hand, the development of the inflammatory microenvironment is necessary for the immunomodulatory actions of MSCs. The immunosuppressive functions of MSCs are triggered by IFN-γ and other proinflammatory cytokines (IL-1α, IL-1β, or TNF-α) via high level expression of inducible iNOS and chemokines. This is further supported by the rapid elevation of Treg/Th17 ratio in the RA patients treated with MSCT+IFN-γ. On the contrary, dexamethasone influences the immunoregulatory ability of MSCs by interfering with the expression of iNOS and IDO, suggesting an avoidance of combining immunosuppressive agents and MSCs [10].

MSCT's therapeutic effects may persist for at least three

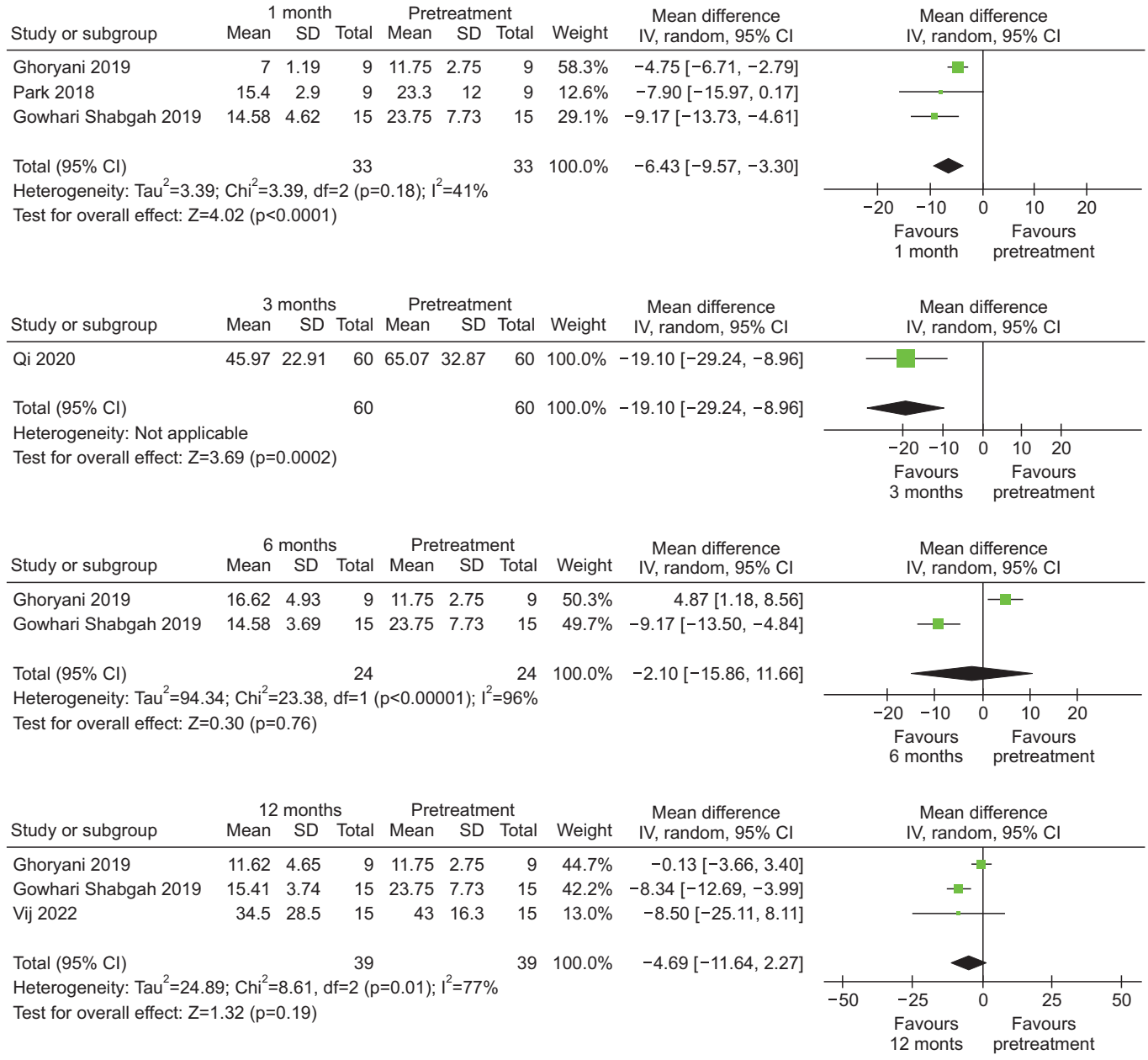


Figure 5. Forest plot of erythrocyte sedimentation rate after 1-, 3-, 6-, and 12-month mesenchymal stem cell transplantation. SD: standard deviation, CI: confidence interval.

months before fading or fluctuating. Repetitive treatment would stabilize clinical outcomes and improve patients' quality of life, which was found to be substantially associated with an increase in regulatory T cells level in peripheral blood [5,9].

Clinically significant improvements were observed in 50% of follow-up visits in 8 of 12 patients following HSCT [22]. Nonetheless, the positive effects were seen to diminish over time. According to the study by Verburg et al. (2005) [20], failure to achieve long-term remission in patients could be linked to failure of eradicating autoreactive B cells, resulting in residual serum autoantibodies in many transplant patients. This result is confirmed by observations in synovial tissue infiltrates from post-transplant RA patients, which revealed significant decrease in T cells in the synovium but followed by re-emergence of T cells. Furthermore, the T lymphocytes have been demonstrated to trigger osteoclasts, which could be a mechanism for joint injury [21].

The HAQ has become the most utilized tool for assessing

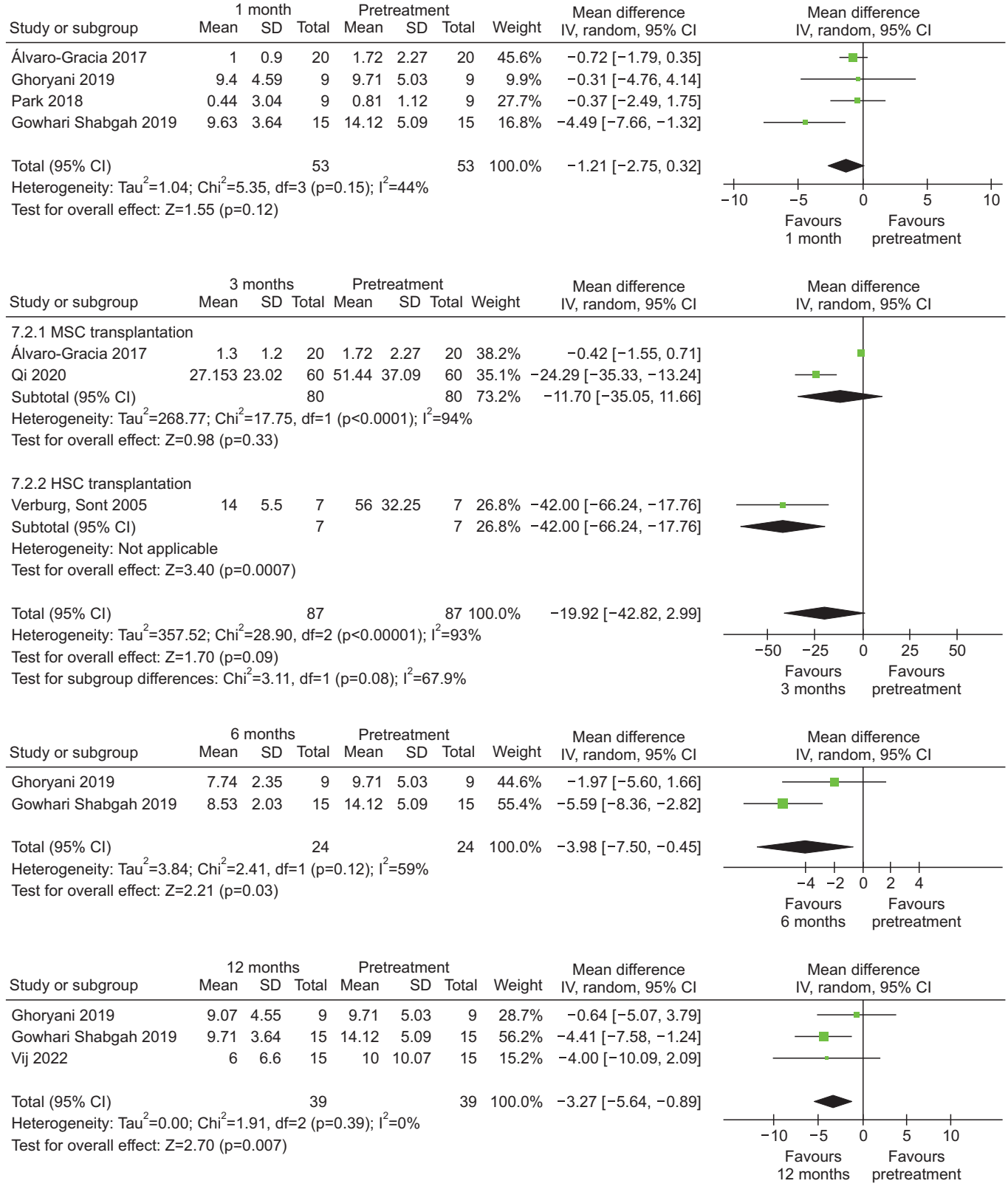


Figure 6. Forest plot of C-reactive protein after 1-, 3-, 6-, and 12-month mesenchymal stem cell transplantation. SD: standard deviation, CI: confidence interval.

Table 3. Adverse events of included studies

Adverse event	Adverse events incidence (n)	
	MSC (n=297)	HSC (n=73)
Fever	19	30
Malaise	3	0
Respiratory tract infection	8	0
Ear infection	2	0
Gastroenteritis	2	0
Rash	2	19
Muscular weakness/pain	2	27
Headache/migraine	8	24
Nausea and/or vomiting	7	49
Diarrhea	2	20
Dental caries	2	0
Anemia	4	0
Influenza like illness	14	0
Urinary tract infection	6	0
Febrile neutropenia	0	7
Neutropenic sepsis	0	3
Bilateral pleural effusion	0	1
Pancytopenia	0	1
Hair loss or alopecia	0	32
Bacteremia	0	1
Mucositis	0	14
Hypotension	0	7
Elevated liver enzyme	0	3
Anxiety	0	5
Joint pain	1	0
Rhinitis	10	0
Allergic reaction	2	0
Sleepiness	5	0
Thrombosis	0	2
Hydradenitis	0	2
Metrorrhagia	0	2
Herpes zoster	0	3
Enterocolitis	0	2
Pneumothorax	0	2
Hematuria	1	0
Thrombocytopenia	1	0

MSC: mesenchymal stem cell, HSC: hematopoietic stem cell.

functional capacity and impairment in RA patients. Teng et al. (2005) [19] found that clinical improvement after HSCT occurred primarily in the first 9 months after transplantation and persisted for up to 2 years. During the entire follow-up period, the HAQ scores improved by 0.22 units, which is regarded as clinically significant. Despite the favorable findings for DAS28 measures, we discovered no statistically significant improvement in HAQ score following 3 months stem cell therapy (mean difference [MD]: −0.09; p=0.78; 95% CI: −0.71, −0.53). Qi et al. (2020) [7] discovered a higher HAQ score 3 months following MSC therapy. However, all the other measures, including DAS28 and laboratory indicators, have been improved. Therefore, a higher HAQ score may be attributed to relatively subjective and broad features questions that may be influenced by respondents' overall health status.

Our study found significant improvements in inflammatory markers after MSC and HSC transplantation. A statistically significant decrease was found in ESR after 1 month (MD: −6.43; p=0.001; 95% CI: −9.57, −3.30) and 3 months (MD: −19.10; p=0.001; 95% CI: −29.24. −8.96) of treatment with MSC [7,14,17,18]. A decrease in pooled mean difference of ESR after 6 months and 12 months of treatment with MSC was also found although not statistically significant [14,18,23]. The study by Gowhari Shabgah et al. (2019) [18] reported a decrease of ESR at 1-month post-treatment and ESR level was maintained at 6-month and 12-month post-treatment with autologous bone marrow-derived MSCs. Another study by Ghoryani et al. (2019) [14] also reported significant decrease of ESR at 1-month post-treatment and ESR level was maintained at 12-month post-treatment with autologous bone marrow-derived MSCs. However, this study showed a significant increase of ESR between 1-month and 6-month post-treatment. An explanation behind this finding is that Treg cells were found to increase at 1-month post-treatment and decrease at 6-month and 12-month post-treatment. This suggests that MSCs can exert the anti-inflammatory effect through the increased expression of Treg cells. However, as patients with RA are known to have a progressive decline in Treg cells over time, Treg cells population were lower at 6-month and 12-month post-treatment. Therefore, a higher dose of MSCs or multiple injections may be required to maintain Treg cells. These findings show the efficacy of MSCs to decrease ESR in the first 3 months and the potential to act as a maintenance of ESR at 6-month and 12-month post-treatment.

The use of MSC and HSC transplantation showed significant improvements in CRP level. A non-statistically significant decrease in CRP level was found in 1-month post-treatment (MD: −1.21; p=0.12; 95% CI: −2.75, 0.32) and 3-month post-treatment (MD: −19.92; p=0.08; 95% CI: −42.82, 2.99) [5,14,17,18]. The study by Álvaro-Gracia et al. (2017) [5] reported CRP level at 1-month and 3-month post-treatment with MSCs. The result

showed a non-significant decrease in CRP level, but showed an overall decreasing trend from baseline, 1-month, and 3-month post-treatment. Contrastingly, at 3-month post-treatment, a statistically significant decrease of CRP level was found in HSC transplantation (MD: –42.00; p=0.001; 95% CI: –66.24, –17.76). The study administered autologous HSCs mobilized with a single infusion of high dose cyclophosphamide to create an "immune reset" in patients with RA. Patients who have undergone transplantation were reported to have a markedly decrease in T cells in the synovium which explains the statistically significant reduction in CRP level reported in the study [21].

Furthermore, a statistically significant decrease in CRP level was observed in 6-month (MD: –3.98; p=0.03; 95% CI: –7.50, –0.45) and 12-month post-treatment (MD: –3.27; p=0.007; 95% CI: –5.64, –0.89) with MSC transplantation [14,18,23]. Shabgah et al. (2019) [18] reported a decrease in CRP level at 6-month post-treatment (8.53±2.03 mg/L) and 12-month post-treatment (9.71±3.64 mg/L) compared to baseline (14.12±5.09 mg/L). Another study by Ghoryani et al. (2019) [14] found no statistically significant decrease in CRP level at 6-month and 12-month post-treatment. However, a decrease was observed in 6-month post-treatment (7.74±2.35 mg/L) compared to baseline (9.73±5.03 mg/L). Nevertheless, fluctuation was also observed when CRP level increased at 12-month post-treatment (9.07±4.55 mg/L). Both studies showed the fluctuation of CRP level from baseline, 6-month, and 12-month post-treatment. The rationale behind this finding is due to the nature of RA to induce a progressive decline of Treg cells over time followed by the increase of inflammation as shown by the increase of CD4+ T cells at 12-month post-treatment [14,18]. These findings indicated the dose and the single administration used in the studies were not sufficient for long-term maintenance of CRP level.

Applicability in clinical practice

MSC-based therapy for various diseases therapy in clinical practice have been well known. The potent immunomodulatory properties make MSCs an effective modality to treat autoimmune diseases [3]. There have been studies evaluating the use of stem cell in management of autoimmune diseases, particularly RA [33]. Up to this writing, the Indonesian Ministry of Health have reported over 350 MSC-based clinical studies are currently ongoing with ten of them are related with RA therapy development [34].

In Indonesia, stem cell treatment is a growing modality for the treatment of various diseases. Efficacy and safety of stem cells is promising with good outcomes and few adverse events in RA patients. This sheds light for the management of RA patients with regenerative medicine, specifically stem cells. However, the use of stem cells in clinical practice still requires a very high cost [34].

Study limitations

Our systematic review and meta-analysis assessed the effectiveness and safety profile of stem cell therapy as the treatment modality of RA. Various randomized and non-randomized trials were included in our review to data regarding the therapeutic benefits of stem cell treatment in RA. Our findings showed the potential of stem cells as an option of RA therapy. However, current result should be interpreted with caution as most of the studies did not identify risk of selection bias and bias due to confounding. Although promising, the variability in follow-up period made it impossible to consider the safety parameters accurately. Lastly, dose, repetition, and best administration route of MSCT are still undefined. Further investigations with longer follow-up period and variable repetitive administrations are needed to confirm the safety.

CONCLUSION

Stem cell transplantation in RA showed favorable clinical outcomes with no significant changes in safety parameters.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2023.0076

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was re-

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AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization of the study and design. Literature searching, data extraction, and qualitative analysis were performed E.F., G.K., P.A. Quantitative analysis and data interpretation were conducted by E.F., G.K., P.A. The first draft of the manuscript was written by E.F., G.K., P.A. All authors reviewed and commented on the previous version of the manuscript. All authors have read and approved the final manuscript.

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