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Review article

Mesenchymal stromal cell therapy for patients with rheumatoid arthritis

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ABSTRACT

Management of relapses and refractory rheumatoid arthritis (RA) patients is complex and difficult. Even after the administration of new biological disease-modifying anti-rheumatic drugs (DMARDs), only a few patients achieve the complete remission phase. DMARDs help only in modifying the disease activity, which sooner or later fails. They do not manage the disease at the patho-etiological level. There are some serious side effects as well as drug interaction with DMARDs. There are few subsets of RA patients who do not respond to DMARDs, reasons unknown. Mesenchymal stem cells (MSCs) provide a promising alternative, especially in such cases. This review elaborates on the studies pertaining to the application of MSCs in rheumatoid arthritis over the last two decades. A total of 14 studies (one review article) including 447 patients were included in the study. Most of the studies administered MSCs in refractory RA patients through the intravenous route with varied dosages and frequency of administration. MSCs help in RA treatment via various mechanisms including paracrine effects. All the studies depicted a better clinical outcome with minimal adverse events. The functional scores including the VAS scores improved significantly in all studies irrespective of dosage and source of MSCs. The majority of the studies depicted no complications. Although the use of MSCs in RA is still in the early stages requiring further refinement in the source of MSCs, dosage, and frequency. The role of MSCs in the management of RA has a promising prospect. MSCs target the RA at the molecular level and has the potential to manage refractory RA cases not responding to conventional treatment. Multicentric, large sample populations, and long-term studies are required to ascertain efficacy and safety.

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1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease characterized by progressive synovitis, destructive arthropathy, and systemic complications [1]. Globally, the age-standardized point prevalence and annual incidence rates of RA were 246.6 and 14.9 in 2017, which increased by 7.4% and 8.2% from 1990, respectively [2]. The heavy burden of the disease requires a better understanding of immunopathogenesis and treatment. Considering the inflammatory cells and various cytokines, interleukin is involved in the pathogenesis [3,4], development of biological DMARDs (Disease-modifying antirheumatic drugs) including anti-CD20, antitumor necrosis factor α (TNF-α), and anti-interleukin- 6 (IL-6) monoclonal antibody and targeted synthetic DMARDs such as Janus kinase inhibitors have achieved significant clinical efficacy in patients with RA [5–8].

Even on multidrug treatment, only a small proportion of the patients achieve persistent disease remission. Most of the patients had multiple relapses and with a brief duration of disease remission [9–12]. Targeting a single pathway may not be sufficient as seen by variable studies [13,14]. Therefore, there is a need for novel and effective treatment strategies, especially for refractory RA. Mesenchymal stromal cells (MSCs) have the potential to provide a one-stop solution to all the complexities in the management of RA. The ultimate goal of ideal treatment in RA would be to restore immune tolerance. MSCs have attracted a lot of attention in recent times due to their reparative, paracrine effects, and anti-inflammatory effects [15–17]. The application of MSCs in the management of RA has escalated in the last two decades. Currently, many clinical trials and studies have been published to evaluate the efficacy and safety of MSCs in RA. The immunomodulatory effect of MSCs provides a promising treatment strategy for autoimmune diseases including RA [18,19]. MSCs have the property of being readily isolated and expanded *in vitro*. The immune privilege allows the transfer of allogeneic cells to the patients. This provides a possibility of abundance availability of the MSCs in near future. In this review, the studies about the application of MSCs in the management of RA over the last two decades have been discussed. This review provides evidence on the safety and clinical efficacy of MSCs in RA now.

2. Materials and methods

2.1. Search strategy

A comprehensive search of the literature was carried out using the online databases PubMed, EMBASE, Google Scholar, Scopus, Web of Science, and the Cochrane database for all studies published in the English language before 30th April 2022 and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [20].

Two researchers performed an independent electronic search using the terms - 'Mesenchymal stem cells' OR 'Mesenchymal stromal cells' OR 'Stem cells' AND 'Rheumatoid Arthritis' OR 'rheumatism' OR 'Rheumatological disorder'. The search was restricted to articles on human subjects in the English language. References of the studies whose full texts were studied were also hand-searched for any other relevant studies. Any discrepancy between the authors was resolved through discussion until a consensus was obtained.

Inclusion criteria: Human adult patients with diagnosed rheumatoid arthritis undergoing treatment/management with help of mesenchymal stem/stromal cell administered via any route, *in vivo* studies, completed clinical trials or Randomized control trials, and articles published after the year 2000 (last 20 years).

Exclusion criteria: Studies including patients with other types of inflammatory arthritides or other autoimmune diseases and not RA, *in vitro* studies, studies not evaluating the safety and functional outcome of mesenchymal stem/stromal cells in treatment or management of rheumatoid arthritis, animal model studies, and pre-clinical trials were excluded. Articles primarily evaluating the only immunopathogenesis and mechanism of action of mesenchymal stem/stromal cells were also excluded.

2.2. Data extraction

Various types of studies, case reports & series, original studies, clinical trials, and review articles were considered. The systematic review was carried out by two authors who independently analyzed the data. Any controversy was sorted out by mutual agreement. Data from full-text articles were extracted into Microsoft Excel. The following data were extracted: (i) study characteristics: year of publication, authors, country, and the number of patients enrolled, (ii) source, dosage, and frequency of MSC injection, (iii) efficacy outcomes, and (iv) safety outcomes: adverse events in the included studies. Due to heterogeneity in the type of studies and data, statistical analysis could not be done.

3. Results

The electronic database search resulted in 73 studies. The title and abstract of all these articles were studies for potential inclusion in the systemic review. The data not available in the abstract was searched in the full paper and if not available the study was excluded. After assessing the studies against the inclusion criteria and removing the duplicates 12 studies were finally included in this review. A flow chart of the literature search using the format is presented (Fig. 1).

A total of 423 patients were included in the 11 studies. One review study comprising 9 completed clinical trials and 8 ongoing clinical trials was included in the study. One study was published in 2011 and 2012; two studies were published each in 2017 and 2019; three studies in 2018 and 2020 as shown in Fig. 2. Maximum publications were from the China region followed by South Korea and Spain. Most of the studies included patients with refractory RA as shown in Table 1. The source of MSCs is varied involving both allogeneic and autologous sources. The MSCs can be derived from bone marrow (n = 5), adipose tissue (n = 3), and umbilical cord (n = 7). Few studies used multiple types of MSCs. The dose and frequency differ among studies. Seven studies used a single fixed dose of MSCs. It ranges from 1×10^6/kg to 4×10^7/kg. Other studies used different doses of MSCs in different groups of patients. Most of the studies administered a single dose only. Only in 1 study, 2–4 doses were given whereas the other study gave 3 doses. Only one study gave an exclusive intra-articular injection of MSCs in the knee, whereas only one study administered MSCs via intravenous and intra-articular routes. The rest of the studies administered MSCs only intravenously.

In this systemic review, only one type of study was a review article, one was an original article, two studies were pilot studies and 7 were registered clinical trials. All the studies represented better clinical outcomes as depicted by Erythrocyte sedimentation rate (ESR), Disease activity score 28 (DAS28), C-reactive protein (CRP), American College of Rheumatology 20/50 (ACR20, ACR50), and a few other indicators. Only one study depicted 141 adverse events in the study whereas another study reported transient fever in 3 patients only. One study reported gastrointestinal symptoms and mild leukocytopenia as adverse effects. One study used Lugua polypeptide along with MSCs whereas others used DMARDs along with MSCs as shown in Table 2. There are few on-going or completed clinical trials, the results of which are still awaited as shown in Table 3.

4. Discussion

RA is a complex and peculiar disease owing to its etiopathogenesis. The pathogenesis of the disease is still not clear. Though the mechanism affecting the joint has been elaborated, its varied destructive effects on multiple tissue and organs are still unclear. Various cytokines such as TNF-α, IL-1, and IL-6 have been associated with disease pathogenesis.

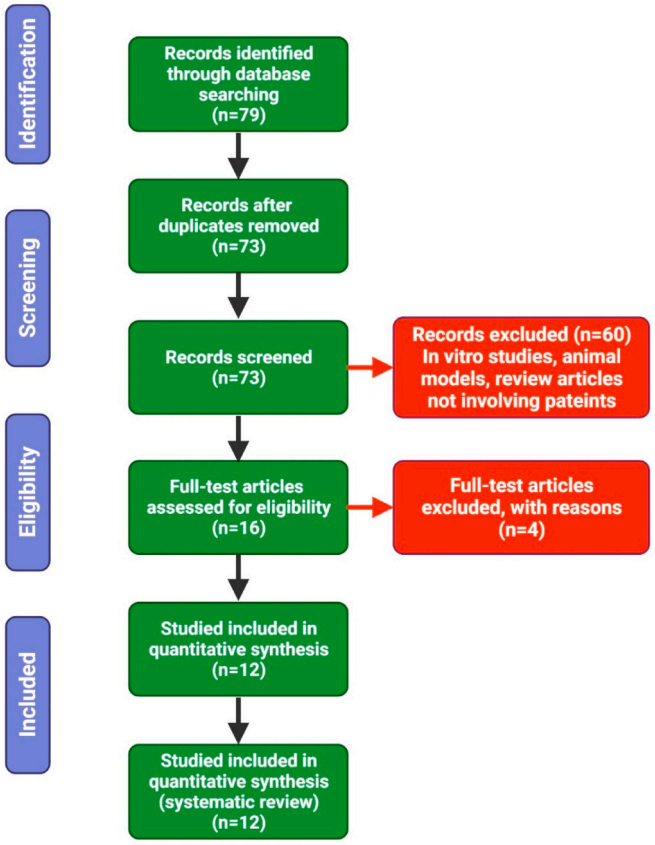


Fig. 1. Flow chart of literature search. Created with BioRender.com.

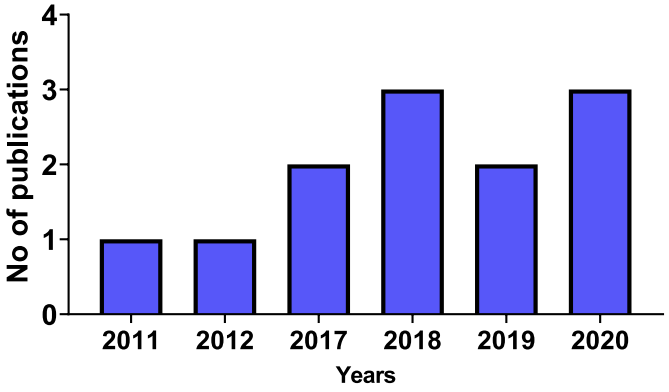


Fig. 2. Bar chart depicting the number of publications year-wise.

Table 1
Demographic data of the study.

S.No	Author	Year	Country
1	RA et al. [21]	2011	South Korea
2	Liang et al. [22]	2012	China
3	Kafaja et at [23].	2017	USA
4	Alvaro-Gracia et al. [24]	2017	Spain
5	Park et al. [25]	2018	South Korea
6	Shadmanfar et al. [26]	2018	Iran
7	Yang et al. [27]	2018	China
8	Ghoryani et al. [28]	2019	Iran
9	Wang et al. [29]	2019	China
10	Xiao et al. [30]	2020	China
11	Qi et al. [31]	2020	China
12	Lopez-Santalla et al. [32]	2020	Spain

These cytokines are incriminated for joint destruction and systemic effects on various other tissues and organs [33]. The traditional medications including DMARDs are not successful enough to limit these cytokines but also have unavoidable side effects [10,34].

In recent times, targeted therapy against specific cytokines such as the etanercept (TNF-α competitive inhibitor) and infliximab (TNF-α monoclonal antibodies) have been developed to influence the disease process [6–8]. Still, most of these patients have relapses and remission of the disease [10–12]. Thus, it is essential to formulate a new therapy targeting the immune pathogenesis of the disease. MSCs have shown a promising result in tackling all the problems in the management of RA.

4.1. Mesenchymal stromal cells

MSCs are self-renewing 'multipotent' cells. They can differentiate various cell lineages such as adipocytes, chondrocytes, osteoblasts, and vascular smooth muscle cells under appropriate conditions. Mesenchymal cells have the ability to decrease expression levels of various inflammatory cytokines and chemokines, the increased percentage of regulatory T cells in peripheral blood, and the upregulated IL-4 producing Th2 (T helper cell) cells, suggesting anti-inflammation along with the improved immune-modulation and the induced immune-tolerance [23]. The role of stem cells in RA has been under consideration for the past 30 years but it has gained popularity, especially in the last 5 years. Different sources of mesenchymal stromal cells administered through different modes have been described in the literature [19,21–23]. In this article, the studies pertaining to the use of MSCs in the treatment of RA over the last two decades were reviewed.

4.2. Source and mechanism of action

MSCs can be harvested from various sources including fetuses, neonates, and adults. Bone marrow is the most common source of MSCs, others are adipose tissue, dental pulp, brain, skeletal muscles, synovium, umbilical cord, peripheral blood, and others [24–31]. The amniotic fluid and tissue, fetal liver and lung as well as placenta are also rich sources of MSCs [32]. The MSCs derived from different sites have different characteristics and differentiation potentials [33,34]. Currently, bone marrow-derived, adipose-derived, as well as umbilical cord-derived MSCs are the most commonly utilized stem cells. This can be influenced by the ease of harvesting MSCs from the source, isolating process, and the preferential characteristics of the cells. There can be advantages and disadvantages pertaining to specific MSCs. Bone marrow-derived MSCs were most rampantly used in various medical disciplines, but there were a few hurdles like harvesting bone marrow MSCs is difficult and painful and carries a risk of infection. The yield and differentiation potential are dependent on donor characteristics like age, ethnicity, autoimmune disorders, etc. All these shortcomings have led to the increasing use of adipose-derived MSCs. The adipose tissue is abundant and easily accessible. The adipose tissue-derived MSCs have stronger immunosuppressive effects but lesser osteogenic and chondrogenic potential as compared to bone marrow-derived MSCs [35]. Dental pulp-derived MSCs have more colony-forming potential as compared to bone marrow-derived MSCs [36]. Similarly, the MSCs derived from amnion or placental tissue or umbilical cord have higher expansion and engraftment capacity but lower osteogenic potential compared to bone marrow-derived MSCs [33]. The MSCs from different sources demonstrated a difference in the level of paracrine effects [37]. Even the CD markers expressed by these cells are different for cells from different sources [38–40]. All these lead to different responses in different diseases like RA [41].

MSCs differentiate into osteoblasts, osteocytes, or chondrocytes depending upon on conditioning medium [42]. Inflammatory stimuli like IL-1 help to differentiate into osteoblast/osteocytes whereas IL-6 helps conversion of MSCs into chondrocytes. MSCs inhibit osteoclastogenesis by producing osteoprotegerin [43].

Zheng et al. studied the allogeneic mesenchymal stem cell and mesenchymal stem cell-differentiated chondrocyte in rheumatoid arthritis [44]. Both MSCs and MSC-chondrocytes suppressed collagen II-reactive T-cell responses in RA. Chanda et al. evaluated the therapeutic potential of adult bone marrow-derived mesenchymal stem cells in the disease of the skeleton [45]. Not only describing the developmental origins and mechanisms of action of MSCs but its application in various orthopaedics diseases including RA. In RA, systemic injection of MSC engineered to express IL-10 significantly reduced the symptoms as compared to naïve MSCs [46]. Allogenic MSCs significantly reduced the

Table 2
Depicting the study data and outcomes.

Ref no	No. of patients	Status of disease	Source of MSCs	Dose	Frequency	Route of administration	Type of study	Clinical outcome	Adverse Events
[21]	3	RA	Adipose-derived	6×10^8-$8X10^8$ cells/ patient	2-4 Doses	Intravenous, Intra-articular	Pilot Study	Improvement was seen clinically, reduction in VAS score and WOMAC score, and steroid dose	None
[22]	4	Refractory RA	Allogenic Bone marrow or umbilical cord-derived	1×10^6/kg	Single	Intravenous	Pilot Study	Three out of four patients: reduction in ESR, das28, and VAS score. 2 out of 4 EULAR response but relapse at 7 and 23 months.	None
[23]	32	Refractory RA	Bone marrow-derived Mesenchymal precursors cells	1×10^6/kg to 2×10^6/ kg	Single	Intravenous	Phase 1B/2A	Higher ACR20, ACR50, ACR70 levels achieved	None
[24]	53	Refractory RA	Allogenic adipose-derived	1million/ kg, 2million/ kg, 4 million/kg	3	Intravenous	Phase 1B/2A	DAS28-ESR, CRP decrease	141 adverse events: lacunar infarction, transient fever, diarrhoea, tendon rupture, arthritis, rheumatoid nodule, sciatica
[25]	9	RA moderate activity despite methotrexate treatment	Umbilical cord-derived	2.5×10^7, 5×10^7, 1×10^8 cells/ patient	Single	Intravenous	Phase 1A	Reduced ESR, DAS 28, level of IL-1B, IL-6, IL-8 and TNF-A	None
[26]	15	RA (affecting knee joint)	Bone marrow-derived	40 million cells/joint	Single	Intra-articular	Phase1/ 2	Improved WOMAC score, pain-free walking distance, standing time, decreased VAS, time to jelling	None
[27]	52	Refractory RA	Umbilical cord-derived	1×10^6/kg	Single	Intravenous		Reduction of DAS28, CRP, ESR, HAQ, Anti-CCP, RF improvement in Hb, albumin, IFN-γ decrease in platelets, clinical improvement in 28 patients with DAS28	Transient fever in 3 patients
[28]	9	Refractory RA	Autologous bone marrow-derived	1×10^6 MSCs/kg	Single	Intravenous	Clinical trial	Decrease Th17%. DAS28-ESR and VAS decreased. No difference in serum CRP and anti-CCP	None
[29]	64	RA	Umbilical cord-derived	4×10^7 cells/ patient + DMARDs	Single	Intravenous	Phase 1/ 2	ESR, CRP, RF, Anti-CCP, Health index and DAS28 decreased	None
[30]	63	Refractory RA	Umbilical cord-derived	1×10^6 cells/ patient	Single	Intravenous	Phase 1/ 2	53.3% of patients with MSC monotherapy and 93.3% of patients with MSC combined with IFN gamma treatment achieved ACR20 response	None
[31]	119	Refractory RA	Umbilical cord-derived (Plus Lugua Polypeptide LG in the treatment group)	4×10^7 cells/ patient	Single	Intravenous	Clinical trial	The treatment group (MSC + Lugua polypeptide) showed a better clinical outcome	2 gastrointestinal symptoms, 6 mild leukocytopenia; MSC group: 6 GI symptoms, 7 leukocytopenia, 3 transaminase elevation
[32]	9 completed clinical trials 8 ongoing clinical trials	Refractory RA	Adipose tissue-derived Bone marrow-derived Umbilical cord-derived	Variable 1×10^6 to 3×10^8 cells/ patient	Variable 1 to 4	Intravenous, intraarticular	Review	No sufficient data on efficacy	None

Table 3
List of Clinical Trial pertaining to Stem cells in Rheumatoid arthritis registered with ClinicalTrial.gov (US National Library of Medicine).

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Locations
1	NCT01985464	Umbilical Cord Tissue -derived Mesenchymal Stem Cells for Rheumatoid Arthritis	Unknown status	No Results Available	• Rheumatoid Arthritis	• Biological: Umbilical cord mesenchymal stem cells	Study Type: Interventional Phase: • Phase 1 • Phase 2 Study Design: • Allocation: N/A • Intervention Model: Single Group Assignment • Masking: None (Open Label) • Primary Purpose: Treatment	• Stem Cell Institute, Panama City, Panama
2	NCT03333681	Evaluation of Stem Cell Therapy Effects on the Immune Response in Rheumatoid Arthritis Patients	Completed	No Results Available	• Rheumatoid Arthritis	• Biological: Autologous mesenchymal stem cells	Study Type: Interventional Phase: Phase 1 Study Design: • Allocation: N/A • Intervention Model: Single Group Assignment • Masking: None (Open Label) • Primary Purpose: Treatment	
3	NCT04170426	Autologous Adipose-derived Stem Cells (AdMSCs) for Rheumatoid Arthritis	Not yet recruiting	No Results Available	• Rheumatoid Arthritis	• Biological: autologous adipose derived stem cells	Study Type: Interventional Phase: •Phase 1 •Phase 2 Study Design: •Allocation: Randomized •Intervention Model: Sequential Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	
4	NCT01547091	Safety and Efficacy Study of Umbilical Cord-Derived Mesenchymal Stem Cells for Rheumatoid Arthritis	Unknown status	No Results Available	• Rheumatoid Arthritis	• Biological: Umbilical Cord- Derived Mesenchymal Stem Cells (UC-MSCs) • Drug: Rheumatoid Arthritis With Disease-Modifying Drugs (DMARDs) • Biological: UC-MSC + DMARDS	Study Type: Interventional Phase: • Phase 1 • Phase 2 Study Design: • Allocation: Non-Randomized • Intervention Model: Single Group Assignment • Masking: None (Open Label) Primary Purpose: Treatment	The 323 Hospital of Chinese People's Liberation Army, Xi'an, Shaanxi, China
5	NCT02643823	Human Umbilical Cord-Mesenchymal Stem Cells for Rheumatoid Arthritis	Unknown status	No Results Available	• Rheumatoid Arthritis	• Biological: hUC-MSC + DMARDs • Drug: DMARDs	Study Type: Interventional Phase: Phase 1 Study Design: • Allocation: Randomized	The Fourth People's Hospital of Shenzhen, Shenzhen, Guangdong, China

(*continued on next page*)

Table 3 (*continued*)

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Locations
							• Intervention Model: Parallel Assignment • Masking: None (Open Label) Primary Purpose: Treatment	
6	NCT03067870	Transplantation of Autologous Bone Marrow Derived Stem Cells in Patients With Rheumatoid Arthritis	Unknown status	No Results Available	• RheumatoId Arthritis • Osteoarthritis, Knee • Osteoarthritis, Hip	• Biological: Stem Cell Transplantation	Study Type: Interventional Phase: Phase 1 Study Design: • Allocation: N/A • Intervention Model: Single Group Assignment • Masking: None (Open Label) Primary Purpose: Treatment	
7	NCT01663116	Cx611-0101, eASCs In travenous Administration to Refractory Rheumatoid Arthritis Patients	Completed	No Results Available	• Rheumatoid Arthritis Aggravated	• Genetic: Stem cells • Genetic: Placebo	Study Type: Interventional Phase: • Phase 1 • Phase 2 Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Single (Participant) Primary Purpose: Treatment	• Hospital U. Central de Asturias, Oviedo, Asturias, Spain • Hospital General de Mérida, Mérida, Badajoz, Spain • Hospital U. de Canarias, La Laguna, Tenerife, Spain • Hospital de Cruces, Barakaldo, Vizcaya, Spain • Hospital de Basurto, Bilbao, Vizcaya, Spain • Complejo Hospitalario U. A Coruña, A Coruña, Spain • Hospital Vall d'Hebron, Barcelona, Spain • Hospital Clinic i Provincial, Barcelona, Spain • Hospital Santa Creu i Sant Pau, Barcelona, Spain • Hospital Reina Sofía, Córdoba, Spain and 13 more
8	NCT01873625	Transplantation of Bone Marrow Derived Mesenchymal Stem Cells in Affected Knee Osteoarthritis by Rheumatoid Arthritis	Completed	No Results Available	• Rheumatoid Arthritis	• Biological: mesenchymal cell transplantation • Biological: placebo	Study Type: Interventional Phase: • Phase 2 • Phase 3 Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: None (Open Label) Primary Purpose: Treatment	• Royan Institute, Tehran, Iran, Islamic Republic of
9	NCT04971980	Safety and Efficacy Study of Human Umbilical Cord-Derived Mesenchymal Stem	Recruiting	No Results Available	• Rheumatoid Arthritis	• Drug: hUC-MSC infusion (BC– U001)	Study Type: Interventional Phase: • Phase 1 • Phase 2	• Peking Union Medical College Hospital (Dongdan campus), Beijing, Beijing, China

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Table 3 (*continued*)

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Locations
		Cells(BC- U001) for Rheumatoid Arthritis					Study Design: • Allocation: N/A • Intervention Model: Sequential Assignment • Masking: None (Open Label) Primary Purpose: Treatment	
10	NCT03691909	Phase 1/2a Clinical Trial to Assess the Safety of HB-adMSCs for the Treatment of Rheumatoid Arthritis	Completed	Has Results	• Rheumatoid Arthritis	• Biological: HB-adMSCs	Study Type: Interventional Phase: • Phase 1 • Phase 2 Study Design: • Allocation: N/A • Intervention Model: Single Group Assignment • Masking: None (Open Label) Primary Purpose: Treatment	• Accurate Clinical Research, Pasadena, Texas, United States
11	NCT03186417	Mesenchymal Stem Cells in Early Rheumatoid Arthritis	Recruiting	No Results Available	• Rheumatoid Arthritis	• Biological: 2 million hMSC/kg • Biological: 4 million hMSC/kg • Biological: 6 million hMSC/kg • Biological: placebo	Study Type: Interventional Phase: Phase 1 Study Design: • Allocation: Randomized • Intervention Model: Sequential Assignment • Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	• UH Hospitals Cleveland, Cleveland, Ohio, United States • MetroHealth Medical Center, Cleveland, Ohio, United States
12	NCT03798028	The Safety and Effects of Mesenchymal Stem Cell (MSCs) in the Treatment of Rheumatoid Arthritis	Unknown status	No Results Available	• Rheumatoid Arthritis	• Biological: UC-MSCs	Study Type: Interventional Phase: Not Applicable Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Single (Participant) Primary Purpose: Treatment	• Xijing Hospital, Xi'an, Shaanxi, China
13	NCT05003934	Safety of Cultured Allogeneic Adult Umbilical Cord Derived Mesenchymal Stem Cell Intravenous Infusion for RA	Recruiting	No Results Available	• Rheumatoid Arthritis	• Biological: AlloRx	Study Type: Interventional Phase: Phase 1 Study Design: • Allocation: N/A • Intervention Model: Single Group Assignment • Masking: None (Open Label) Primary Purpose: Treatment	• Medical Surgical Associates Center, St. John's, Antigua and Barbuda • Center for Investigation in Tissue Engineering and Cellular Therapy, Buenos Aires, Argentina • Medyca Bosques, San Pedro Garza García, N.L, Mexico
14	NCT03828344	Safety and Tolerability of a Single Intravenous	Not yet recruiting		• Rheumatoid Arthritis	• Biological: hUC-MSC suspension	Study Type: Interventional	•

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Table 3 (*continued*)

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Locations
		Infusion of BX-U001 in Refractory Rheumatoid Arthritis		No Results Available		• Biological: Placebo	Phase: Phase 1 Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	
15	NCT02348086	Outcomes Data of Adipose Stem Cells to Treat Rheumatoid Arthritis	Unknown status	No Results Available	• Rheumatoid Arthritis	•	Study Type: Observational Phase: Study Design: • Observational Model: Cohort Time Perspective: Prospective	• StemGenex, San Diego, California, United States
16	NCT01978639	Injections of FloGraft Therapy, Autologous Stem Cells, or Platelet Rich Plasma for the Treatment of Degenerative Joint Pain	Unknown status	No Results Available	•Osteoarthritis • Rheumatoid Arthritis	•	Study Type: Observational Phase: Study Design: • Observational Model: Cohort Time Perspective: Prospective	• Arizona Pain Specialists, Scottsdale, Arizona, United States
17	NCT02221258	Safety of FURES TEM-RA Inj. in Patients With Moderate to Severe Rheumatoid Arthritis(RA)	Completed	No Results Available	• Rheumatoid Arthritis	• Biological: FURESTEM-RA Inj.	Study Type: Interventional Phase: Phase 1 Study Design: • Allocation: N/A • Intervention Model: Single Group Assignment • Masking: None (Open Label) Primary Purpose: Treatment	• Seoul national University Boramae medical center, Seoul, Korea, Republic of
18	NCT03618784	Safety and Efficacy of FURESTEM-RA Inj. in Patients With Moderate to Severe Rheumatoid Arthritis	Completed	No Results Available	• Rheumatoid Arthritis	• Biological: FURESTEM-RA Inj • Other: sterile saline	Study Type: Interventional Phase: • Phase 1 • Phase 2 Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	• Chonnam National University Hospital, Gwangju, Korea, Republic of • Gangdong Kyung Hee University Hospital, Seoul, Korea, Republic of • Konkuk University Medical Center, Seoul, Korea, Republic of • Kyung Hee University Hospital, Seoul, Korea, Republic of • Seoul Hospital attached to Soonchunhyang University, Seoul, Korea, Republic of • Seoul national University Boramae, Seoul, Korea, Republic of • Seoul National University

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Table 3 (*continued*)

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Locations
								Hospital, Seoul, Korea, Republic of
19	NCT00006055	Autologous Peripheral Blood Stem Cell Transplantation in Patients With Life Threatening Autoimmune Diseases	Unknown status	No Results Available	• Purpura, Schoenlein-Henoch • Graft Versus Host Disease • Anemia, Hemolytic, Autoimmune • Rheumatoid Arthritis • Churg-Strauss Syndrome • Hypersensitivity Vasculitis • Wegener's Granulomatosis • Systemic Lupus Erythematosus • Giant Cell Arteritis • Pure Red Cell Aplasia • and 4 more	• Drug: anti-thymocyte globulin • Drug: cyclophosphamide • Drug: cyclosporine • Drug: filgrastim • Drug: methylprednisolone • Drug: prednisone • Procedure: Autologous Peripheral Blood Stem Cell Transplantation	Study Type: Interventional Phase: Not Applicable Study Design: Primary Purpose: Treatment	• Fairview University Medical Center, Minneapolis, Minnesota, United States

inflammation of the joint and helped in cartilage formation. MSCs have the ability for modulating the immune system as a part of the paracrine effect. Immune system tolerance induction has been incriminated for systemic effects in RA. Ichim et al. elaborated on the role of autologous stromal vascular fraction cells in the management of RA [47]. MSCs are 'smart immune modulators' producing anti-inflammatory factors such as TGF-β, HLA-γ, IL-10, etc only in response to immune/inflammatory stimuli not in the basal state [42]. Systemically administered MSCs have the additional benefit of homing at injured or damaged tissue, apart from their regenerative capability. This selective homing ability does not cause global immune suppression and adverse effects [48–50]. The MSCs not only differentiate into articular tissue but also growth factors that augment the endogenous regenerative process [51]. The therapeutic role of MSCs was studied extensively in the last decade. Various sources of the MSCs were evaluated including bone marrow-derived MSCs, vascular stromal MSCs, umbilical cord-derived MSCs, adipose tissue-derived MSCs, and allogenic MSCs. The umbilical cord-derived MSCs had better properties as allogenic cell therapy, especially for resistant RA. This might be due to superior immunomodulatory capacity compared to bone marrow-derived MSCs [52]. The adipose tissue-derived MSCs showed promising results due to various factors including easy accessibility, an abundance of adipose tissue, and stronger immunosuppressive effects. Similarly, the synovium-derived MSCs can be extracted from various sites and had an extensive proliferative ability, multilineage differentiation potential, and low immunogenicity [53].

RA is an autoimmune disease involving the production of autoantibodies such as an anti-cyclic citrullinated peptide or rheumatoid factor in 80% of the patients [54]. B cells play a key function in the production of these antibodies and cytokines regulating the T cells and macrophages. B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL) are two cytokines from a large family of TNF promoting differentiation and survival of B cells. In patients with RA, an increase in the APRIL and BAFF levels in serum, synovial fluid, and saliva (only BAFF) is seen. The concentrations of these cytokines in the synovial fluid are more than those of serum, thereby causing the survival of B cells in the joint [55]. The concentration of these cytokines was assessed after intravenous administration of MSCs in the study by Shabgah et al. [55]. There was a significant decrease in plasma concentration of BAFF after 1 and 6 months; APRIL concentration decreased after 1 month of MSCs administration. The MSCs seem to decrease B cell response and thus the autoimmune response in RA.

Pro-inflammatory T cell plays an important role in the development of autoimmune disease. The study by Baharlou et al. analyzed the regulatory effect of human adipose tissue-derived MSCs on peripheral blood mononuclear cell activation in RA [56]. The adipose-derived MSCs inhibited IL-17 secretion by peripheral blood mononuclear cells. Thus, acts as a key regulator of immune tolerance by inhibiting inflammation in RA. The study by Baharlou et al. depicted that adipose-derived MSCs upregulated Th2 and T-regulatory cell transcription factors like GATA3 and Foxp3, and downregulated Th1 and Th 17 transcription factors like T-bet and RORγt [57]. Thus, these MSCs resulted in an immunosuppressive environment for inflammation in RA. The study by Lamas et al. depicted the efficacy of bone marrow-derived MSCs in lowering the CD 25+ and CD25 high/CD127 low-negative peripheral blood mononuclear cells in RA patients and healthy controls [58]. Vasilev et al. showed the secretory factors produced by adipose mesenchymal stem cells downregulate Th17 and increase T regulatory cells in peripheral blood mononuclear cells from 17 rheumatoid arthritis patients [59]. Interesting research by Oshita et al. depicted the inhibitory osteoclast differentiation effect after MSCs administration [60]. Thus, MSCs not only act as an anti-inflammatory but also plays an important role in bone metabolism and repair in RA patients (Fig. 3).

4.3. MSCs and immunomodulation

In the study by Mascarenhas et al. the role of stem cells in autoimmune rheumatologic disorders was evaluated [61]. The immunomodulatory function of MSCs was emphasized. Mesenchymal stem cells have little immunogenicity due to low levels of major histocompatibility complex-I (MHC-I) and the absence of MHC-II or co-stimulatory molecules such as B7-1(CD-80), B7-2 (CD86), or CD40.

Tyndall et al. described the role of autologous MSCS in severe autoimmune diseases including RA [62]. The immune-modulating properties and low acute toxicity were highlighted. Feng et al. described the role of the A20 protein in bone marrow-derived MSCs which regulates T-cell balance in RA [63]. A20 is TNF-α induced protein-3 which inhibits pro-inflammatory cytokine secretion. MSCs could regulate a Th17/T-regulatory balance and A20. The A20 was decreased in RA patients' bone marrow MSCs, and with more IL-6

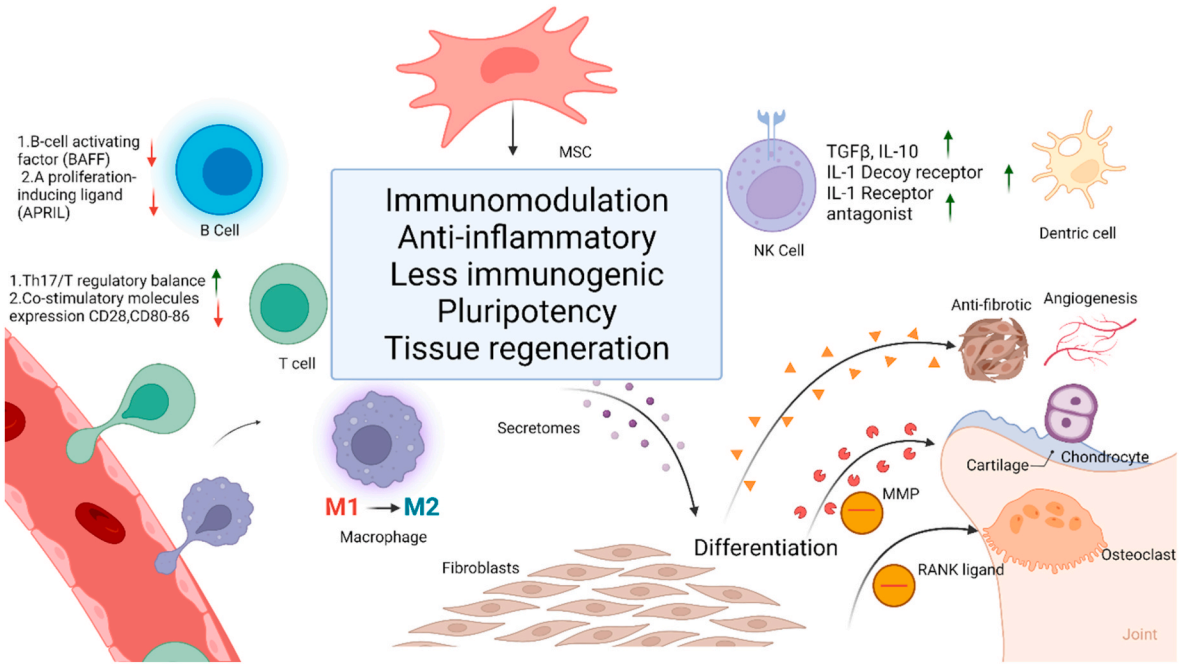


Fig. 3. Mechanism of action of MSCs on various cell types that mediates the pathogenesis of rheumatoid arthritis, Created with BioRender.com.

secretion, the balance of Th17/T-regulatory was disturbed. The importance and promising results of adipose tissue-derived MSCs have led to extensive research on these cells in RA. A study by Ra et al. involving 10 autoimmune disease patients including RA reported good outcomes with culture-expanded human adipose-derived MSCs [64]. The study described these calls as a promising alternative for treating autoimmune diseases. The pooled Wharton jelly-derived MSCs have superior immunosuppressive properties and reduce the heterogeneity of individual donors [65].

Vizoso et al. depicted *the vivo* studies showing MSC paracrine mechanisms showing proliferative, immunoregulatory, anti-oxidative, or angiogenic activity [66]. The depletion or dysfunction of MSCs is associated with autoimmune disorders including RA. The study opens the possibility for the use of secretome-derived products from MSCs as new therapeutic agents in order to restore tissue homeostasis.

The latest review update on the clinical application of MSCs for RA treatment by Lopez-Santalla et al. reiterated the immunomodulatory properties of MSCs in RA [67].

4.4. Clinical application of MSCs in RA

With the success of autologous stem cell use in autoimmune diseases including RA, the role of allogenic MSCs was evaluated. The study by Liang et al. reported the use of allogenic MSCs transplantation in patients with refractory RA [68]. The study included 4 refractory RA patients. Three of four patients had a reduction in ESR, DAS-28, and VAS scores in the follow-up. Two patients had no response according to the European league against rheumatism (EULAR) criteria. There were no serious adverse events. MSCs were considered safe in severe and resistant RA.

In a phase1/2 clinical trial by Shadmanfar et al. the efficacy and safety of intra-articular implantation of autologous bone marrow-derived MSCs in the rheumatoid knee were studied [69]. The study involves 15 patients in two groups each. The MSCs group was given 40 million autologous bone marrow-derived MSCs per joint, whereas the placebo group was given normal saline. The results showed superior findings in MSCs assessed by WOMAC, VAS scores, jelling time, and pain-free walking distance. The MSCs appeared to be safe and well-tolerated.

Qi et al. showed enhanced efficacy of umbilical cord MSCs when combined with Cervus and Cucumis peptides in the management of RA [70]. In the study by Wang et al. the 172 active RA patients were divided into two groups [71]. One group was given only DMARDs whereas the other was given DMARDs plus human umbilical cord-derived MSCs (4×10^7 cells per time) through intravenous injection. The results showed in the MSCs group there was a decreased serum level of TNF-alpha and IL-6. The percentage of $CD4^+$, $CD25^+$, and Foxp3+ regulatory T cells of peripheral blood was increased. The treatment induced a significant remission of disease according to the ACR improvement criteria, the DAS28, and the Health Assessment Questionnaire. The therapeutic effects were maintained for 3–6 months without continuous administration. MSCs provide safe, significant, and persistent clinical benefits in the management of active RA.

The phase 1B/2A clinical trial by Kafaja et al. included 48 patients divided into 3 groups: Group 1 received one intravenous infusion of 1 million cells/kg Mesenchymal Precursor cells (MPCS), Group 2 received 2 million/kg MPCS intravenously and Group 3 was given placebo in 2 sequential dose cohorts [72]. The results depicted no adverse effects over 12 weeks with clinical improvement in group 2 and group 1 compared to group 3. The study by Yang et al. correlated the efficacy of MSCs and IFN-γ levels [73]. The 105 persistently active RA patients not responding to the traditional medication were divided into two groups: the MSC group and the Control Group. The MSC group depicted response in 28 patients as indicated by high serum IFN-gamma level. The therapeutic effect lasted for 48 weeks. The effect was accompanied by an increase in IL-10 levels & T regulatory/Th 17 ratio as well as a reduction in IL-6 levels. Further assessing the clinical efficacy of MSCs and IFN, the study by Xu et al. demonstrated IFN as a key factor in determining the efficacy of MSCs in the treatment of RA [74]. The study consists of 63 refractory RA patients categorized into two groups receiving human umbilical cord MSCs plus IFN-γ and others receiving human umbilical cord MSCs only. The results confirmed that MSCs with IFN-γ combination therapy synergistically enhance the efficacy of MSC transplantation in patients with RA without any side effects during a 1-year observation period. The phase 1B/2A clinical trial by Alvaro-Gracia et al. evaluated the safety and tolerability of the intravenous administration of Cx611, allogenic expanded adipose-derived stem cells in patients with active refractory RA (failure to at least two biological therapy) [75]. The study

population of 53 patients was divided into 4 cohorts: 20 in group A were given 1 million/kg, 20 in group B were given 2 million/kg, 6 in group C were given 4 million/kg and 7 in placebo group D. A total of 141 adverse events were reported. The results showed intravenous infusion of Cx611 was in general well tolerated, without evidence of dose-related toxicity at the dose range.

Wang et al. depicted the efficacy and safety of umbilical cord-derived MSCs plus DMARDs in the treatment of RA [76]. There was a significant decrease in ESR, CRP, Rheumatic factor (RF), anti-CCP, DAS28, and Health index over 3 years. Ghoryani et al. studied the role of autologous bone marrow-derived MSCs in refractory RA [77]. The clinical trial included 9 patients who were given a single intravenous dose of 1×10^6/kg autologous bone marrow-derived MSCs. The results showed a significant decrease in Th17%, DAS28-ESR, and VAS score and a significant increase in regulatory T cells. Though there was no significant difference in serum CRP and anti-CCP levels but significant amelioration of clinical symptoms.

The phase 1A clinical trial by Park et al. studied the immunomodulatory action of umbilical cord-derived MSCs in RA [78]. The study included 9 patients divided into 3 clusters of 3 patients each. The patients were given a single intravenous infusion of 2.5×10^7, 5×10^7, and 1×10^8 cells in respective clusters over 30 min. The results showed reduced levels of IL-1β, IL-6, IL-8, and TNF-α at 24 h in the cluster infused with 1×10^8 MSCs. In clinical trial phase I/II A by Vij et al. [79] 15 patients suffering from RA were given a single intravenous dose of 2×10^8 autologous adipose-derived MSCs. The patients were followed up at 4, 12, 26, and 52 weeks and depicted significant improvement in ACR66/68 score for swollen and tender joint counts at 52 weeks follow-up. Levels of inflammatory markers, TNF-α, IL-6, and ESR remained unchanged. There were no acute or long-term serious adverse events. The MSCs were found to be safe and provide promising results in various preclinical, clinical, and proof-of-concept clinical studies.

4.5. Limitation of the study

The authors' analysis has some limitations. All the immunopathological parameters were not evaluated in this review. Due to heterogeneity in the methodology and outcomes of the clinical trials and studies, comparative evaluation could not be performed. The studies mainly involve refractory RA patients being treated by MSCs. There is a dire need to conduct large, multicentric randomized controlled trials to evaluate various therapeutic and safety parameters of MSCs in RA including refractory cases.

4.6. Future directives

Although MSCs have a potential role in the management of RA, the scope of regenerative medicine in the field of rheumatological disorders has to be evaluated by large, randomized, controlled interventional trials for the optimization of therapeutic protocols in terms of the type of MSCs, preparation methods and quality and quantity of MSCs to be transplanted. Studies are also needed for the validation of the use of MSCs in various stages of the disease and routes of administration, especially in mono-articular involvement. The potential adverse effects of MSCs involving the promotion of tumour growth needs to be studied further [80]. Newer avenues of cell-free therapeutics such as MSC-derived exosome or secretomes therapy need further investigation to explore their therapeutic potential in RA patients.

5. Conclusions

MSCs provide promising results in the treatment of RA, especially in refractory cases. The efficacy and safety profile of MSCs in RA is still under consideration but the preliminary results are encouraging. MSCs appeared to be a safe and effective way of managing refractory RA with minimal side effects. Though the guidelines for the type of MSCs and dosage are yet not clearly defined in the literature. Further randomized control trials with a large number of patients are required to ascertain the results. There is an increasing number of publications and clinical trials pertaining to the use of MSCs in the management of autoimmune disorders, especially refractory RA patients.

Authors' contributions

Conceptualization and design, B.H., P.K., S.A. and M.J.; Administrative support, N.J., A.N. and M.J.; Provision of study materials or patients, B.H., P.K., S.A. and M.J.; Collection and assembly of data, B.H., P.K., S.A., M.J., U.M.R., E.J.O., R.L.R., P.G., and B–C.A; Data analysis and interpretation: B.H., P.K., S.A., M.J., N.J., A.N. and M.K.; Manuscript writing, all authors; Funding acquisition, R.L.R. and P.G.; All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Data availability

No data was used for the research described in the article.

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