Journal of Clinical Orthopaedics and Trauma 26 (2022) 101804

Contents lists available at ScienceDirect

Journal of Clinical Orthopaedics and Trauma

journal homepage: www.elsevier.com/locate/jcot

The promising role of autologous and allogeneic mesenchymal stromal cells in managing knee osteoarthritis. What is beyond Mesenchymal stromal cells?

Vivek Pandey [a, *], Sandesh Madi [a], Pawan Gupta [b]

[a] Sports Injury and Arthroscopy Division, Orthopaedics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India
[b] Stempeutics Research Pvt. Ltd, Manipal Hospital, Whitefield, Banaglore, 560048, India

ARTICLE INFO

Article history:
Received 30 November 2021
Received in revised form
25 January 2022
Accepted 5 February 2022
Available online 9 February 2022

Keywords:
Osteoarthritis
Stromal cells
Autologous
Allogeneic
Pooled human bone marrow-derived mesenchymal stromal cells
Stempeucel®

ABSTRACT

Mesenchymal stromal cells (MSCs) express a wide range of properties anticipated to be beneficial for treating genetic, mechanical, and age-related degeneration in diseases such as osteoarthritis (OA). Although contemporary conservative management of OA is successful in many patients with mild-moderate OA, it often fails to improve symptoms in many patients who are not a candidate for any surgical management. Further, existing conservative treatment strategies do not prevent the progression of the disease and therefore fail to provide a long-term pain-free life. On the other hand, tremendous progress has been taking place in the exciting field of regenerative medicine involving MSCs (autologous and allogeneic), with promising translation taking place from basic science to the bedside. In this review, we comprehensively discuss the potential role of MSCs in treating OA, both autologous and off-the-shelf, allogeneic stem cells. Further, newer therapies are in the offing to treat OA, such as exosomes and growth factors.

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1. Introduction

Osteoarthritis (OA) is a frequent and disabling condition affecting a large part of the world population, which imposes substantial economic over the individual and the health systems.[1,2] The National Health Portal of India has reported that 22–39% of the Indian population is affected by OA.[2] Among the three regions, Knee, hip, and hand, 85% of cases are of the knee.[3]

Basic science of OA: OA is characterised by widespread changes in cartilage, subchondral bone, synovium, ligaments, and capsule due to various pro-inflammatory substances with an altered balance between repair and damage.[4,5] An imbalance in the synthesis and release of inflammatory cytokines (IL-1α, IL-1β, and tumor necrosis factor α (TNFα)) by OA cartilage leads to an increase in the production of matrix-degrading enzymes, which leads to further degradation of the cartilage. Further, an increase in the levels of interferon γ (IFNγ) in the joint worsens joint inflammation, leading to degradation of proteoglycans such as sulfated glycosaminoglycan's (sGAG).[6,7]

2. Management of OA

While the severe form of OA is offered a joint replacement or corrective osteotomy, patients with a mild-moderate form of OA are managed conservatively with lifestyle modification, weight loss, pain management, and other strategies. Lately, the focus has been shifting towards biological modalities that offer pain relief, minimize cartilage degeneration, and help in the cartilage regeneration process-killing two birds with one stone approach. This includes injection of either platelet-rich plasma or MSCs.

2.1. Traditional management

It involves lifestyle modification, weight loss, shoe wedges, physiotherapy, pain management, glucosamine-chondroitin sulfate, and intra-articular hyaluronic acid injection. The pain of OA is managed using non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and occasional intraarticular corticosteroid injections. Although clinicians have also been using glucosamine-

* Corresponding author. Sports injury and arthroscopy division, Orthopaedics, Kasturba medical college, Manipal. Manipal academy of Higher education, Manipal, 576104, India.
E-mail addresses: vivekortho@gmail.com (V. Pandey), sandesh.madi@gmail.com (S. Madi), pawan.gupta@stempeutics.com (P. Gupta).

https://doi.org/10.1016/j.jcot.2022.101804
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chondroitin sulfate and intraarticular hyaluronic acid injection, the evidence regarding their role in reducing pain and chondroprotection has been scarce and debatable.[8,9]

2.2. Killing two birds (pain & degeneration) with one stone- role of platelet-rich plasma (PRP) and Mesenchymal stromal cells (MSCs)

PRPs: *The PRP seems to be the current flavor to treat OA knee* due to the beneficial action growth factors and cytokines stored in α granules of platelets, such as platelet-derived growth factor, transforming growth factor-β, vascular endothelial growth factor, hepatocyte growth factor, insulin-like growth factor-1, epidermal growth factor, and prostaglandin E2 (PGE2).[10] These growth factors decrease inflammation, inhibit catabolic enzymes, and stimulate chondroprogenitors.[11] However, clinical data suggest that the beneficial effect of PRP seems to dwindle by the end of the year.[10,12]

MSCs- The emerging contender! MSCs have recently emerged as a serious contender in OA management as they have immunomodulatory and regenerative potential and, therefore, are projected to provide sustained clinical improvement. MSCs are derived from pericytes, the precursor of MSCs in all vascularised tissues.[13] In 2006, the International Society of Cellular Therapy (ISCT) proposed the name multipotent MSCs and defined that 1) MSCs must adhere to the criteria of being plastic adherent, 2) express surface markers CD105, CD73, and CD90, 3) lack the expression of hematopoietic markers CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR, and 4) differentiate into osteoblasts, chondrocytes, and adipocytes under suitable conditions in vitro.[14] Typically, MSCs can modulate immunosuppression and interact with many immune cells, including B cells, T cells, dendritic cells (DC), natural killer (NK) cells, and macrophages. Mechanisms of interaction rely on either by secretion of immune-modulatory factors like prostaglandin E2, indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), and transforming growth factor-β (TGF- β), or cell-cell interaction, thus making them ideal cell type for treatment of diseases including OA.[15,16] Due to anti-inflammatory properties and ability to differentiate into chondrocytes, MSCs are believed to be candidate cell types to treat OA. In order to achieve cartilage regeneration in situ, the tissue engineering strategies involving stromal cells comprise homing of endogenous stem cells or implantation of exogenous stromal cells (MSC).[17]

3. Mechanism of action of MSCs

The possible mechanisms of action of MSCs for the treatment of OA include; 1) *Differentiation theory*, which is about the ability of the MSCs to differentiate into mature chondrocytes directly; 2) *Paracrine theory* wherein MSCs modulate the local microenvironment by secreting several growth factors and cytokines, thereby promoting cartilage regeneration and repair and inducing the homing of endogenous stem cells. The immunomodulatory potential of MSCs is primarily because of their potential to significantly suppress the proliferation of inflammatory T-cells, monocytes, and dendritic cells by direct cell-to-cell contact. In addition, MSCs secrete a wide range of anti-inflammatory molecules such as PGE-2, IDO, IL-1Ra, and IL-10.[18,19] Further, MSCs influence the local osteoarthritic microenvironment by stimulating resident chondrogenic progenitor cells and promoting their differentiation into mature chondrocytes mediated by secretion of bone morphogenic proteins (BMPs) and TGFβ1.[20] With the increase in these factors locally in the joint cavity and mediated by change in expression of master regulatory genes such as Sox9, HoxA, HoxD, and Gli3, BMMSCs could differentiate into chondrogenic progenitor cells (CPC) *in vivo*. The CPC further differentiate into chondroblasts characterized by definitive upregulation of collagen type II B, IX, and XI. Thus, MSCs have multimodal mechanisms of action and, therefore, are an ideal candidate that could significantly contribute to an effective and long-term treatment for OA.

4. Type of MSCs and their comparison: autologous or allogenic; bone-marrow vs. adipose-derived

For OA treatment, both autologous and allogeneic MSCs are used. While Autologous MSCs are harvested from the patient, allogeneic stromal cells are pooled from two or more donors. Regarding sourcing, MSCs utilised in OA treatment are commonly sourced either from bone marrow (posterior iliac crest) or adipose tissue (abdomen/trunk). Other uncommon sources are peripheral blood and synovium. Although the safety profile between the bone marrow (BM) stromal cells and adipose tissue sourced MSCs are similar, there are many differences, including the cell yield and chondrogenic potential.[21] Yet, there seems to be no consensus regarding the superiority of one over another.[22]

While comparing the advantages and disadvantages of autologous and allogenic MSCs, the most crucial advantage of autologous MSCs is the *lack of immunogenic reaction* as it is harvested from the patient's body. On the downside, the harvest procedure can lead to donor site morbidity ranging from pain at the site to significant haematoma formation. Further, the viability and vitality of MSCs harvested can be quite unpredictable and vary from person to person. It has been observed that MSCs obtained from bone marrow are negatively influenced in numbers and quality by the patient's advancing age,[23] while MSCs derived from adipose tissue correlate negatively with the BMI.[24] Further, the time taken for culture and processing the harvested MSCs is also a deterrent in quick treatment of OA as an outpatient.

Due to these prevailing shortcomings of the autologous MSCs, allogenic MSCs appear to be a viable alternative that can be readily used as an 'off-the-shelf' product without any concerns of local morbidity, cell variability issues, and the time taken for processing of autologous MSCs. Commercially available allogeneic MSCs are primarily sourced from placental tissues.

A pertinent question regarding MSCs is their post-administration safety in the human body. A meta-analysis, which included 36 studies having 1012 participants with different clinical conditions, reviewed the safety profile of MSCs.[25] The meta-analysis did not detect an association between MSC administration and acute infusional toxicity, organ system complications, infection, death, and tumor formation.[25] In another systematic review of clinical trials involving autologous MSCs, Wiggers et al. analyzed the associated adverse events (AEs).[26] They concluded that only minor AEs such as temporary joint pain and effusion are associated with intraarticular administration of MSCs.[26] Hence, it can be concluded that MSC administration by a different injection route, including intra-articular administration, is safe.

5. Treatment of OA with MSCs

Although both autologous and allogeneic MSCs have been used to manage OA in various trials, no head-to-head trial has compared the two.

Autologous MSCs- Wakitani et al. were the first to report the usage of autologous MSCs in managing cartilage defects.[27] Since then, there have been a host of clinical studies utilizing MSCs in OA, concluding that autologous MSCs are safe and have the potential to improve symptoms of OA.[28] The important studies and their clinicoradiological outcome using autologous MSCs in OA of the knee are summarized in Table 1. Despite having heterogeneity in studies,

Table 1
Chronological list of publications of autologous mesenchymal stromal cell application for cartilage repair. *Note that studies published in last five years have been included in the table. AAPBSC - autologous activated peripheral blood stem cells; AD-MSC – adipose tissue derived Mesenchymal stromal cells; AE – adverse events; Auto – autologous; Allo – allogeneic; AM – Arthroscopic microfracture; AQoL-4D - Assessment of quality of life 4D questionnaire; BMAC – bone marrow aspirate concentrate; BMMSC- bone marrow derived Mesenchymal stromal cells; C2C - type II collagen C2C peptide; CTX – 1 - C-terminal telopeptide of type I collagen; CTX – II – C-terminal telopeptide of type II collagen; dGEMRIC - delayed gadolinium-enhanced magnetic resonance imaging of cartilage; FRI – Functional rating index; HA - hyaluronic acid; G-CSF - granulocyte colony-stimulating factor; IA – intra-articular; ICOAP - Intermittent and Constant Osteoarthritis Pain; ICRS - International Cartilage Repair Society Cartilage Injury Evaluation Package; IKDC - International Knee Documentation Committee subjective knee evaluation form; JKOM - Japanese Knee Osteoarthritis Measure; KL grade – Kellgran and Lawrence grade; KOOS - Knee Injury and Osteoarthritis Outcome Scores; KSS - Knee Society clinical rating system; MIF - macrophage migration inhibitory factor; MOAKS – MRI Osteoarthritis Knee Score; MOCART - Magnetic Resonance Observation of Cartilage Repair Tissue; MCS – Mesenchymal cell stimulation; MRI - magnetic resonance imaging; NPRS, Numeric pain rating scale; NC- nucleated cells; PCI – poor cartilage index; PBPC – peripheral blood progenitor cells; PGA - Patient Global Assessment; PR-FG – platelet rich fibrin glue; PRP – platelet rich plasma; QOL - Quality of Life; RCT – randomized controlled trial; RHSSK - Revised Hospital for Special Surgery Knee scores; ROM – range of motion; SAE – Serious adverse event; SAS - Short Arthritis Assessment Scale; SF-36- Short Form-36 quality of life questionnaire; SUSAR – suspected unexpected serious adverse reaction; SVF – stromal vascular fraction; TEAE – Treatment Emergent Adverse Event; TKA – total knee arthroplasty; TUG - timed up-and-go; UC-MSC – Umbilical cord derived MSC; VAS – visual analog pain score; WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; WORMS – Whole Organ Magnetic Resonance Imaging Score.*

Author/Year	Sample size	Study design/ Level	Grade of OA	Cell type & dose	Control group	Outcome measures	Follow up period	Outcomes
Soler R/ 2016[37]	15	Single arm, open-label phase I/II trial	KL grade 2 or 3	Auto BMMSC; 41 × 10^6 cells	Nil	VAS score, QOL, SF-36 questionnaire, Lequesne functional index and WOMAC score, MRI (T2 mapping)	12 months	The clinical scores improved; SF-36 showed improvement of parameters. *T2 mapping showed signs of cartilage regeneration*
Koh YG/ 2016[33]	80	RCT	ICRS grade 3 or 4	Auto AD-MSC + fibrin glue + Microfracture, 5 × 10^6 cells (Group 1)	n = 40 (Group 2) microfracture	Lysholm score, KOOS, VAS score, MRI - Cartilage Repair Tissue scoring system, arthroscopy, & Histology	24 months	*MRI – better signal intensity for repair tissue in group 1 (80%) as compared to 72.5% in group 2.* KOOS pain and symptom subscores - significantly greater for group 1, Arthroscopy & histology - no significant difference
Lamo-Espinosa JM/2016[34]	30	Phase I/II, RCT	KL grade 2 to 4	Auto BMMSC + HA, two doses – 10 & 100 × 10^6 cells	N = 10, (HA)	Safety, VAS score, WOMAC, MRI - WORMS	12 months	Safety established. VAS, WOMAC, and *WORMS scores significant in high dose group at* 12 months *follow up.*
Turajane T/ 2017[38]	60	RCT	KL grade 1 to 3	3 groups – 20 each; 1st group: AAPBSC + PRP + G-CSF + HA + MCS; 2nd group: AAPBSC + PRP + HA + MCS; (all given weekly × 3 injections)	20 patients – IA: HA alone	Avoidance of TKA intervention and WOMAC scores	12 months	TKA done in 3 patients in the control group but not in the cell group; WOMAC - all groups reached statistically significant improvements within the individual (intra) groups
Shapiro SA/ 2017[36]	25 patients, 50 knees	RCT, single-blind, placebo-controlled	Bilateral OA, KL grade 1 to 3	25 knees; 5 ml of Auto BMAC + 10 ml of platelet poor bone marrow plasma	25 knees; Sterile saline – 15 ml	ICOAP, VAS scores, MRI – T2 mapping	6 months	No SAE, Patients had a similar decrease in scores in VAS & ICOAP scores in both BMAC- and saline-treated arthritic knees
Nguyen/ 2017[35]	30	Placebo controlled trial	KL grade 2 or 3	15 patients. AM + Auto AD – SVF + PRP; 10^7 SVF cells/ml	15 patients, AM	Safety, WOMAC, Lysholm, and modified VAS scores, MRI	18 months	WOMAC scores not significant between two arms at 6 & 12 months but significant at 18 months. Increased Lysholm and VAS scores in the treatment group. *MRI demonstrated cartilage layer was thicker in the treatment group.*
Garay Mendoza D/2017[32]	61	Open-label, phase I/II RCT	Knee OA	Cell group - BM stimulation with subcutaneous administration of G-CSF (n = 30)	Control group - oral acetaminophen (n = 31)	VAS & WOMAC scores	6 months	BM-SC group showed significant improvement in knee pain and quality of life
Emadedin M/2018[30]	43	RCT, placebo-controlled, triple-blind	KL grade 2-4	Auto BM MSC, 40 × 10^6 cells (n = 19)	5 ml normal saline (placebo) (n = 24)	VAS, WOMAC, walking distance, painless walking distance, standing time and knee flexion compared	6 months	WOMAC - significantly improvements in total score, pain and physical function subscales and improvement in painless walking distance compared with placebo
Frietag 2019[31]	30	RCT	KL grade 2-3	Two treatment groups: Intra-articular ADMSC therapy either a single injection (100 × 10^6 ADMSCs) or two injections (100 × 10^6 ADMSCs at baseline and 6 months).	3rd group-conservative management.	NPRS, KOOS, WOMAC. MRI for cartilage assessment with MOAKS	12 months	No serious AEs. Significant improvement in the clinical scores. Two injection group showed improvement in cartilage loss.
Bastos 2020[29]	47	Controlled, double blind clinical trial	KL grade 1-4	Two treatment group IA injection of Group 1- MSC Group 2- MSC + PRP	Group 3- IA injection of steroid	KOOS, knee range of motion and synovial fluid interleukins	12 months	MSC injections with/without steroid showed improvement in KOOS score.

Table 2
Summary of studies using Allogenic stem cell therapy in OA. Note that studies published in last five years have been included in the table. AQoL-4D - assessment of quality of life 4D questionnaire; Allo – allogeneic; BMAC – bone marrow aspirate concentrate; BMMSC- bone marrow derived Mesenchymal stromal cells; C2C - type II collagen C2C peptide; CTX – 1 - C-terminal telopeptide of type I collagen; CTX – II – C-terminal telopeptide of type II collagen; HA - hyaluronic acid; HKA, hip-knee-ankle; HTO – High Tibial Osteotomy; ICOAP - Intermittent and Constant Osteoarthritis Pain; ICRS - International Cartilage Repair Society Cartilage Injury Evaluation Package; IKDC - International Knee Documentation Committee subjective knee evaluation form; KL grade – Kellgren and Lawrence grade; KOOS - Knee Injury and Osteoarthritis Outcome Scores; KSS - Knee Society clinical rating system; MIF - macrophage migration inhibitory factor; MOAKS – MRI Osteoarthritis Knee Score; MOCART - Magnetic Resonance Observation of Cartilage Repair Tissue; MCS – Mesenchymal cell stimulation; MRI - magnetic resonance imaging; NA, not available OA – Osteoarthritis; RCT – randomized controlled trial; ROM – range of motion; SAE – Serious adverse event; SF-36- Short Form-36 quality of life questionnaire; SUSAR – suspected unexpected serious adverse reaction; TEAE – Treatment Emergent Adverse Event; UC-MSC – Umbilical cord derived MSC; VAS – visual analog pain score; WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; WORMS – Whole Organ Magnetic Resonance Imaging Score.

Author/ Year	Sample size	Study design	Grade of OA	Treatment group- Cell type & dose	Control group	Outcome measures	Follow up period	Outcomes
Vega/ 2015[56]	30	RCT. Multicentric, phase I/II study	KL grade 2 to 4	Allo-BMMSC 40×10^6 cells	N = 15 intra-articular Hyaluronic Acid (HA) (60 mg, single dose)	Pain, disability, and quality of life. Articular cartilage quality was assessed by quantitative MRI T2 mapping	1 year	Significant improvement in algofunctional indices in treatment group versus the active controls treated with hyaluronic acid. *MRI T2 mapping-significant decrease in poor cartilage areas, with cartilage quality improvements in MSC-treated patients.*
Gupta PK/ 2016[46]	60	Double-blind, phase II, RCT	KL grade 2 or 3	Allo-BMMSC + HA, four doses– 25, 50, 75, 150×10^6 cells	N = 20 (placebo + HA)	Safety, VAS, ICOAP, WOMAC scores. MRI-WORMS score	24 months	Safety established. AE were predominant in the higher dose groups. VAS, ICOAP, WOMAC scores best in the lowest dose. *MRI– no significant difference*
Wang/ 2016[57]	18	RCT	Moderate or severe degenerative knee OA	I/A injection of 2.5 –3.0 mL HUC MSCs suspension containing (2 –3) $\times 10^7$ cells -once a month for 2 times	Sodium hyaluronate IA injection- once a week for 5 times	SF-36 scale score, Lysholm score, and WOMAC score.	6 months	Significant improvement in joint function and quality of life with use of IA injection of HUC MSCs. It takes effect after 1 month and the treatment effect can be sustained for 6 months.
de Windt TS/ 2017[47]	10	Phase I/II single centre study	Modified Outerbridge-Grade 3 or 4	Allo BMMSCs +10 or 20% autologous chondrons	Nil	Safety, KOOS, VAS, MRI, Second look arthroscopy, and histology	12 months	No SUSAR. KOOS & VAS scores improved significantly. *MRI – complete filling of the defect.* Arthroscopy - effective defect fill, and integration in the surrounding tissue. Histology - positive staining for both type I, type II collagen & proteoglycan
Park YB/ 2017[53]	7	Open-label, single arm, Phase I/II	KL grade 3 and ICRS grade 4	Two doses; allo hUCB _MSCs and HA hydrogel	Nil	ICRS cartilage repair, VAS, IKDC, MRI, Histological findings	7 years	VAS & IKDC improved at 24 weeks & stable till 7 years, Histology at 1 year showed hyaline-like cartilage, *MRI at 3 years showed the persistence of regenerated cartilage.*
Kuah D/ 2018[49]	20	RCT, double-blind, Placebo-controlled	KL grade 1 to 3	Randomized 4:1; Progenza (PRG) (Allo AD MSC + culture supernatant); 2 groups – 8 pts each – 3.9 or 6.7 million cells	4 patients, placebo administered	Safety, WOMAC, VAS, AQoL-4D, Biomarkers: urine– C2C & CTX – II, serum - MIF & CTX-I, MRI – MOAKS score	12 months	All patients experienced at least one TEAE, VAS & WOMAC - statistically significant within-group reduction from baseline in PRG group, no statistically significant differences at any time point between placebo and PRG groups, *MRI - no decrease in lateral tibial cartilage volume while the placebo group showed a statistically significant cartilage loss*
Matas J/ 2018[52]	29	Phase I/II RCT, triple _blind trial	KL grade 1 to 3	Allo UC-MSC, single (20×10^6) or repeat dose	9 patients, HA (baseline & 6 months)	VAS, WOMAC, MRI– WORMS score	12 months	No SAEs. Repeat dose group had a significant decrease in VAS &

Table 2 (*continued*)

Author/ Year	Sample size	Study design	Grade of OA	Treatment group- Cell type & dose	Control group	Outcome measures	Follow up period	Outcomes
				(20×10^6- baseline & 6 months), 10 pts each.				WOMAC scores as compared to HA group. No changes in function subscale, SF_36 & MRI
Khalifeh Soltani S/ 2019[48]	20	RCT, double-blind, placebo-controlled	KL grade 2 to 4	Placental-derived MSC − 50 -60×10^6 cells (n = 10)	Normal saline (n = 10)	VAS, KOOS, knee flexion range of motion (ROM), MRI	24 weeks	No SAEs, Significant knee ROM improvement at 2 & 24 wks, VAS − no change, KOOS − improvement till 8 wks, MRI - Chondral thickness improved in about 10% of the total knee joint area AT 24 weeks
Ryu/ 2020[54]	52	Retrospective cohort study	(K-L) grade ≤2 ICRS grade IV	hUCB-MSCs (Cartistem®, Medipost Inc.) composite of hUCB-MSCs 0.5×10^7/ml and freeze-drying sodium hyaluronate (HA)	N = 25 BMAC + HA scaffold HA membrane (Hyalofast®, Anika Therapeutics Inc., Bedford, MA, USA)	VAS, IKDC, KOOS Scores. Cartilage repair was assessed with modified Magnetic Resonance Observation of Cartilage Repair Tissue (M-MOCART) score and the ICRS cartilage repair scoring system.	2 years	Both groups showed satisfactory clinical and MRI outcomes. Implantation of MSCs from BMAC or hUCB-MSCs is safe and effective for repairing cartilage lesion.
Song/ 2020[55]	128	Retrospective case series	Full-thickness cartilage lesions ICRS grade 4 and K-L grade ≤3)	Therapeutic dosage of CARTISTEM® was 500 μL/cm^2 for a defect area with a cell concentration of 0.5×10^7 cells/ mL	No control group	VAS, WOMAC, IKDC Scores	2 years	Implantation of hUCB-MSCs is effective for treating knee osteoarthritis based on a follow-up lasting a minimum of 2 years
Lim/ 2021[51]	73	RCT, Phase 3 clinical trial	ICRS- grade 4 in a single compartment of the knee joint, as confirmed by arthroscopy	7.5×10^6 cells per 1.5 mL	43 in the UCB-MSC-HA group and 46 in the microfracture group	Proportion of participants who improved by ≥ 1 ICRS grade. Macroscopic Cartilage Repair Assessment at 48-week arthroscopy. Histologic assessment; VAS score, WOMAC, & IKDC score from baseline	5 years	UCB-MSCs implantation resulted in improved cartilage grade at second-look arthroscopy and provided more improvement in pain and function up to 5 years compared with microfracture.
Lee/ 2021[50]	74	Retrospective cohort study	Medial Uni-compartmental OA with kissing lesion, which was shown full-thickness cartilage defect (≥ICRS grade 3B) in medial femoral cartilage and medial tibial cartilage	Cartistem, hUCB-MSCs-HA hydrogel composites. Dose NA	N = 42 BMAC + HTO + Micro-fracture a fibrin sealant patch (TachoSil; Takeda Pharma A/S) soaked with the prepared BMAC was fixed with fibrin glue (Greenplast kit; Green Cross)	HSS score, KSS pain and function, and WOMAC score. Cartilage regeneration was graded by the ICRS grading system at second-look arthroscopy. Radiological measurement including HKA angle, posterior tibial slope angle, and correction angle were assessed.		hUCB-MSC procedure was more effective than the BMAC procedure for cartilage regeneration in medial uni-compartmental knee OA even though the clinical outcomes improved regardless of which treatment was administered

almost all studies showed improvement in clinical symptoms, whereas many confirmed cartilage regeneration in the therapeutic group (Table 1).[29–38]

Use of allogeneic MSCs and our experience with Stempeucel® - The disadvantages of the use of autologous MSCs include donor site morbidity, few weeks for the release of the product, variability of total cell count from patient to patient, and variability in cell yield with aging has shifted the focus towards allogeneic MSCs, which are gaining popularity as an alternative. It is an instantly available, off-the-shelf product with efficacy similar to autologous MSCs.

The allogeneic MSC could be obtained from single or multiple donors. The usual practice is to screen several healthy voluntary donors, aspirate bone marrow, culture, expand and isolate the MSCs. A product made using a single donor MSC bank may not have the same functional attributes, although presumably similar in essential characteristics qualifying the identity and safety criteria, which may lead to varied therapeutic outcomes. Donor to donor variability has been demonstrated in multiple studies with respect to properties of MSCs, such as their clonogenicity, growth kinetics, differentiation potential, and immunosuppressive properties.[39,40] A comparative analysis of 5 different BMMSC populations showed a mere 13% similarity in the proteomic profile, including transcriptional and translational regulators, kinases, receptor proteins, and cytokines. Furthermore, a maximum of 72% similarity in the proteome was observed between 2 of the five analyzed cell populations.[41] Therefore, a product manufactured using a master cell bank made from a single donor will result in exhaustion and disparities in clinical trial outcomes. To overcome the disadvantages of single donor issues, the pooling of bone marrow MSCs (BMMSCs) from two or more donors has been attempted to compensate for

the variation and balance the properties between different donor cell populations.[39,42–44] Stempeutics group, which developed Stempeucel®, established that pooled human BMMSCs show enhanced growth kinetics and differentiation propensity into adipocytes, osteocytes, and chondrocytes compared to the individual donor MSCs. Most importantly, Stempeucel® exhibited a more significant and consistent *in-vitro* immunosuppression of mixed lymphocyte reaction than varied immunosuppressive effects of individual donor MSCs.[43]

The preclinical safety and toxicity of Stempeucel® in rodent and non-rodent models were evaluated. Stempeucel® was non-toxic, non-tumorigenic, non-teratogenic, non-immunogenic, and did not induce genotoxicity.[45] In an animal study, Stempeucel® administered groups indicating significant cartilage regeneration in both cell groups compared to the HA alone and disease control groups.[46] Further, a phase II randomized controlled clinical trial involving Stempeucel® in a dose-escalating fashion established the safety of pooled allogenic stem cells and trend in efficacy for treating OA of the knee.[46] Stempeucel® study confirmed that low dose (25 million cells) intraarticular injection in Kellegren-Lawrence grade 2/3 OA positively improved all clinical parameters. However, the differences with the placebo group (only hyaluronic acid injection) were not significantly different. To further evaluate the Stempeucel®, phase III multicentric randomized controlled trial (CTRI/2018/09/015785) is ongoing, and the results are awaited. Furthermore, numerous studies have also established the safety and efficacy of allogeneic MSCs (Table 2).[46–57]

Hence, it appears that both autologous and allogeneic MSCs show promising results in the OA treatment both by improving clinical signs and possibly cartilage growth. However, the downside of almost all the studies is shorter follow-up. A longer follow-up would undoubtedly establish the clinical utility and cost-effectiveness of the MSCs in comparison to other biological products such as PRP or Hyaluronic acid.

6. Limitations of MSCs in OA therapy

Despite many advantages, there are several important limitations of MSCs. Although the safety of MSCs is widely accepted,[58] the biggest fear is of tumorigenesis after MSCs implantation and is widely discussed.[59] In patients suffering from diabetes mellitus, obesity, or other metabolic syndromes can affect the differentiation potential of MSCs, and they may differentiate to adipocytes than to chondrocytes.[60] Further, if MSCs are used after long term cultures and extensive in vitro manipulations, it can cause chromosomal aberrations, genetic instability and may lose their ability to proliferate as they enter a state of senescence.[61,62] Lastly, there may be an immunological response with the production of alloantibodies on repeated administration of MSCs.[63] Hence, extensive follow-up studies are required to study the long-term adverse events associated with MSC therapy, if any.

7. Looking further: treatment of OA with newer techniques like MSC derived exosomes and usage of scaffolds

Exosomes are derived from the endosomal compartment and are membrane-bound extracellular vesicles released into the extracellular matrix under physiological and pathophysiological conditions.[64] Exosomes mediate intercellular communication and cellular immune response. They are rich in proteins, lipids, and nucleic acids, including mRNA, microRNA, and long non-coding RNA.[65] Like many other cells, MSCs have been shown to produce extracellular vesicles, including exosomes.[66] MSC-derived exosomes have a protective effect on the cartilage in OA by decreasing the catabolic (ADAMTS5, MMP-13) and inflammatory markers (iNOS), increasing the expression of chondrogenic markers (type 2 collagen, aggrecan), and blocking macrophage activation to a pro-inflammatory phenotype.[67] Promising results are observed in rat models of OA using MSCs derived exosomes, wherein BM-MSCs derived exosomes could promote hyaline cartilage repair, including extracellular matrix synthesis, and decrease knee pain.[68] Furthermore, the use of exosomes derived from synovium MSCs and induced pluripotent stem cells (iPSCs) could attenuate disease scores by promoting chondrocyte proliferation and migration[69] and delaying cartilage degeneration.[70] The advantages of using MSC-derived exosomes in OA over cell therapy include low immunogenicity, no risk of tumor formation, and fewer ethical issues.[71] There is an ongoing Phase I clinical study in 10 patients to assess the safety and efficacy of a single intra-articular injection of MSC-derived exosomes in grade II and III OA (NCT05060107). The results of this ongoing study are highly awaited for the start of a new era of cell-free therapy in OA.

Apart from MSCs and MSC-free therapies, cartilage tissue engineering has emerged as an upcoming field of research that combines the activities of chondrogenic cells, biomaterials/scaffolds, and biofactors for cartilage regeneration. The biomaterials or scaffolds are classified as protein-based (collagen, fibrin, silk), polysaccharides (hyaluronic acid, chitosan, cellulose, alginate), and synthetic (Poly(lactic-co-glycolic acid), polylactic acid, polyethylene glycol).[72] Ideally, biomaterial should be biocompatible to minimize inflammatory and immunological reactions, adhesive to enable attachment of cells, permeable to nutrients and growth factors, and biodegradable. If possible, it should be injectable to be inserted by minimally invasive methods.[73] However, commercially available scaffolds used for OA do not entirely fulfill the role of hyaline cartilage regeneration. New solutions are constantly sought, and currently, hybrid scaffolds - a combination of synthetic and natural materials may provide promising results for cartilage regeneration. Also under investigation is the role of relevant growth factors (TGF-beta, BMP) and appropriate types of cells (mainly focusing on autologous chondrocytes or MSC) to ensure articular hyaline cartilage regeneration.[74]

8. Conclusion

Mesenchymal stromal cell therapy shows promising results in OA treatment in improving clinical symptoms and cartilage regeneration and theoretically weighs more than PRPs. Indeed, the pooled allogenic BMMSCs have several advantages over autologous ones. However, the need of the hour is a longer follow-up of already conducted study to establish sustained efficacy and cost-effectiveness of MSCs in OA treatment. Furthermore, extensive basic science and clinical studies are warranted to overcome challenges of the possibility of tumorigenesis, senescence, and chondrocyte phenotype instability, avoiding metabolic syndrome induced adipocyte conversion, standardizing the dose, type of MSCs, intervention time (grade of disease), and outcome measurements. Newer therapies such as exosomes, scaffold, and growth factors are in the offing. Hence, in the future, the key to successful regeneration of cartilage tissue would possibly involve combining multiple techniques to bioengineer articular cartilage for the successful long-term treatment of OA.

CRediT author statement

Vivek Pandey: Conceptualization, Methodology, Literature review, Editing. Pawan Gupta: Data curation, Writing- Original draft preparation. Sandesh Madi: Reviewing, Editing.

Funding

None.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

None.

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