The efficacy of different sources of mesenchymal stem cell for the treatment of osteoarthritis

This item was submitted to Loughborough University's Institutional Repository by the/an author.


Additional Information:

- This is an Open Access Article. It is published by Springer under the Creative Commons Attribution 4.0 Unported Licence (CC BY). Full details of this licence are available at: http://creativecommons.org/licenses/by/4.0/

Metadata Record: https://dspace.lboro.ac.uk/2134/38345

Version: Published

Publisher: © The authors. Published by Springer Verlag

Rights: This work is made available according to the conditions of the Creative Commons Attribution 4.0 International (CC BY 4.0) licence. Full details of this licence are available at: http://creativecommons.org/licenses/by/4.0/

Please cite the published version.
The efficacy of different sources of mesenchymal stem cells for the treatment of knee osteoarthritis

Maryam Shariatzadeh · Jianing Song · Samantha Louise Wilson

Received: 30 April 2018 / Accepted: 14 June 2019 © The Author(s) 2019

Abstract
Osteoarthritis (OA) is a common cause of chronic pain and disability. Regenerative therapies using mesenchymal stem cells (MSCs) provide an option for OA treatment as it could potentially regenerate the damaged cartilage. Bone marrow, adipose tissue and synovium are common MSC sources. The aim is to compare the therapeutic effect of MSCs from bone marrow, adipose tissue and synovium; combining its differentiation potential and accessibility, to decide the optimal source of MSCs for the treatment of knee OA. A comparison of preclinical and clinical studies using MSCs has been made with regard to treatment outcomes, isolation procedure and differentiation potential. All types of MSCs are effective at improving the clinical and structural condition of OA patients, but the longevity of the treatment, i.e. an effect that is maintained for at least 2 years, cannot be guaranteed. This review highlighted great variations in selection criteria and culture expansion conditions of MSCs between the literature and clinical trials. It also emphasised a substantial diversity and lack of consistency in the assessment mythology of clinical outcome after completion of MSC therapies procedures. A more cohesive methodology is required to evaluate the outcome of MSC treatments using quantitative and standardised frameworks in order to be able to directly compare results. Larger population of patients are recommended to assess the quality of MSC when designing studies and clinical trials to reaffirm the efficacy of MSC treatment prior to and within the clinical trials and follow up studies.

Keywords Mesenchymal stem cells · Clinical outcome · Osteoarthritis · MSC therapies · Clinical trials

Introduction
Osteoarthritis (OA) is a degenerative and inflammatory joint disease (Fig. 1). The limited capacity of healing in articular cartilage results in cartilage destruction, osteophyte development and inflammation. The prevalence of knee OA has doubled since the mid-twentieth century, becoming one of the leading causes of chronic pain and lower-limb disability among elderly people in developed countries (Wallace et al. 2017).

Traditional pharmacological treatments, non-pharmacological treatments and surgical procedures can only offer symptomatic benefits, whereas the damaged cartilages currently cannot be effectively repaired. With the advance in regenerative medicine, mesenchymal stem cells (MSCs) have emerged as an alternative cellular therapy for the treatment of knee OA.

MSCs are a type of multipotent stromal cell (Fig. 2) which have the potential to differentiate into osteocytes and chondrocytes and are commonly used in regenerative therapies to treat cartilage defects. MSCs can be isolated and derived from a variety of autologous and allogenic locations such as bone marrow (BM MSC), adipose tissue (ADMSC), umbilical cord blood and dental pulp. However, evidence of the optimal source of MSCs remains unclear. A serious gap in knowledge remains whether the currently used cellular treatments are beneficial long-term or if one cell therapy offers significant clinical benefit with regard to reduced pain and improved quality of life (QoL).

Comparison of cell courses
Autologous bone marrow concentrate (BMAC) is a prevalent source of MSCs for the treatment of OA; this is due to the
positive healing effect to the environment where they are injected. However, there is still no evidence as to how effective BMACs are for treating orthopaedic conditions when compared with other MSC sources and delivery procedures. Adipose tissue provides a rich source of MSCs in comparison to bone marrow, and as such is frequently used in a variety of

---

**Fig. 1** A comparison of a healthy knee (left) and a demonstrating OA pathology (right); reproduced from (O’Connell et al. 2019)

**Fig. 2** The differentiation lineages of mesenchymal stem cells (MSCs)
clinical and regenerative medicine research studies. The cellular components can be extracted as a cell pellet through washing and centrifugation steps which may also be referred to in literature as a stromal vascular fraction (SVF).

When deciding the optimal source of MSCs, information such as cell isolation procedure, harvest volume and differentiation potential should be considered. BMMSCs can be obtained from bone marrow, although the quantities are relatively low, with the number of MSCs often declining with increasing donor age (Wolffstadt et al. 2015); thus making it difficult to obtain sufficient cell numbers, especially among elderly donors. In contrast, 10 to 30 times more SMSCs can be derived from the same number of donors (Nimura et al. 2008; Sekiya et al. 2015) with yields of ADMSCs in the region of 500-fold more in comparison to BMMSCs (Hass et al. 2011). Furthermore, adipose tissue can be easily obtained by liposcopy and liposuction procedures, which are more well-established and less invasive in comparison to bone marrow aspiration (Puissant et al. 2005).

BMMSCs are more prone to chondrogenic differentiation in comparison to ADMSCs both in vitro and vivo (Danišović et al. 2007; Koga et al. 2008b). However, Kim and Im (2009) have suggested that the addition of paracrine or cytokines factors increases chondrogenic potential in ADMSCs to levels similar to BMMSCs (Kim and Im 2009). Comparatively, SMSC studies have indicated that they possess higher chondrogenic potential in comparison to BMMSCs and ADMSCs (Sakaguchi et al. 2005; Futami et al. 2012). An interesting study by Shirasawa et al. 2006 demonstrated that when growth factors such as bone morphogenetic factor 2 (BMP2), transforming growth factor beta (TGF-β) and dexamethasone are added to cultures, SMSCs produce more cartilaginous tissues compared with BMMSCs isolated from the same donors (Shirasawa et al. 2006). This suggests that SMMSCs may be more advantageous regarding chondrogenic differentiation potential.

Although the use of stem cell preparations for knee OA is becoming increasingly prevalent, well-designed studies with conclusive proof of comparative effectiveness and identification of the optimal cell source, delivery mechanism and “dose” have not been performed. Autologous BMMSCs and ADMSCs are two of the most commonly used cell sources in clinical trials (Wyles et al. 2015) (Table 3). However, researchers have increasing interest in synovial mesenchymal stem cells (SMSCs), which have been reported to have chondrogenic potential both in vivo and in vitro (Sakaguchi et al. 2005; Koga et al. 2008a). The beneficial effect of promoting cartilage regeneration has been reported in leporine models (Koga et al. 2008b) and porcine studies (Nakamura et al. 2012), resulting in SMSCs now being considered to be an alternative for MSCs treatment of knee OA.

This review focuses in comparing clinical studies and different types of MSC-based treatments to identify a preferential source of stem cells for the treatment of knee OA. Completed and active clinical trials (Table 3) and approved/authorised market products (Table 4) have all been evaluated.

### Comparison of European pre-clinical studies

Many preclinical studies have investigated the use of MSCs from different sources for the treatment if knee OA (Table 1). In general, BM-derived MSC’s are the most prevalent source in the EU, followed by adipose-derived MSCs. The literature search revealed that only one study reported the use of SM-MSC’s for the treatment of knee OA.

Within the EU, currently Spain is the most prevalent with regard to published literature regarding MSC therapies for the treatment of OA. Of the studies reviewed, five studies performed intra-articular injection of both allogenic and autologous BM-MSCs and favourably presented the benefit of MSC therapies in improving both knee movement and pain management (Vega et al. 2015; Soler et al. 2016).

The number of MSCs utilised in published literature varies widely from $2 \times 10^6$ to $5 \times 10^7$ cells per patient (Soler et al. 2016; de Windt et al. 2017, Orozco et al. 2013; Pers et al. 2016). However, it is not clear if the dosage represents the total number of MSCs for each injection procedure or is referring to the number of injected cells per kg body weight. Furthermore, not all studies provide specific details regarding cell passage number, although it is apparent that MSCs with lower passage number (passage 2/3) are more commonly used.

To determine the cell phenotype, a variety of surface markers and transcription factors varying dependent upon the different types and sources MSCs used can be used. However, regardless of the variation in the source of isolated MSCs, there are a number of surface markers that are commonplace; these include CD90, CD45 and CD34 which are used to characterise culture-expanded MSCs prior to use (Akgun et al. 2015; Vega et al. 2015; Pers et al. 2016; Soler et al. 2016; de Windt et al. 2017).

Of the studies examined, it became apparent that a range of medium and growth factors are utilised for in vitro and ex vivo expansion of stem cells including: DMEM, αMEM, (Orozco et al. 2013, (Vega et al. 2015) whilst, Russo et al. (2017) and Hudetz et al. (2017) reported the use of Lipogems® processing kit for processing MSCs which contains no medium (Hudetz et al. 2017; Russo et al. 2017).

The results of these European studies highlighted the variation in the number of patients that have currently undertaken MSCs therapy, which was reported between 7 and 56 patients per study. Regardless of the differences in MSC types, sources and/or the culture expansion conditions, most studies performed either a single or multiple intra-articular injection(s) to deliver the MSCs into the cartilage defect. A small number
<table>
<thead>
<tr>
<th>Source of MSCs and study location</th>
<th>Cell density/Passage (P) number</th>
<th>Phenotype characterisation</th>
<th>Culture conditions/Medium</th>
<th># of patients</th>
<th>Mode of delivery</th>
<th>Measurement of clinical outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous BMSC (2014) Spain</td>
<td>40 × 10^6 cells/5.5 mL</td>
<td>No information</td>
<td>Dulbecco’s Modified Eagle Medium (DMEM) +10% fetal bovine serum (FBS)/M199 medium</td>
<td>12</td>
<td>Single intra-articular injection</td>
<td>MSC injections were beneficial in OA knees. No local or systemic adverse events. The effect starts to decline after 6 months but is still improved at 5 years compared to the baseline.</td>
<td>(Vega et al. 2015)</td>
</tr>
<tr>
<td>Autologous micro-fragmented/ADSC (2017) Italy</td>
<td>No information</td>
<td>No information</td>
<td>Processed using a Lipogems® kit</td>
<td>30</td>
<td>Single intra-articular injection</td>
<td>A total median improvement of 20 points has been observed in IKDC subjective knee evaluation. KOOS, VAS and Tegner Lysholm Knee scores reduced</td>
<td>(Russo et al. 2017)</td>
</tr>
<tr>
<td>Allogenic culture expanded BM-MSC (2015) Spain</td>
<td>40 × 10^6 MSCs/P3</td>
<td>CD90, CD14, CD73, CD106, CD166, HLA-DR, CD45, CD34, CD19</td>
<td>DMEM-low glucose +10% FCS, 1% Penicillin/Streptomycin</td>
<td>30</td>
<td>Medial parapatellar injection</td>
<td>The MSC-treated patients displayed significant improvement in algofunctional index and cartilage quality.</td>
<td>(Vega et al. 2015)</td>
</tr>
<tr>
<td>Autologous culture expanded ADSCs (2016) France, Germany</td>
<td>Low dose: 2 × 10^6 cells Medium dose: 10 × 10^6 cells High dose: 50 × 10^6 cells</td>
<td>CD14, CD45, CD34, CD73, CD90, CD105</td>
<td>Minimum essential medium (MEM), human platelet growth factor-enriched plasma, 10 mg/mL ciprofloxacin, and 1 U/mL heparin</td>
<td>18</td>
<td>Single intra-articular injection</td>
<td>Patient treated with low-dose ADSCs showed significant improvements in pain levels and function compared with baseline measurements.</td>
<td>(Pers et al. 2016)</td>
</tr>
<tr>
<td>Autologous ADMSCs (2017) Croatia</td>
<td>No information</td>
<td>No information</td>
<td>Processed using Lipogems® processing kit</td>
<td>17</td>
<td>Single intra-articular injection</td>
<td>The use of autologous and micro-fragmented adipose tissue increased glycosaminoglycan (GAG) content in hyaline cartilage and was in line with observed VAS values.</td>
<td>(Hudetz et al. 2017)</td>
</tr>
<tr>
<td>Autologous culture expanded BM-MSCs (2013) Spain</td>
<td>40 × 10^6 cells /P3</td>
<td>CD90, CD14, CD73, CD106, CD166, HLA-DR, CD45, CD34, CD19</td>
<td>DMEM-low glucose +10% FCS, 1% Penicillin/Streptomycin</td>
<td>12</td>
<td>Single intra-articular injection</td>
<td>Patients exhibited rapid and progressive improvement of algofunctional indices and cartilage quality</td>
<td>(Vega et al. 2015)</td>
</tr>
<tr>
<td>Autologous culture extended BM-MSC (2016) Spain</td>
<td>40 × 10^6 ± 10 × 10^6 viable MSCs/ no information</td>
<td>CD31, CD45, CD90, CD73, CD105 and HLA-DR</td>
<td>DMEM-Low Glucose+10% HS</td>
<td>15</td>
<td>Single intra-articular injection</td>
<td>Reduced bodily pain and improved physical functioning at month 12. Cartilage regeneration.</td>
<td>(Soler et al. 2016)</td>
</tr>
<tr>
<td>Allogenic BM-MSC’s mixed with 10% or 20% recycled autologous cartilage-derived cells (2017) Netherlands</td>
<td>1.5-2 × 10^6 cells/mL/P3</td>
<td>CD73+, CD105+, CD90, CD45+, CD3+</td>
<td>αMEM, L-glutamine +5% platelet lysate and 3.3 IU/mL heparin</td>
<td>10</td>
<td>Single defect site-specific implantation</td>
<td>All patients showed statistically significant improvement in clinical outcome, with hyaline-like regeneration.</td>
<td>(de Windt et al. 2017)</td>
</tr>
<tr>
<td>Autologous culture expanded SMSC (2015) Turkey</td>
<td>8 × 10^6 cells P2–3</td>
<td>CD105, CD73, CD90 and lack of surface expression of CD45, CD34, CD14 (or CD11b), CD70a (or CD19), and HLA-DR</td>
<td>DMEM+1% penicillin/streptomycin +10% autologous serum.</td>
<td>7</td>
<td>Implantation via mini-arthrotomy knee</td>
<td>Improvement in AOFAS, and MOCART scores, MRI results showed osteochondral repair.</td>
<td>(Akgun et al. 2015)</td>
</tr>
<tr>
<td>Bone marrow concentrate (2016) Italy</td>
<td>2 mL + Autologous platelet-rich fibrin</td>
<td>No information</td>
<td>No information</td>
<td>56</td>
<td>Arthroscopic or open-field procedure</td>
<td>Improvement in AOFAS, and MOCART scores, MRI results showed osteochondral repair.</td>
<td>(Buda et al. 2016)</td>
</tr>
</tbody>
</table>
of studies delivered the MSCs via mini-arthrotomy or single defect site-specific knee implantation (Akgun et al. 2015; Buda et al. 2016)

The clinical outcome and effectiveness of MSC therapies are predominantly measured by qualitative test and questionnaires (Table 2) including the use of; the Visual Analogue Scale (VAS), Knee injury and Osteoarthritis Outcome Scores (KOOS), The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and International Knee Documentation Committee Questionnaire (IKDC). Although two studies performed GAG formation GAG in hyaline cartilage (Hudetz et al. 2017) and magnetic resonance imaging (MRI) analysis (Buda et al. 2016) to determine regeneration and osteochondral repair. The reliance on qualitative means that data collection is difficult to achieve using blinding strategies. Lack of binding may lead to false-positive results reported by patients and researchers and an overestimation of the efficacy of the treatments under investigation. Moreover, the lack of control groups or comparative randomised trials and the tendency to compare results with baseline values may also lead to an over-estimation of the success of the treatment strategies.

It is difficult to directly compare the results of pre-clinical studies since the inclusion criteria lack consistency between studies; for example, patients often have existing preoperative conditions and have previously undergone surgical procedures which may significantly influence the clinical outcomes with varied efficacy of interactions. Furthermore, there is a lack of consistency in the methodologies employed, for example, the cell culture conditions, mode of delivery and the outcome measurements are variable and often reliant upon qualitative measures. This makes the efficacy of different sources difficult to compare. Furthermore, the predominant outcome measurements focus on cartilage regeneration, whilst overlooking the effect of MSCs on the surrounding milieu, such as paracrine effects, which although not as important as cartilage regeneration for treatment of knee OA, however, may still contribute to healing by inducing the signalling changes in nearby tissues.

**Comparison of completed phase I/II/III clinical trials using MSC therapies for the treatment of knee OA**

To date, there have been 22 completed clinical investigating the use of MSCs as a therapy for the treatment of knee OA at phase I, II and III between 2012 and 2018. Table 3 provides a comparison of these studies with criteria including cell source, dosage, expansion culture conditions, clinical outcome measures and information regarding the quality of utilised stem cells such as phenotype and passage number. Autologous and allogenic BM-MSCs are predominantly utilised, with nine studies reporting the use of either ex vivo or in vitro expanded culture of MSCs. Dependent upon the source of MSCs, the number of cells utilised in each clinical trial varied between $2.5 \times 10^6$ and $1 \times 10^8$ cells/kg body weight, or in total. It was apparent that information regarding the cell passage number, phenotypes and expansion conditions were often absent on the clinical trials webpage (NIH US National Library of Medicine 2019). The mode of delivery was largely reported as intra-articular injection; however, a clinical trial carried out in Jordan reported the use of multiple intra-articular injections (Al-Najar et al. 2017).

For the majority of published trial studies, a follow up period of 12 months is commonplace following treatment with MSCs; however, the CARTISTEM® clinical trial in Korea reported a follow up period of up to 60 months (Lim et al. 2017). Among the 22 clinical trials, only two countries, Korea and Iran, have to date, completed their phase III trials in 2017 and 2013 respectively, in which, allogenic hUCB-MSCs, under the commercial name “CARTISTEM”, and autologous BM-MSC’s were used as sources of stem cells for the treatment of OA (Park et al. 2017). However, there was no information available in the published Iranian clinical trial regarding the cell dosage and condition of culture expansion. In most clinical trials, the effectiveness of the MSC treatment are measured by qualitative clinical tests and questionnaires including; VAS, WOMAC, IKDC and KOOS; the studies have no or limited quantitative data available to support the effectiveness of stem cells treatments for cartilage regeneration. In addition, only seven studies performed MRI tests to assess the cartilage status prior and after receiving stem cell therapies.

Currently, the effect of MSC therapies cannot be guaranteed long-term (> 60 months), since further significant improvement usually ceases during follow-up studies. Jo et al. (2017) pointed out that the effect of MSC-therapy does not last for long term. Although results are improved compared with baseline measurements, the outcomes still eventually plateau or start to decline within 2 years following intervention. Thus, combined treatment strategies combining other injectable agents, such as platelet-rich plasma (PRP) (O’Connell et al. 2019), should be investigated to determine their effect on enhancing engraftment efficiency (Atashi et al. 2015). Furthermore, there is a requirement for improved management of OA following treatments; this could include post-intervention rehabilitation to optimise the therapeutic effect and guarantee a long-lasting efficacy (Fahy et al. 2017).

**Market authorised MSC products**

Despite the completion of the clinical and preclinical studies investigating the efficacy of MSC therapies for OA, to date, only five products have reached the market (Table 4). Remarkably, the dosage of these stem cell products is much
lower than the cell numbers reported in either clinical trials or research studies.

TRINITY EVOLUTION®, an allogenic graft-containing adult MSCs, osteoprogenitor cells (OPCs) and demineralised cortical components has been approved by the Musculoskeletal Transplant Foundation (MTF) committee (Musculoskeletal Transplant Foundation 2013) in the USA for administration in the treatment of OA-related cartilage damage and for ankle and foot surgical applications. However, there is no information available regarding the cell dosage and expansion culture conditions for MSCs and OPCs cell components (Rush 2010). Nevertheless, the published phase III large animal clinical studies demonstrated that an increase in MSC dosage resulted in increased fusion and healing rates (Wheeler et al. 2014). Other studies have confirmed that there is a minimum cell dose required for effective

Table 2  A summary of the rating scales and scores commonly used to evaluate the success of therapies of the knee

<table>
<thead>
<tr>
<th>Name of rating scale</th>
<th>Brief description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)</td>
<td>A widely used self-evaluated questionnaire of knee OA. There are 3 subscales to assess pain (5 items, 0–20 scores), stiffness (2 items, 0–8 scores) and physical function (17 items, 0–68 scores) separately. Higher scores suggest increased pain, stiffness and functional limitation.</td>
</tr>
<tr>
<td>Magnetic resonance observation of cartilage repair tissue (MOCART)</td>
<td>A 9-part and 29-item system, that gives a final cartilage repair tissue score between 0 and 100 points; 0 points represents a poor outcome; 100 points represents a positive outcome.</td>
</tr>
<tr>
<td>The American Orthopaedic Foot and Ankle Society Score (AOFAS)</td>
<td>One of the most widely used measures for foot and ankle conditions comprised of subjective and objective questions; each section is designed to be used independent of the others. However, each measure is comprised of nine questions and cover three categories: pain (40 points), function (50 points) and alignment (10 points). These are all scored together for a total of 100 points.</td>
</tr>
<tr>
<td>Lequesne indexes</td>
<td>An index of severity for knee OA, which can also be used to assess the effectiveness of therapeutic interventions. 3 sections include pain or discomfort, maximum distance walked, and activities of daily living. A score of 0 indicates no limitation; whilst a score &lt; 8 is regarded as a severe limitation. Detailed scoring systems and modifications had been published (Lequesne et al. 1987; Lequesne 1991, 1997).</td>
</tr>
<tr>
<td>Knee Injury and Osteoarthritis Outcome Score (KOOS)</td>
<td>A self-administered multiple-choice questionnaire comprised of categories: Symptoms; Stiffness; Pain; Function (daily living); Function (Sports and Recreational activities); Quality of Life</td>
</tr>
<tr>
<td>Visual Analogue Scale (VAS)</td>
<td>A self-administrated evaluation to measure the amount of the pain that patients feels across a continuum number presenting from none to an extreme amount of pain (D. Gould et al. 2001).</td>
</tr>
<tr>
<td>International Knee Documentation Committee (IKDC)</td>
<td>A group of knee surgeons from Europe and America founded in 1987: A common terminology and an evaluation form were created. This form is the standard form for use in all publications on results of treatment of knee ligament injuries.</td>
</tr>
<tr>
<td>Lysholm knee scores</td>
<td>A self-evaluated questionnaire consisted by 8 sections, &lt; 65 scores are defined as ‘Poor’, 65–83 scores are ‘Fair’, 84–90 scores are ‘good’, and &gt; 90 scores are ‘Excellent’. Detailed score and grading were previously described (Tegner and Lysholm 1985; Mitsou et al. 1990).</td>
</tr>
<tr>
<td>Tegner activity level scale</td>
<td>A complement for Lysholm scale focussed on activities of daily living, recreation and competitive sports. The scores vary from 0 to 10. Scores &gt; 6 can only be achieved by recreational or competitive sports participants.</td>
</tr>
<tr>
<td>36-Item Short Form Survey (SF-36)</td>
<td>A patient-reported survey has 36 items which concerning on quality-of-life. SF-36 consists of 8 scales, with 100 scores in each scale, and higher scores indicate the less disability. Detailed information had been previously published (Ware and Sherbourne 1992; McHorney et al. 1993; McHorney et al. 1994)</td>
</tr>
<tr>
<td>Kellgren-Lawrence grade</td>
<td>The grade classifies the severity of knee OA into 5 grades, 0 refers to no radiographic features, and grade 4 is the most severe with large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity. Further information refers to the study of Kellgren and Lawrence (1957)</td>
</tr>
<tr>
<td>Whole-Organ Magnetic Resonance Imaging Score (WORMS)</td>
<td>An MRI scoring method that incorporates articular cartilage integrity, subarticular bone marrow abnormality, subarticular cysts, subarticular bone attrition, marginal osteophytes, medial and lateral meniscal integrity, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, synovitis/effusion, intraarticular loose bodies, and periarticular cysts/bursitis.</td>
</tr>
<tr>
<td>MSC source</td>
<td>Cell density</td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Allogenic UC-MSC</td>
<td>$20 \times 10^6$ and hyaluronic acid (3 mL)</td>
</tr>
<tr>
<td>Ex vivo cultured adult allogenic MSCs</td>
<td>No information</td>
</tr>
<tr>
<td>Autologous bone marrow aspirate concentrate</td>
<td>$5 \text{ mL of treatment cells combined with } 10 \text{ mL platelet poor bone marrow plasma}$</td>
</tr>
<tr>
<td>Autologous ex vivo cultured-extended BM-MSC's</td>
<td>$10 \times 10^6$ or $100 \times 10^6$ cells</td>
</tr>
<tr>
<td>Autologous adipose tissue-derived MSC</td>
<td>$1 \times 10^7$ cells /3 mL or $2 \times 10^7$ cells /3 mL or $5 \times 10^7$ cells /3 mL</td>
</tr>
<tr>
<td>Autologous haematopoietic stem cells from bone marrow (BMASC)</td>
<td>$5 \times 10^7$ cells /3 mL</td>
</tr>
<tr>
<td>Autologous bone marrow mesenchymal stem cells (MSV)</td>
<td>$40 \times 10^6$ MSCs</td>
</tr>
<tr>
<td>Autologous stromal vascular cells (SVF) and PRP</td>
<td>Total SVF (stromal vascular fraction): $1.0 \times 10^7$ to $5 \times 10^7$</td>
</tr>
<tr>
<td>Allogenic ex vivo cultured extended BM-MSC</td>
<td>$40 \times 10^6$ MSC</td>
</tr>
<tr>
<td>Autologous in vitro extended BM-MSC</td>
<td>Total cells: 61 $\times 10^6$ ± 0.6 $\times 10^6$</td>
</tr>
<tr>
<td>Autologous in vitro extended adipose tissue-derived mesenchymal progenitor cells (MPCs)</td>
<td>No information</td>
</tr>
<tr>
<td>Autologous in vitro extended</td>
<td>No information</td>
</tr>
<tr>
<td>MSC source</td>
<td>Cell density</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Autologous culture extended BM-MSC’s</td>
<td>5–6 mL of BMAC</td>
</tr>
<tr>
<td>Autologous bone marrow aspirate concentrate (BMAC)</td>
<td>Three dosage of cells /no information</td>
</tr>
<tr>
<td>Autologous culture extended BM-MSC’s</td>
<td>40 × 10^6 cells</td>
</tr>
<tr>
<td>Autologous culture extended BM-MSC’s</td>
<td>5 × 10^5 cells/kg/body weight</td>
</tr>
<tr>
<td>Autologous bone marrow aspirate concentrate (BMAC)</td>
<td>No information</td>
</tr>
<tr>
<td>Autologous bone marrow aspirate concentrate (BMAC)</td>
<td>5 mL of cells +10 mL of platelet poor bone marrow plasma</td>
</tr>
<tr>
<td>CARTISTEM allogenic hUCB-MSCs</td>
<td>Single dose of 500 μl/cm² containing 2.5 × 10^6 cells</td>
</tr>
<tr>
<td>CARTISTEM allogenic hUCB-MSCs</td>
<td>Single dose of 500 μl/cm² containing 2.5 × 10^6 cells</td>
</tr>
<tr>
<td>Autologous BM-MSCs</td>
<td>No information</td>
</tr>
<tr>
<td>Ex vivo cultured adult allogenic BM-MSCs</td>
<td>25, 50, 75 or 150 × 10^6 cells</td>
</tr>
</tbody>
</table>

KOOS Knee Injury and Osteoarthritis Outcome Score, WORMS Whole Organ MRI Score, COMP Cartilage oligomeric matrix protein, IKDC The international knee documentation committee, Lysholm Knee Scoring Scale (LKSS): grade the knee function of patients, and examine the changes or improvement compared with baseline, Area Measurement And DEpth & Underlying Structures (AMADEUS): assessment of preoperative cartilage defect severity, Function in daily living (ADL), Patient-Reported Outcomes Measurement Information System (PROMIS 29): The PROMIS-29 assesses seven health domains: physical function, anxiety, depression, fatigue, sleep disturbance, pain interference, and ability to participate in social roles and activities, EuroQuality of Life (EQSD-3 L): EuroQuality of Life (EQSD-3 L), Change in Hip disability and osteoarthritis Outcome Score (HOS)
regenerative outcomes, although more MSCs do not necessarily result in increased rates of healing. Although the reason for this is unclear, some studies have highlighted that a minimum number of MSCs are essential to enhance the healing cascade; whereas high doses of MSCs may lead to overpopulation and stem cell competition for nutrients within the graft area (Liebergall et al. 2013).

CARTISTEM®, the world’s first allogeneic cord blood-derived mesenchymal stem cell drug was received its market approval by the Food and Drugs Administration (FDA) and was released in South Korea in 2012. The MSC-based product contains 2.5 × 10^6 cells/500 μL/cm² area of the knee cartilage defect and was recently approved by the European Medicines Agency (EMA) as an advanced therapy medicinal product (ATMP) approved in EU South Korea, Medipost, UK Intra-articular injection to the knee

CARTISTEM® Allogeneic umbilical cord blood-derived MSC (Park et al. 2017; Lee 2018)

CARTISTEM® Allogeneic umbilical cord blood-derived MSC (Park et al. 2017; Lee 2018)

Stempeucel® Allogenic ex vivo cultured, pooled, human BM-MSC (Gupta et al. 2016a; STEMPEUTICS RESEARCH PVT LTD 2019)

Joint Stem Autologous adipose derived mesenchymal stem cells (Jo et al. 2014)

regenerative outcomes, although more MSCs do not necessarily result in increased rates of healing. Although the reason for this is unclear, some studies have highlighted that a minimum number of MSCs are essential to enhance the healing cascade; whereas high doses of MSCs may lead to overpopulation and stem cell competition for nutrients within the graft area (Liebergall et al. 2013).

CARTISTEM®, the world’s first allogeneic cord blood-derived mesenchymal stem cell drug was received its market approval by the Food and Drugs Administration (FDA) and was released in South Korea in 2012. The MSC-based product contains 2.5 × 10^6 cells/500 μL/cm² area of the knee cartilage defect and was recently approved by the European Medicines Agency (EMA) as an advanced therapy medicinal product (ATMP) approved in EU South Korea, Medipost, UK Intra-articular injection to the knee

CARTISTEM® Allogeneic umbilical cord blood-derived MSC (Park et al. 2017; Lee 2018)

Stempeucel® Allogenic ex vivo cultured, pooled, human BM-MSC (Gupta et al. 2016a; STEMPEUTICS RESEARCH PVT LTD 2019)

Joint Stem Autologous adipose derived mesenchymal stem cells (Jo et al. 2014)

regenerative outcomes, although more MSCs do not necessarily result in increased rates of healing. Although the reason for this is unclear, some studies have highlighted that a minimum number of MSCs are essential to enhance the healing cascade; whereas high doses of MSCs may lead to overpopulation and stem cell competition for nutrients within the graft area (Liebergall et al. 2013).

CARTISTEM®, the world’s first allogeneic cord blood-derived mesenchymal stem cell drug was received its market approval by the Food and Drugs Administration (FDA) and was released in South Korea in 2012. The MSC-based product contains 2.5 × 10^6 cells/500 μL/cm² area of the knee cartilage defect and was recently approved by the European Medicines Agency (EMA) as an advanced therapy medicinal product (ATMP) approved in EU South Korea, Medipost, UK Intra-articular injection to the knee

CARTISTEM® Allogeneic umbilical cord blood-derived MSC (Park et al. 2017; Lee 2018)

Stempeucel® Allogenic ex vivo cultured, pooled, human BM-MSC (Gupta et al. 2016a; STEMPEUTICS RESEARCH PVT LTD 2019)

Joint Stem Autologous adipose derived mesenchymal stem cells (Jo et al. 2014)

Conclusion

The application of MSC therapies for the treatment of OA is evolving swiftly despite a current lack of concrete evidence to support its long-term efficacy. Regardless of differences in
MSC sources, the literature and clinical trials have no cohesive information regarding the collection/isolation, culture conditions and characterisation criteria, quality, mode of action or administration of the stem cells. We have reported that defining the cell dosage and MSC characteristics are currently present a hurdle that must be overcome to identify the quality of MSCs as therapeutic agents, particularly when comparing the clinical outcomes and efficacy of preclinical, clinical and market authorised cell therapy treatments.

Currently, numerous qualitative often subjective, clinical measurements are applied to assess the efficacy and effectiveness of MSC treatments, which may not faithfully represent the accurate potency and efficiency of the therapy. Therefore, efficacy follow-up systems are required to monitor the dynamics of efficacy and to help in evaluating the requirement for re-application of the MSC product. Moreover, the efficacy monitoring allows the generation of the information that will appropriately reflect the periods of required reapplication in clinical practice. Such systems include more sensitive (and less subjective) quantitative tests, acceptable surrogate methods and more comparative design that are essential in long-term follow-up assessment of clinical, safety and efficacy of MSC-based products. The results of number of European studies and clinical trials revealed that BM-MSCs are the predominant cell source; however, the optimal source of MSCs is still speculative when considering combining the cell preparation procedure, differentiation potential and durable effect of MSCs. Additionally, a more consistent methodology is vital to evaluate the outcome of regenerative treatment in a more standardised and comparable frame whilst, larger patient number reaffirm the efficacy of MSC treatment within clinical trials and follow-up studies. Despite the numerous clinical trials and research studies that have used MSC for the treatment of knee OA, only five MSC products have reached the market with only two products including: CARTISTEM® and Stempeucell®, receiving approval by ATMPs for clinical application in EU. The massive gaps between clinical trials, cell therapies regulatory bodies and the market show that completion of clinical trial and approval of an MSC product does not guarantee its clinical application due to the issues with reimbursement and the cost of final product.

Compliance with ethical standards

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

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References


Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.