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Umbilical Cord Derived Mesenchymal Stem Cell Therapy for Osteoarthritis: A Consolidated Review

(Tali Pusat Terbitan Terapi Sel Stem Mesenkima untuk Osteoartritis: Suatu Ulasan Lengkap)

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ABSTRACT

Osteoarthritis (OA) is a leading cause of degenerative disease and is the most common persistent condition worldwide. The common burden imposed by OA significantly damages the articular cartilage, which results in pain and seriously impacts the quality of life in the affected people. Disease progression is assumed to increase with obesity and aging. The current therapies include weight loss, activity adjustment, traditional pain management and replacement of the affected joint. To overcome these limitations, recently, cell-based therapies mainly Umbilical cord derived Mesenchymal stem cell (UC-MSC) have become an attractive cell source for an allogeneic mesenchymal stem cell to repair and regenerate the structure and function of articular tissues. Although the mechanism is not clearly defined, it is believed that the paracrine signaling, inflammatory response, and immunomodulatory role of UC-MSCs play a crucial role in developing a treatment approach of OA. The purpose of this review was to outline the advantages of using UC-MSCs in treating OA. This review also discusses the possible hurdles that stand in the way of successful implementation of UC-MSC as a routine treatment regimen for OA.

Keywords: Allogeneic stem cell; mesenchymal stem cell; osteoarthritis; umbilicalcord tissue

ABSTRAK

Osteoartitis (OA) adalah penyebab utama penyakit degeneratif dan merupakan keadaan yang paling biasa di seluruh dunia. Beban umum yang disebabkan oleh OA dengan ketara merosakkan artikul rawan yang mengakibatkan kesakitan dan memberi kesan serius terhadap kualiti hidup orang yang mengalaminya. Janjang penyakit ini dianggap meningkat dengan keobesan dan penuaan. Terapi semasa termasuklah penurunan berat badan, pelarasan aktiviti, pengurusan sakit secara tradisi dan penggantian sendi yang terjejas. Untuk mengatasi keterbatasan ini, terbaru, terapi berasaskan sel terutamanya tali pusat terbitan terapi sel stem mesenkima (UC-MSC) telah menjadi sumber sel yang menarik untuk sel stem alogen mensenkima untuk membaiki dan menjana semula struktur dan fungsi tisu artikul. Walaupun mekanisme itu belum ditakrifkan dengan jelas, dipercayai bahawa isyarat parakrin, tindak balas keradangan dan peranan imunomodul UC-MSC memainkan peranan penting dalam membangunkan pendekatan rawatan OA. Tujuan kajian ini adalah untuk menggariskan kelebihan menggunakan UC-MSC dalam merawat OA. Ulasan ini juga membincangkan kemungkinan halangan yang berlaku dalam pelaksanaan UC-MSC dengan jayanya sebagai regimen rawatan rutin untuk OA.

Kata kunci: Osteoartitis; sel stem alogen; sel stem mesenkima; tisu tali pusat

INTRODUCTION

Osteoarthritis is a common degenerative and inflammatory disease that affects the cartilage, joint tissues, and subchondral bone. It results in bones scuff, which induces rigidity, pain, and impaired movements in all ages (Hatched et al. 2017). Half of the world's population aged 60 years and above have asymptomatic OA and the percentage of OA is higher with women (Arthritis Information 2017). This might be coupled with risk factors, including lack of exercise, obesity, occupational injury, bone density, genetic tendency, trauma, and aging (Blagojevic et al. 2010; Silverwood et al. 2015). In addition, the increase in the level of oxidative stress and senescence related secretory factors are related to the pathogenesis of OA (Li et al. 2013).

At present, the literal cause of OA and effective treatment to restore the original structure and function of damaged articular cartilage remain out of reach (Mobasheri et al. 2014). Current treatment modalities for OA are expected to reduce the pain rather than disease modification. Furthermore, the existing pharmaceutical treatments are inadequate and can have redundant side effects (Bagga et al. 2006). Surgical treatments mainly focus on relieving the pain and restoring joint function, but has limited benefits on degenerative changes that take place (Vaishya et al. 2016). Meanwhile, total knee arthroplasty (TKA) is the most commonly performed procedure in the elderly and advanced OA. However, the TKA procedure does not recover the patients completely. In particular, the results for younger patients who expect to have anactive lifestyle

after surgery are minimal. Patient satisfaction remains at only 80% to 83% after TKA (Kennedy et al. 2013; Robertsson et al. 2000). In recent years, the numbers and costs of TKA have increased dramatically - in 2001, the procedure cost an average of $25,500 per surgery but in 2012 it cost $52,000 per surgery (Centeno et al. 2015).

In recent years, there has been increasing interest in the use of cell-based therapy for the treatment of OA. In particular, autologous chondrocyte implantation in damaged OA cartilage is the most preferred therapeutic approach. Although it is an obscure procedure to harvest and culture the chondrocytes from the elderly people (de Windt et al. 2014), the recent advances in stem cell engineering have progressed towards its development. Mesenchymal stem cell (MSCs) have gained interest because they are considered to be readily available and are able to differentiate into chondrocytes. The multi-lineage differentiation potential of MSCs is considered to possess an added advantage of treating cartilage defects (Orth et al. 2014). Originally, bone marrow was considered as a key resource of MSCs; however, MSCs derived from bone marrow significantly decline with aging. Studies have reported that MSC can be generated from liver, heart, skin, umbilical cord, and cord blood. Among these, umbilical cord derived MSCs stand out because they can grow infinitely, pose lesser ethical issues and can be rapidly explanted under *in vitro* conditions (Rao & Matson 2001; Subramani et al. 2016; Wang et al. 2004). However, the maintenance of the chondrogenic characteristics of differentiated stem cells, their combination with resident tissue, and impersonating the natural strength presents a challenge when adopting stem cell therapy for OA (Diekman & Guilak 2013). In this review, we have summarized the recent position of UC-MSC therapies in OA and we have also discussed the potential areas of further research needed in regenerative medicine.

CHONDROGENIC DIFFERENTIATION OF UC-MSC

MSCs have an added advantage in the field of tissue regeneration and cartilage repair because they can retain their differentiation potency after *ex vivo* expansion. Nevertheless, the stemness, proliferation and differentiation potency vary based on the source, environment, signaling molecules, physical and chemical factors (Lavrentieva et al. 2013). Studies have shown that MSCs have been isolated from different sources and display different potentials to differentiate towards certain cell lineages (Stockmann et al. 2012; Wen et al. 2013; Zuk et al. 2002). MSCs derived from adipose tissue (AD) and bone marrow (BM) express cartilage-specific genes and proteins, which include aggrecan and Type II collagen. However, the chondrogenic potential is statistically weaker in terms of matrix formation and cell morphology in AD when compared to the bone marrow-derived MSCs (Estes et al. 2010; Im et al. 2005; Payne et al. 2010; Scharstuhl et al. 2007). UC-MSCs have an advantage over BM-MSCs because they show higher chondrogenic potential and collagen production three times higher than BM-MSC (Wang et al. 2009a). In addition, stem cell derived from UC has additional advantages compared to other sources. They recline between embryonic and adult stem cells on the development map, they do not induce tumorigenesis, and are hypoimmunogenic (Kim et al. 2013). Meanwhile, hyaluronate naturally occurs within the cartilage and synovial fluid. The UCs naturally contain hyaluronic acid, which adds advantage to use UC- MSC for chondrogenic differentiation (Can & Karahuseyinoglu 2007) because hyaluronate has special healing actions and is already a routine therapeutic option for various complications.

Recently, Kwon et al. (2016) demonstrated that MSCs from amnion (AMSCs), chorion(CMSCs), and umbilical cord (UC-MSCs) are able to differentiate into chondrocyte-like cells. Their study concluded that prenatal tissue is an excellent source of MSCs in the terms of proliferation and differentiation into osteocytes, adipocytes, and chondrocytes. They are predicted to be superior sources to BM-MSCs due to their innate differentiation potency and HLA-G expression. When a comparative study between human UC-MSC and BM-MSC for cartilage tissue engineering was performed, it was detected that UC-MSCs showed strong upregulation of cartilage-specific transcript expression and showed higher Type II collagen synthesis than BM-MSC at both transcript and protein levels (Reppel et al. 2015). Fong et al. (2012) showed that the WJ-MSC cultured with nanofibrous substrates enhanced chondrogenic differentiation and these authors were able to get upregulated with the production of hyaluronic acid and GAGs, as well as the expression of key genes as SOX9, COMP, Collagen Type II and FMOD. The results of the various approaches performed so far utilizing the UC-MSCs are tabulated in Table 1, which shows effective chondrogenic differentiation.

POSSIBLE MECHANISM OF UC-MSC IN OA

Articular cartilage is typically known as diarthrodial joints and is particularly made up of hyaline cartilage that comprises chondrocytes residing in a dense extracellular matrix (ECM), to facilitate smooth and painless movement. The mesenchymal origin of chondrocytes plays a vital role in protecting and maintaining the anatomical structure of cartilage and contributes about 2% of the total volume of the cartilage (Lee & Wang 2017). In the case of any injury, owing to the lack of blood vessels in the articular region and the limited potential of the chondrocytes replication, the damage results in poor cartilage regeneration. The pathophysiology of OA indicates that OA is not only associated with cartilage damage but is also associated with the damage of synovium and subchondral bone (Brandt et al. 2009; Mobasheri et al. 2014). Therefore, the therapeutic approach should be designed to target multi-cellular regeneration in OA.

Emerging evidence claims that cell-based therapy is a more promising therapeutic tool for OA than the current regimen dealing with pain management. In particular,

mesoderm lineage of MSC has the ability to differentiate into a bone cell (osteocyte) and cartilage tissue (chondrocyte). Thus, MSC has come to the fore of modern science for OA. It has been reported that MSC proliferation, differentiation potential, and host survival are age dependent (Pelttari et al. 2006; Steinert et al. 2007). With this limitation, patient specific (autologous) MSC therapy may not be advisable to meet the requirement. To overcome this issue, an outsource of (allogeneic) MSC may appear to be an alternative or tangible 'off-the-shelf' source for OA. Among those, umbilical cord derived MSC (UC-MSC) stands out because of the infinite availability of samples, lesser ethical issues, and rapid *in vitro* isolation and expansion. Various clinical studies have implicated the significance of UC-MSC in cartilage regeneration for the treatment of OA (Chang et al. 2018, 2016; Matas et al. 2019). Although a large number of studies suggested that umbilical cord derived MSCs have the potential to improve the overall condition of OA, their mechanism of action has not been completely explored. The paracrine effect of UC-MSC is considered as one of the crucial factors found in cartilage regeneration. In an important study by Chang et al. (2018), HUMSC derived conditional media supported and recovered the chondrocytes from impaired proliferation and also protected them from caspase-3 mediated apoptosis under laboratory conditions. Specifically, intra-articular injection of UC-MSC assisted the repair and regenerated cartilage in OA induced mice model. In addition, Zhang et al. (2018) also demonstrated that UC-MSC potentially improves the cartilage regeneration in OA induced canine model, which promoted the chondrocyte proliferation and reduced or inhibited the inflammatory response. It has also been reported that UC-MSCs promoted the OA chondrocytes proliferation and inhibited the inflammatory cytokines (Wang et al. 2018b). In addition, MSCs could adjust the cell signaling environment, increase the production of collagen Type II, promote the migration of chondrocytes to the injured area and repair the damage by synthesizing the lost extracellular matrix (Horie et al. 2012; Iwata et al. 1993). Based on the existing evidence, UC-MSC seems to be a highly promising therapeutic regimen for OA by the following mechanisms: inhibits the inflammatory response; inhibits the apoptosis mediated cell death; promotes the chondrocyte proliferation, and migration; promotes the extracellular matrix synthesis; and directly differentiates into chondrocytes or by inducing the differentiation of the native healthy chondroprogenitors into mature chondrocytes or both (Figure 1).

PRECLINICAL OUTCOME OF UC-MSC IN OA

The immunomodulatory and anti-inflammatory properties of MSCs have encouraged researchers to focus on the therapeutic application of MSCs for OA. In the past two

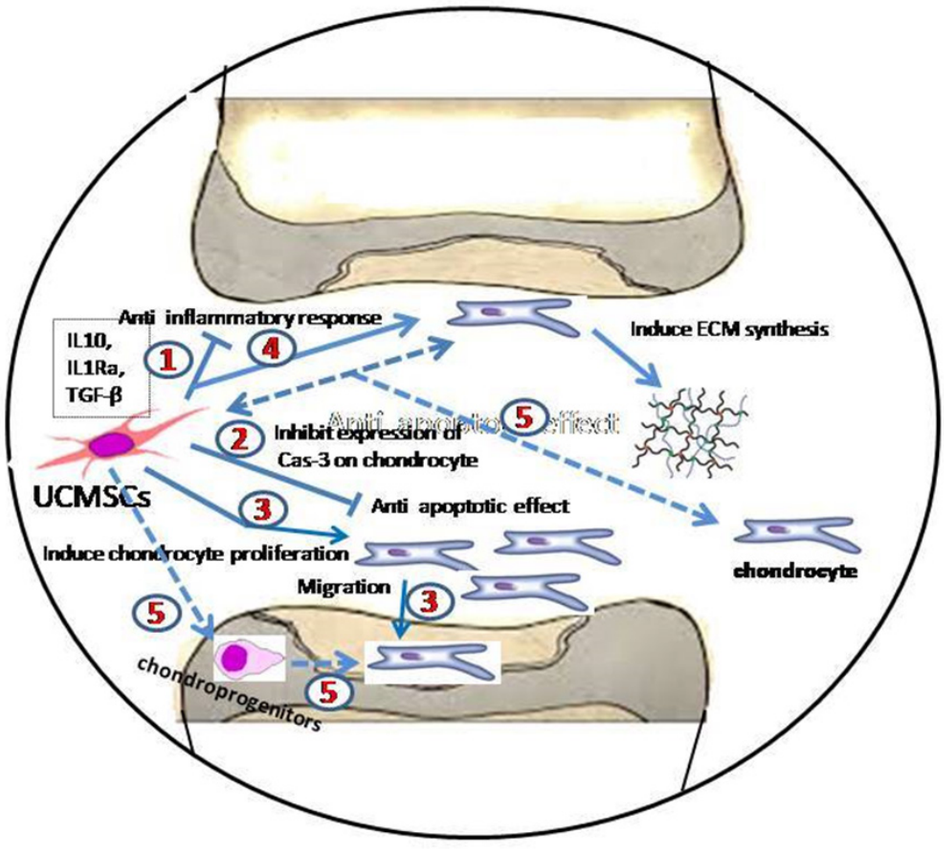

FIGURE 1. Schematic representation of possible mechanism of UCMSCs in OA

decades, many preclinical studies showed promising results of OA with the use of MSCs (MacFarlane et al. 2013). Intra-articular (IA) injection of MSCs for cartilage restoration has become a new cell therapy option for OA. Interestingly, Murphy et al. (2003) demonstrated that the bio-distribution of IA injection of MSCs has shown that the transplanted cells moved into the synovial membrane rather than the cartilage itself. This data suggests that MSCs have paracrine properties that are capable of chondrogenic differentiation. Some of the studies have proven the benefits of MSCs are due to its paracrine activity (Barry & Murphy 2013). Recently, Saulnier et al. (2015) confirmed the IA injection of UC-MSC in the rabbit model. The data showed that the IA injection might be more efficient in reducing inflammation and preventing OA progression by inducing chondrocytes to produce extracellular matrices and collagen types II, IX, and XI in the superficial and central regions (Akkiraju & Nohe 2015). Zhang et al. (2018) showed UC-MSCs treatment through articular cavity injection in a canine model, where two doses of 1×106 UC-MSCs were injected and the therapeutic effect and mechanism of MSCs were observed. The results showed that the inflammatory reaction and joint effusion decreased after 7 days of post-transplantation. It was concluded that MSCs would be effective in treating OA by adjusting the repair response of the joint rather than replacing the damaged area directly.

Despite the allogeneic UC-MSCs shown promising therapeutic outcome in OA, the critical issue of the immune privilege needs to be assessed in the host of the animal model. The literature has outlined that UC-MSCs have peculiar immune-privileged properties, such as low expression of HLA-I and no expression of HLA-II (Kim et al. 2013; Liu et al. 2012). Furthermore, these cells are highly express HLA-G, which involve immune tolerance and also secrete various immunosuppressive biomolecules (TGF-β1, TNF-alpha, PEG2, IDO, NO) to suppress the primary and secondary immune cells, such as T, NK, B cell, DC, and neutrophils (Figure 2) (Kim et al. 2013). One recent finding demonstrated that immune-privileged status of UC-MSC has to be extended until specific lineage (chondrogenic) differentiation (Liu et al. 2012). Meanwhile, several studies have reported that rejection of allogeneic MSCs may hamper the tissue regeneration process (Eliopoulos et al. 2005; Huang et al. 2010; Tano et al. 2016). Oliveira et al. (2017) reported that allogeneic MSCs were rejected from the host kidney tissue by not more than 28 days after transplantation. This result may partially postulate that immuno-privileged status of MSC isreduced during differentiation and thus these cells were gradually eliminated by the host's immune system. A similar paradigm has been confirmed in humans by de Windt et al. (2014) in a clinical trial for cartilage repair using allogeneic MSCs. Although an encouraging clinical outcome reported, no allogeneic cells were found at the repair site after 1- year post-transplantation. Overall, these reports declared that there are some limitations on the use of allogeneic MSCs, although recent findings have reported that the safety and some promising results promote their use as a therapeutic tool for OA.

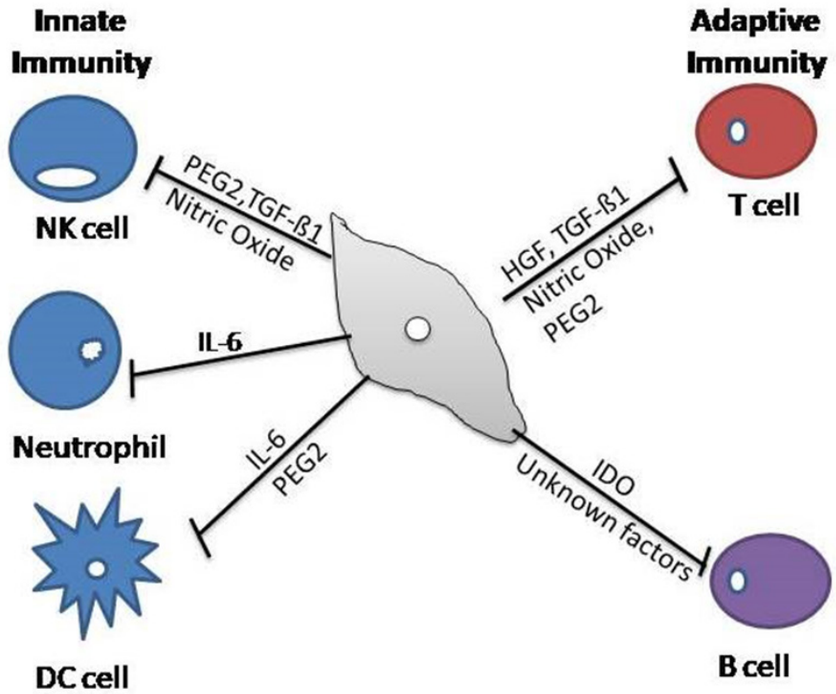

FIGURE 2. Schematic representation of immunomodulatory effects of MSCs on innate and adoptive immune system

OVERALL CLINICAL OUTCOME OF UC-MSC IN OA PATIENTS

In view of the fact that certain ethical concerns and poor chondrogenic property of the use of embryonic stem cell (ESC) and induced pluripotent stem cell (iPSC) are limited in OA treatment, it is thus inevitable to find an alternative type of stem cell source that would bypass the concerns of ESCs and iPSCs (Lee & Wang 2017). Recent clinical research suggests that human fetal tissues derived MSCs are more promising cell types to treat OA than other sources of MSCs. Various studies have proposed that human umbilical cord is the primary source for MSCs due to less ethical concern, easy harvest, expansion, high proliferation potency, low morbidity rate, higher migration potential non-invasive procedure and less side effects (Bartolucci et al. 2017). Moreover, UC-MSCs naturally have a high content of hyaluronic acid, glycosaminoglycans and collagens, which reflect the bio-composition of native cartilage tissue (Valiyaveettil et al. 2004). These UC-MSCs have several advantages than other existing MSCs and, therefore, researchers are encouraged to use UC-MSC for OA. According to the international clinical trial registry (Table 2) (www.clinicaltials.com), in 2019, 10 open clinical trials are to be conducted to address the safety, feasibility and therapeutic effect of UC-MSC in patients with OA. Most of the on-going clinical trials aim to deliver the MSCs through direct IA or surgical implantation in the presence or absence of scaffold (hyaluronic acid or platelet rich plasma) to assess the magnitude of cartilage regeneration (Wyles et al. 2015). An emerging database from phase I and II trials has reported that repeated dose (40×10^6) of UC-MSC in a patient with OA is safer and more logistically convenient than the autologous source. The same clinical trial has showed promising outcomes with repeated IA injection of UC-MSC, leading to a decrease in the level of pain and disability (Matas et al. 2019). The clinical application of UC-MSC for OA is still in its infancy and high-quality clinical trials are warranted to reproduce the outcome and resolve many questions, including dose (optimum number of cells) and mode of injection at each stage of OA.

FUTURE DIRECTION AND CONCLUSION

Clinical application of UC-MSC for OA treatment is still in infancy. Based on the preclinical and phase 1 or 2 clinical studies, UC-MSC based therapies have widely been explored to treat OA and hold promising therapeutic outcomes, including successful cartilage renewal and pain relief (Matas et al. 2019). However, an insufficient number of clinical trials on UC-MSC in cartilage regeneration means that there is currently no clear picture or evidence on the restoration of the native hyaline cartilage for permanent cure or at least long-term improvement. The clinical outcome of OA using UC-MSC is not consistent because of the technical challenge to produce UC-MSC in an optimized manner. Therefore, the development of universally standardized protocol is still detrimental. Meanwhile, the clinical improvement of UC-MSCs depends on the mode of injection and cell number (dose). Specifically, IA mode of implantation shows better clinical outcome. At the same time, the long-term consequence remains debatable. Very few clinical trials have shown that the therapeutic effect of MSC on OA is dose-dependent and declared that a large number of cells gives more beneficial effects. A randomized controlled study with a larger population would be an effective model to deal with the optimization of the dose required for cell therapy using UC-MSCs. Furthermore, a routine follow-up of the subjects is considered vital to assess the regeneration. This would ultimately provide better data to propose the target cell population are superior to other sources to handle OA. Several studies have emphasized that administration of UC-MSC directly to the joint space is associated with limitations such as massive cell death (cells are likely exposed to pathological environments such as hypoxic, acidic, nutritional deprivation, high concentration of inflammatory cytokines and reactive oxygen species) and risk of cell leakage (tendency of MSCs to migrate and because of the low level of cell engraftment) (Hached et al. 2017; Wyles et al. 2015; Zhang et al. 2018). To overcome these limitations, MSCs might be implanted into the abnormal microenvironments that have already been biochemically compromised. Nevertheless, cells have to be pre-treated or genetically modified to manage and withstand any pathophysiological environment. The generation of genetically modified MSCs is a more complex process and is more expensive, needs a sophisticated lab, and skilled personnel. Therefore, the current research prospected towards encapsulation of MSCs through three-dimensional (3D) method using hydrogels or scaffolds (ex. collagen or hyaluronic acid) to enhance the retention of MSCs at the targeted tissues would be a feasible approach. Furthermore, the 3D scaffold may potentially improve the development of cartilage tissue. which is similar to native cartilage by providing an essential microenvironment and mechanical stimuli. In addition, encapsulated MSC together with growth factors (ex. platelet rich plasma) have shown better cartilage regeneration in a patient with OA; however, further extensive clinical studies are warranted to identify long-term beneficial and potential risks.

CONCLUSION

Although multiple published preclinical or clinical studies have stipulated the therapeutic outcome of UC-MSCs alone or together with scaffold or growth factors in OA, standardization of suitable dose of UC-MSCs, mode of injection, scaffold in OA with large sample size and long-term follow ups are needed to reach a successful clinical translation. Considering the clinical instability and lack of effective mode of treatment for OA, this important approach could be explored further by bridging the current research gaps. Scientists in association with clinical specialists should explore and construct a concrete plan to understanding the pathophysiology and mechanism of

action using UC-MSCs, which have already had a considerable impact.

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